

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

B.P.J., by her next friend and mother,
HEATHER JACKSON

Plaintiff,

v.

WEST VIRGINIA STATE BOARD OF
EDUCATION, HARRISON COUNTY BOARD
OF EDUCATION, WEST VIRGINIA
SECONDARY SCHOOL ACTIVITIES
COMMISSION, W. CLAYTON BURCH in his
official capacity as State Superintendent,
DORA STUTLER in her official capacity as
Harrison County Superintendent, and THE
STATE OF WEST VIRGINIA

Defendants

and

LAINIEY ARMISTEAD

Defendant-Intervenor.

Case No. 2:21-cv-00316

Hon. Joseph R. Goodwin

Oral Argument Requested

**DEFENDANT-INTERVENOR AND THE STATE OF WEST VIRGINIA'S MOTION TO EXCLUDE
EXPERT TESTIMONY OF DR. DEANNA ADKINS**

Defendant-Intervenor Lainiey Armistead and the State of West Virginia move to exclude the testimony of Dr. Deanna Adkins pursuant to Federal Rule of Evidence 702 and *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993). In support of their motion, they rely on the affidavits, admissions, depositions, expert reports, studies, and other documents included in the Appendix to this motion in addition to the contemporaneously filed Memorandum of Law. Ms. Armistead and the State request oral argument to be heard at a time and date set by the Court under Local Rule of Civil Procedure 9.8. They respectfully pray for this relief and for any further relief this Court may deem just and proper.

Respectfully submitted this 12th day of May, 2022.

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West Virginia Attorney General

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Case No. 2:21-cv-00316

Hon. Joseph R. Goodwin

CERTIFICATE OF SERVICE

I, Brandon Steele, hereby certify that on May 12, 2022, I electronically filed a true and exact copy of the forgoing with the Clerk of Court and all parties using the CM/ECF system.

/s/ Brandon S. Steele

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Case No. 2:21-cv-00316

Hon. Joseph R. Goodwin

**ROGER G. BROOKS' DECLARATION IN SUPPORT OF DEFENDANT-INTERVENOR AND THE
STATE OF WEST VIRGINIA'S MOTIONS TO EXCLUDE EXPERT TESTIMONY OF DRS. ADKINS,
FRY, JANSSEN, AND SAFER**

I, Roger G. Brooks, declare under penalty of perjury of the laws of the United States that the following is true and correct, and state:

I am counsel of record for Defendant-Intervenor Lainy Armistead in this litigation. The following is true of my own personal knowledge, and, if called as a witness, I would and could testify competently thereto.

As set forth below, I have reviewed the articles and studies used in support of the motions to exclude the certain proffered opinions of Dr. Adkins, Dr. Fry, Dr. Janssen, and Dr. Safer. The copies of the articles identified herein, and submitted in the accompanying Appendix to Defendant Intervenor and the State of West Virginia's Motion to Exclude Expert Testimony of Dr. Deanna Adkins ("Daubert Appendix") at

the pages indicated, are true and correct copies of those articles as obtained from public sources. I identify herein where each source was marked as an exhibit in deposition or cited in an expert's report.

1. Balaguer, I., et al., *Motivational Climate and Goal Orientations as Predictors of Perceptions of Improvement, Satisfaction and Coach Ratings Among Tennis Players*, 9 Scand. J. Med. Sci. Sports 381 (1999), doi: 10.1111/j.1600-0838.1999.tb00260.x.

This source was designated as Fry Deposition Exhibit 5 and is in the Daubert Appendix at page 370.

2. Bhargava, A., et al., *Considering Sex as a Biological Variable in Basic and Clinical Studies: An Endocrine Society Scientific Statement*, 42 Endocr. Revs. 219 (2021), doi: 10.1210/endrev/bnaa034.

This source was designated as Adkins Deposition Exhibit 4 and is in the Daubert Appendix at page 379.

3. Carmichael, P., et al., *Short-term Outcomes of Pubertal Suppression in a Selected Cohort of 12 to 15 Year Old Young People with Persistent Gender Dysphoria in the UK*, 16 PLoS ONE e0243894 (2021), <https://doi.org/10.1371/journal.pone.0243894>.

This source was designated as Janssen Deposition Exhibit 40 and is in the Daubert Appendix at page 419.

4. Clark, C.M., & Kosciw, J.G., *Engaged or Excluded: LGBTQ Youth's Participation in School Sports and Their Relationship to Psychological Well-Being*, 59 Psych. Schs. 95 (2021).

This source was cited at ¶ 52, n. 22 of Rebuttal Expert Report and Declaration of Aron Janssen, M.D. and is in the Daubert Appendix at page 445.

5. Durwood, L., et al., *Mental Health and Self-Worth in Socially Transitioned Transgender Youth*, 56 J. Am. Acad. Child Adolesc. Psychiatry 116 (2017).

This source was designated at Janssen Deposition Exhibit 9 and is in the Daubert Appendix at page 465.

6. Fin. Ministry of Soc. Affairs and Health, Council for Choices in Health Care, *Medical Treatment Methods for Dysphoria Associated with Variations in Gender Identity in Minors—Recommendation* (2020).

This source was cited at ¶ 23 of Declaration of James M. Cantor, PHD. and is in the Daubert Appendix at page 475.

7. Fin. Ministry of Soc. Affairs and Health, Council for Choices in Health Care, Medical Treatments for Gender Dysphoria that Reduces Functional Capacity in Transgender People—Recommendation (2020).

This source was cited at ¶ 23 of Declaration of James M. Cantor, PHD. and is in the Daubert Appendix at page 477.

8. Gibson, D.J., et al., *Evaluation of Anxiety and Depression in a Community Sample of Transgender Youth*, 4 JAMA Network Open e214739 (2021), doi:10.1001/jamanetworkopen.2021.4739.

This source was designated as Janssen Deposition Exhibit 17 and is in the Daubert Appendix at page 479.

9. Handelsman, D.J., et al., *Circulating Testosterone as the Hormonal Basis of Sex Differences in Athletic Performance*, 39 Endocr. Revs. 803 (2018), doi: 10.1210/er.2018-00020.

This source was designated as Safer Deposition Exhibit 4 and is in the Daubert Appendix at page 483.

10. Handelsman, D.J., *Perspective, Transgender Women Outpace Cisgender Women in Athletic Tests After 1 Year on Hormones*, Healio News: LGBTQ+ Health Updates (Dec. 16, 2020), <https://www.healio.com/news/endocrinology/20201216/transgender-women-outpace-cisgender-women-in-athletic-tests-after-1-year-on-hormones>.

This source was designated as Safer Deposition Exhibit 13 and is in the Daubert Appendix at page 510.

11. Harper, J., et al., *How does Hormone Transition in Transgender Women Change Body Composition, Muscle Strength and Haemoglobin? Systematic Review with a Focus on Implications for Sport Participation*, Br. J. Sports Med. (Mar. 1, 2021), doi: 10.1136/bjsports-2020-103106 (published online ahead of print).

This source was designated as Safer Deposition Exhibit 12 and is in the Daubert Appendix at page 514.

12. Hembree, W.C., et al., *Endocrine Treatment of Gender-Dysphoric/Gender Incongruent Persons: An Endocrine Society* Clinical Practice Guideline*, 102 J. Clin. Endocrinol. Metab. 3869 (2017), doi: 10.1210/jc.2017-01658.

This source was designated as Adkins Deposition Exhibit 4 and Safer Deposition Exhibit 8 and is in the Daubert Appendix at page 523.

13. Hilton, E.N. & Lundberg, T.R., *Transgender Women in the Female Category of Sport: Perspectives on Testosterone Suppression and Performance Advantage*, 51 Sports Med. 199 (2021), doi: 10.1007/s40279-020-01389-3.

This source was designated as Safer Deposition Exhibit 7 and is in the Daubert Appendix at page 558.

14. Lapinski, J., et al., *Best Practices in Transgender Health: A Clinician's Guide*, 45 Prim. Care Clin. Office Pract. 687 (2018) doi: 10.1016/j.pop.2018.07.007.

This source was designated as Adkins Deposition Exhibit 6 and is in the Daubert Appendix at page 574.

15. Littman, L., *Individuals Treated for Gender Dysphoria with Medical and/or Surgical Transition Who Subsequently Detransitioned: A Survey of 100 Detransitioners*, 50 Arch. Sex. Behav. 3353 (Oct. 2019), doi: 10.1007/s10508-021-02163-w.

This source was cited at ¶¶ 120, 121, 124, 125, 204 of Declaration of Stephen B. Levine, MD and is in the Daubert Appendix at page 591.

16. MacDonald, D.J., et al., *The Role of Enjoyment and Motivational Climate in Relation to the Personal Development of Team Sport Athletes*, 25 Sport Psych. 32 (2011).

This source was cited in the bibliography of Expert Report and Declaration of Professor Mary D. Fry, PHD and is in the Daubert Appendix at page 608.

17. Nainggolan, L., *Hormonal Tx of Youth with Gender Dysphoria Stops in Sweden*, Medscape (May 21, 2021), <https://www.medscape.com/viewarticle/950964>.

This source was designated as Janssen Deposition Exhibit 12 and is in the Daubert Appendix at page 624.

18. National Institutes of Health, Office of Research on Women's Health, *How Sex and Gender Influence Health and Disease*, https://orwh.od.nih.gov/sites/orwh/files/docs/SexGenderInfographic_11x17_508.pdf. (last visited May 10, 2022).

This source was designated as Adkins Deposition Exhibit 8 and is in the Daubert Appendix at page 627.

19. Newton, M., et al., *Psychometric Properties of the Caring Climate Scale in a Physical Activity Setting*, 16 Revista de Psicología del Deporte 67 (2007), <https://www.redalyc.org/articulo.oa?id=235119232005>.

This source was designated as Fry Deposition Exhibit 5 and is in the Daubert Appendix at page 628.

20. Olson, K.R., et al., *Mental Health of Transgender Children who are Supported in Their Identities*, 137 Pediatrics e20153223 (2015), doi: 10.1542/peds.2015-3223.

This source was cited at ¶ 35, n. 9 of Rebuttal Expert Report and Declaration of Aron Janssen, M.D. and is in the Daubert Appendix at page 647.

21. Ommundsen, Y., et al., *Parental and Coach Support or Pressure on Psychosocial Outcomes of Pediatric Athletes in Soccer*, 16 Clin. J. Sport Med. 522 (2006).

This source was cited at ¶¶ 29, 32, 33, 39 of Expert Report and Declaration of Professor Mary D. Fry, PHD and is in the Daubert Appendix at page 655.

22. Only Human, *I'd Rather Have a Living Son Than a Dead Daughter*, WNYC Studios (Aug. 2, 2016), <https://www.wnycstudios.org/podcasts/onlyhuman/episodes/id-rather-have-living-son-dead-daughter>.

This source was designated as Adkins Deposition Exhibit 15 and is in the Daubert Appendix at page 660.

23. Rae, J.R., et al., *Predicting Early-Childhood Gender Transitions*, 30 Psych. Sci. 669 (2019), doi: 10.1177/0956797619830649.

This source was designated as Janssen Deposition Exhibit 27 and is in the Daubert Appendix at page 678.

24. Roberts, T.A., et al., *Effect of Gender Affirming Hormones on Athletic Performance in Transwomen and Transmen: Implications for Sporting Organisations and Legislators*, Br. J. Sports Med. (Dec. 7, 2020), doi: 10.1136/bjsports-2020-102329 (published online ahead of print).

This source was designated as Safer Deposition Exhibit 10 and is in the Daubert Appendix at page 691.

25. Schumm, W.R., & Crawford, D.W., *Is Research on Transgender Children What it Seems? Comments on Recent Research on Transgender Children with High Levels of Parental Support*, 87 Linacre Q. 9 (2020), doi: 10.1177/0024363919884799.

This source was cited at ¶ 35, n. 9 of Rebuttal Expert Report and Declaration of Aron Janssen, M.D. and is in the Daubert Appendix at page 698.

26. Staphorsius, A.S., et al., *Puberty Suppression and Executive Functioning: An fMRI-Study in Adolescents with Gender Dysphoria*, 56 Psychoneuroendocrinology 190 (2015), doi: 10.1016/j.psyneuen.2015.03.007.

This source was cited at ¶ 24, n. 7 of Expert Rebuttal Report and Declaration of Deanna Adkins, M.D. and is in the Daubert Appendix at page 714.

27. Steensma, T.D., et al., *Factors Associated with Desistence and Persistence of Childhood Gender Dysphoria: A Quantitative Follow-Up Study*, 52 J. Am. Acad. Child & Adolesc. Psychiatry 582 (2013), doi: 10.1016/j.jaac.2013.03.016.

This source was designated as Janssen Deposition Exhibit 27 and is in the Daubert Appendix at page 724.

28. Swedish Agency of Health Technology Assessment and Assessment of Social Services, *Gender dysphoria in Children and Adolescents: An Inventory of the Literature* (2019), <https://www.sbu.se/307e>.

This source was cited at ¶¶ 23, 31, 32 of Declaration of James M. Cantor, PHD. and is in the Daubert Appendix at page 733.

29. Turban, J.L., et al., *Association Between Recalled Exposure to Gender Identity Conversion Efforts and Psychological Distress and Suicide Attempts Among Transgender Adults*, 77 JAMA Psychiatry 68 (2020), doi: 10.1001/jamapsychiatry.2019.2285.

This source was designated as Janssen Deposition Exhibit 43 and is in the Daubert Appendix at page 736.

30. U.K. National Health Serv., National Institute for Health and Care Excellence, *Evidence Review: Gonadotrophin Releasing Hormone Analogues for Children and Adolescents with Gender Dysphoria* (2020).

This source was cited at ¶ 23 of Declaration of James M. Cantor, PHD. and is in the Daubert Appendix at page 754.

31. U.K. Sports Councils' Equality Group, Guidance for Transgender Inclusion in Domestic Sport (2021), <https://equalityinsport.org/docs/300921/Guidance%20for%20Transgender%20Inclusion%20in%20Domestic%20Sport%202021.pdf>.

This source was designated as Safer Deposition Exhibit 14 and is in the Daubert Appendix at page 885.

32. Carbmill Consulting, International Research Literature Review: SCEG Project for Review and Redraft of Guidance for Transgender Inclusion in Domestic Sport 2020, <https://equalityinsport.org/docs/300921/Transgender%20International%20Research%20Literature%20Review%202021.pdf> (last visited May 10, 2022).

This source was cited at ¶¶ 172–74 of Declaration of Gregory A. Brown, PH.D., FACSM and is in the Daubert Appendix at page 900.

33. Whisenant, W. & Jordan, J.S., *Fairness and Enjoyment in School Sponsored Youth Sports*, 43 Int'l R. Socio. Sport 91 (2008), doi: 10.1177/1012690208093470.

This source was designated as Fry Deposition Exhibit 6 and is in the Daubert Appendix at page 914.

34. Hughto, J.M.W., et al., *Transgender Stigma and Health: A Critical Review of Stigma Determinants, Mechanisms, and Interventions*, 147 Soc. Sci. Med. 222 (2015), doi: 10.1016/j.socscimed.2015.11.010.

This source was cited at ¶ 52, n. 22 of Rebuttal Expert Report and Declaration of Aron Janssen, M.D. and is in the Daubert Appendix at page 924.

35. World Health Organization, Gender and Health, https://www.who.int/health-topics/gender#tab=tab_1 (last visited May 10, 2022).

This source was designated as Adkins Deposition Exhibit 9 and is in the Daubert Appendix at page 946.

36. World Professional Association for Transgender Health, Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People, 7th Version (2012), https://www.wpath.org/media/cms/Documents/SOC%20v7/SOC%20V7_English.pdf.

This source was cited at ¶ 24, n. 3 of Declaration and Expert Report of Deanna Adkins, M.D. and is in the Daubert Appendix at page 947

37. Saraswat, A., et al., *Evidence Supporting the Biological Nature of Gender Identity*, 21 Endocr. Practice 199 (2015), doi: 10.4158/EP14351.RA.

This source was cited in Exhibit A (Curriculum Vitae) of Expert Report and Declaration of Joshua D. Safer, MD, FACP, FACE, and is in the Daubert Appendix at page 1067.

DECLARATION UNDER PENALTY OF PERJURY

I, Roger G. Brooks, a citizen of the United States and a resident of the State of North Carolina, hereby declare under penalty of perjury pursuant to 28 U.S.C. § 1746 that the foregoing is true and correct to the best of my knowledge.

Executed this 12th day of May, 2022, at Durham, North Carolina.

/s/ Roger G. Brooks

Roger G. Brooks

**APPENDIX TO DEFENDANT-INTERVENOR AND
THE STATE OF WEST VIRGINIA'S MOTIONS TO
EXCLUDE EXPERT TESTIMONY OF DRS.
ADKINS, FRY, JANSSEN, AND SAFER**

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IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA

B.P.J. by her next friend and mother,	)	
HEATHER JACKSON,	)	
<i>Plaintiff,</i>	)	Civil Action No. 2:21-cv-00316
v.	)	
	)	Hon. Joseph R. Goodwin
WEST VIRGINIA STATE BOARD OF	)	
EDUCATION, HARRISON COUNTY	)	
BOARD OF EDUCATION, WEST	)	
VIRGINIA SECONDARY SCHOOL	)	
ACTIVITIES COMMISSION, W.	)	
CLAYTON BURCH in his official capacity	)	
as State Superintendent, DORA STUTLER	)	
in her official capacity as Harrison County	)	
Superintendent, and THE STATE OF	)	
WEST VIRGINIA,	)	
	)	
<i>Defendants,</i>	)	
	)	
and	)	
	)	
LAINY ARMISTEAD,	)	
	)	
<i>Defendant-</i>	)	
<i>Intervenor.</i>	)	
	)	
	)	

DECLARATION AND EXPERT REPORT OF DEANNA ADKINS, MD

1. I have been retained by counsel for Plaintiff as an expert in connection with the above-captioned litigation.

2. I intend to provide my expert opinion on: (1) the nature and impact of treatment protocols for transgender youth; and (2) the different biological characteristics of sex and the ways in which they may not align within a person.

3. I have knowledge of the matters stated in this declaration and expert report and have collected and cite to relevant literature concerning the issues that arise in this litigation in the body of this declaration.

4. In preparing this declaration and expert report, I reviewed the text of House Bill 3293 at issue in this matter. I also relied on my scientific education and training, my research experience, and my knowledge of the scientific literature in the pertinent fields. The materials I have relied upon in preparing this declaration and expert report are the same types of materials that experts in my field of study regularly rely upon when forming opinions on these subjects. I may wish to supplement these opinions or the bases for them as a result of new scientific research or publications or in response to statements and issues that may arise in my area of expertise.

BACKGROUND AND QUALIFICATIONS

5. I received my medical degree from the Medical College of Georgia in 1997. I served as the Fellowship Program Director of Pediatric Endocrinology at Duke University School of Medicine for fourteen years and am currently the Director of the Duke Center for Child and Adolescent Gender Care.

6. I have been licensed to practice medicine in the state of North Carolina since 2001.

7. I have extensive experience working with children with endocrine disorders and I am an expert in the treatment of children with differences or disorders of sex development and in the treatment of children with gender dysphoria.

8. I am a member of the American Academy of Pediatrics, the North Carolina Pediatric Society, the Pediatric Endocrine Society, and The Endocrine Society. I am also a

member of the World Professional Association for Transgender Health (“WPATH”), the leading association of medical and mental health professionals in the treatment of transgender people.

9. I am the founder of the Duke Center for Child and Adolescent Gender Care (“Gender Care Clinic”), which opened in 2015. I currently serve as the director of the clinic. The Gender Care Clinic treats children and adolescents aged 7 through 22 with gender dysphoria and/or differences or disorders of sex development. I had been caring for these patients in my routine practice for many years prior to opening the clinic.

10. I currently treat approximately 400 transgender and intersex young people from North Carolina and across the Southeast at the Gender Care Clinic. I have treated approximately 500 transgender and intersex young people in my career.

11. As part of my practice, I stay familiar with the latest medical science and treatment protocols related to differences or disorders of sex development and gender dysphoria.

12. I am regularly called upon by colleagues to assist with the sex assignment of infants who cannot be classified as male or female at birth due to a range of variables in which sex-related characteristics are not completely aligned as male or female.

13. I have testified twice as an expert at trial or deposition in the past four years.

TREATMENT PROTOCOLS FOR TRANSGENDER PEOPLE

14. A transgender person has a gender identity that differs from the person’s sex assigned at birth.

15. A person’s gender identity refers to a person’s inner sense of belonging to a particular gender, such as male or female. Everyone has a gender identity.

16. Children usually become aware of their gender identity early in life.

17. For some people, their gender identity does not align with the sex they are assigned at birth. This misalignment can create significant distress, known as gender dysphoria, for people with this experience and can be felt in children as young as 2 years old.

18. A person's gender identity (regardless of whether that identity matches other sex-related characteristics) cannot be voluntarily changed, and is not undermined or altered by the existence of other sex-related characteristics that do not align with it.

19. According to the American Psychiatric Association's Diagnostic & Statistical Manual of Mental Disorders ("DSM V"), "gender dysphoria" is the diagnostic term for the condition where clinically significant distress results from the lack of congruence between a person's gender identity and the sex they are designated at birth. In order to be diagnosed with gender dysphoria, the incongruence must have persisted for at least six months and be accompanied by clinically significant distress or impairment in social, occupational, or other important areas of functioning.

20. Gender dysphoria is a serious medical condition that, if left untreated, can result in severe anxiety and depression, self-harm, and suicidality.¹

21. Before receiving treatment, many people with gender dysphoria have high rates of anxiety, depression, and suicidal ideation. I have seen in my patients that without appropriate treatment, this distress impacts every aspect of life.

¹ Spack NP, Edwards-Leeper L, Feldmain HA, et al. Children and adolescents with gender identity disorder referred to a pediatric medical center. *Pediatrics*. 2012; 129(3):418-425. Olson KR, Durwood L, DeMeules M, McLaughlin KA. Mental health of transgender children who are supported in their identities. *Pediatrics*. 2016; 137:1-8.

22. Experiences of discrimination and gender-minority stress associated with rejection and non-affirmation are correlated with suicidal ideation and suicidality, respectively.² The only treatment to avoid this serious harm is to recognize the gender identity of patients with gender dysphoria and follow appropriate treatment protocols to affirm gender identity and alleviate distress.

23. When appropriately treated, gender dysphoria is easily managed. I currently treat hundreds of transgender patients. All of my patients have suffered from persistent gender dysphoria, which has been alleviated through clinically appropriate treatment.

24. The Endocrine Society and the World Professional Association for Transgender Health have published widely accepted standards of care for treating gender dysphoria,³ including the forthcoming Standards of Care Version 8. The precise treatment for gender dysphoria depends on each person's individualized need, and the medical standards of care differ depending on whether the treatment is for a pre-pubertal child, an adolescent, or an adult.

25. The medical treatment for gender dysphoria is to eliminate the clinically significant distress by helping a transgender person live in alignment with their gender identity. This treatment is sometimes referred to as "gender transition," "transition related care," or

² World Prof'l Ass'n for Transgender Health, Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People, Chapter Draft for Public Comment-Mental Health (8th Version, forthcoming 2022).
<https://www.wpath.org/media/cms/Documents/SOC%20v8/SOC8%20Chapters%20for%20Public%20Comment/SOC8%20Chapter%20Draft%20for%20Public%20Comment%20-%20Mental%20Health.pdf?t=1638409644>

³ Hembree WC, et al. Endocrine treatment of gender-dysphoria/gender incongruent persons: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2017; 102: 3869–3903; World Prof'l Ass'n for Transgender Health, Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People (7th Version, 2011),
https://www.wpath.org/media/cms/Documents/SOC%20v7/SOC%20V7_English2012.pdf?t=1613669341

“gender affirming care.” The American Academy of Pediatrics agrees that this care is safe, effective, and medically necessary for the health and wellbeing of children and adolescents suffering from gender dysphoria.⁴

26. The Endocrine Society Guidelines were developed through rigorous scientific processes which “followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation group, an international group with expertise in the development and implementation of evidence-based guidelines.” The guidelines affirm that patients with gender dysphoria often must be treated with “a safe and effective hormone regimen that will (1) suppress endogenous sex hormone secretion determined by the person’s genetic/gonadal sex and (2) maintain sex hormone levels within the typical range for the person’s affirmed gender.”

27. Before puberty, treatment does not include any drug or surgical intervention. For this group of patients, treatment is limited to “social transition,” which means allowing a transgender child to live and be socially recognized in accordance with their gender identity. This can include allowing children to wear clothing that aligns with their gender identity, to cut or grow their hair, to use new or different names and pronouns, and to access activities in line with their gender identity instead of the sex assigned to them at birth. Social transition is a critical part of treatment of patients with gender dysphoria of all ages and it is the only treatment for pre-pubertal children. There are no known risks to social transition or to affirming

⁴ Rafferty J, Committee on Psychosocial Aspects of Child and Family Health, Committee on Adolescence and Section on Lesbian, Gay, Bisexual, and Transgender Health and Wellness, *Pediatrics* October 2018; 142(4): 2018-2162.

transgender youth who have been properly diagnosed with gender dysphoria by competent medical providers.

28. It undermines social transition – a critical part of gender dysphoria treatment – to force a person with gender dysphoria to live in a manner that does not align with the person's gender identity. For example, requiring a girl who is transgender to participate in single-sex activities for boys can be deeply harmful and disruptive to treatment. In the context of activities like athletics, which are typically separated by sex, I know from experience with my patients that it can be extremely harmful for transgender youth to be excluded from the team consistent with their gender identity.

29. For many transgender youth, going through endogenous puberty can cause extreme distress. Puberty blocking treatment allows transgender youth to avoid going through their endogenous puberty thereby avoiding the heightened gender dysphoria and permanent physical changes that puberty would cause.

30. Puberty blocking treatment works by pausing endogenous puberty at whatever stage it is at when the treatment begins. This has the impact of limiting the influence of a person's endogenous hormones on the body. For example, after the initiation of puberty blocking treatment, a girl who is transgender will experience none of the impacts of testosterone that would be typical if she underwent her full endogenous puberty.

31. When treating a transgender young person, when medically indicated, I prescribe puberty blocking treatment at the Tanner 2 stage of puberty. For girls who are transgender, this means that puberty is put on pause usually around the time that the patient has circulating testosterone at a level of 50 ng/dL or 1.735 nMol/L. If managed appropriately, a patient that undergoes puberty blocking treatment at this stage and then proceeds to gender-affirming

hormone therapy will never have circulating testosterone above what is typical of girls who are not transgender.

32. Under the Endocrine Society Clinical Guidelines, once a transgender youth establishes further maturity and competence to make decisions about additional treatment along with their parent and/or guardian, it may then be medically necessary and appropriate to provide gender-affirming hormone therapy to initiate puberty consistent with gender identity. For girls who are transgender, this means administering both testosterone suppressing treatment as well as estrogen to initiate hormonal puberty consistent with the patient's female gender identity. For boys who are transgender, this means administering testosterone.

33. Hormone therapy and social transition can significantly change a transgender youth's physical appearance. For example, boys who are transgender and treated with puberty blockers and gender affirming hormones will receive the same amount of testosterone during puberty that non-transgender boys generate with their testes. They will grow darker and thicker facial and body hair, experience fat distribution away from the hips, have decreased breast growth, and develop lower vocal pitch. Likewise, girls who are transgender and treated with puberty blockers and gender affirming hormones will receive the same amount of estrogen during puberty that non-transgender girls generate endogenously. They will develop breast tissue, fat will be distributed to their hips, their skin will soften, and their vocal pitch will not deepen further.

34. Treatment for transgender youth is safe, effective, and essential for their well-being. My patients who receive medically appropriate hormone therapy and who are treated consistent with their gender identity in all aspects of life experience significant improvement in their health.

35. For many patients, social transition and hormone therapy are sufficient forms of treatment for gender dysphoria. Others also need one or more forms of surgical treatment to alleviate gender dysphoria. Boys who are transgender may receive chest reconstruction surgery no earlier than 16. Genital surgery for women and men who are transgender is not performed until the person has reached the age of at least 18. Genital surgery for women who are transgender can result in a vulva and vagina—external genitalia typical of women—as well as removal of the testes, which eliminates the need for medical testosterone suppression. Because surgery does not produce ovaries, women who are transgender who have had this form of surgery typically continue to need estrogen therapy.

36. Consistent with extensive research literature, my clinical experience with my patients has been that they suffer and experience worse health outcomes when they are ostracized from their peers through policies that exclude them from spaces and activities that other girls and boys are able to participate in consistent with gender identity.

SEX ASSIGNMENT AND BIOLOGICAL SEX CHARACTERISTICS

37. HB 3293 requires school athletics to be separated based on “biological sex” defined as “an individual’s physical form as a male or female based solely on the individual’s reproductive biology and genetics at birth.” W. Va. Code §18-2-25d(b)(1). In addition to being counter to medical science, the notion of a singular “biological sex,” is inherently flawed.

38. When a child is born, a sex assignment is usually made based on the infant’s externally visible genitals. This designation is then recorded and usually becomes the sex designation listed on the infant’s birth certificate.

39. Usually, though not always, a person’s gender identity aligns with the sex designation based on the person’s genitals at birth.

40. For people who are transgender and people with differences of sex development (DSDs), however, there is not complete alignment between gender identity and physical sex-related characteristics.

41. Sex-related characteristics include external genitalia, internal reproductive organs, gender identity, chromosomes, and secondary sex characteristics. These biological sex-related characteristics do not always align as completely male or completely female in a single individual. And none of these characteristics exists in a binary. As the Endocrine Society guidelines explain, the terms “[b]iological sex, biological male or female . . . are imprecise and should be avoided.” Generally speaking, “[t]hese terms refer to physical aspects of maleness and femaleness [but] these may not be in line with each other (e.g., a person with XY chromosomes may have female-appearing genitalia).”⁵

42. Although we generally label infants as “male” or “female” based on observing their external genitalia at birth, external genitalia are not always clearly identifiable as typically male or typically female. And external genitalia do not account for the full spectrum of sex-related characteristics nor are they alone a proxy for how we understand sex.

⁵ Hembree, Wiley C., et al., Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline, J Clin Endocrinol Metab, Vol. 102, Issue 11, 1 November 2017, 3869–3903.; Berenbaum S., et al., Effects on gender identity of prenatal androgens and genital appearance: Evidence from girls with congenital adrenal hyperplasia. J Clin Endocrinol Metab 2003; 88(3): 1102-6; Dittmann R, et al., Congenital adrenalhyperplasia. I: Gender-related behavior and attitudes in female patients and sisters. Psychoneuroendocrinology 1990; 15(5-6): 401-20; Cohen-Kettenis P. Gender change in 46,XYpersons with 5alpha-reductase-2 deficiency and 17beta-hydroxysteroid dehydrogenase-3 deficiency. Arch Sex Behav 2005; 34(4): 399-410; Reiner W, Gearhart J. Discordant sexual identity in some genetic males with cloacal exstrophy assigned to female sex at birth. N Engl J Med 2004; 350(4): 333-41.

43. In one out of every 1,000 live births, the infant's genitals are not typically male or female.

44. For people with DSDs, sex assignment at birth can involve the evaluation of the chromosomes, the external genitalia, the internal genitalia, hormonal levels, and sometimes, specific genes. There are also cases in which the appearance of the external genitalia can change at puberty as well as variations in the appearance of secondary sex characteristics that may signal a difference in sex development in a person.

45. When assignment of sex of an infant with a DSD is made at birth, that assignment is temporary until the individual can express their gender identity. In cases where the initial designation was incorrect, appropriate medical protocols instruct that the sex should be updated to align with the individual's gender identity. Similarly, if the sex designation of an infant without a DSD turns out to be inconsistent with the individual's gender identity, as for transgender people, the sex should be updated to align with the individual's gender identity.

46. Where surgery has been done on children with DSDs before the child's understanding and expression of their gender identity, significant distress can result. Many of these children have had to endure further surgeries to reverse earlier surgical intervention because their gender identity did not match the initial sex designation.

47. At least one out of every 300 people in the world has an intersex variation, meaning that the person's sex characteristic do not all align as typically male or typically female.

48. Some examples of these variations include:

- a. People with Complete Androgen Insensitivity (CAIS) have 46-XY chromosomes, and internal testes that produce testosterone, but do not have the tissue receptors that respond to testosterone or other androgens. The body,

therefore, does not develop a penis, thicker facial hair, or other secondary sex characteristics more commonly associated with men. At birth, based on the appearance of the external genitalia, people with CAIS are generally assigned female. If their testes are left in place, the body will convert the hormones into estrogen. Many do not find out they have XY chromosomes or testes until they do not start menstruating at the expected age.

- b. Androgen Insensitivity can also be partial (known as PAIS). People with PAIS have XY chromosomes, testes, and some (but still lower than typical) response to testosterone. They may be born with genitals that appear like a typical penis, a typical vulva, or somewhere in between.
- c. People with Swyer Syndrome have XY chromosomes and “streak” gonads (gonadal tissue that did not develop into testes or ovaries). Externally, a child with Swyer Syndrome usually develops a vulva. Because their gonads do not produce hormones, they will not develop most secondary sex characteristics without hormone treatment.
- d. People with Klinefelter Syndrome have 47,XXY chromosomes and internal and external genitalia typically associated with males, however, their testicles may have reduced testosterone production. This may lead to breast development, low muscle mass and body hair, and infertility.
- e. People with Turner Syndrome have 45,XO chromosomes which means they have one fewer copy of the X chromosome than expected. In utero, they form sex characteristics typically associated with females, including internal structures like a uterus and fallopian tubes, but the ovaries may degenerate

before birth (or in some cases, not until young adulthood), leading to an inability to make estrogen. Many people with Turner Syndrome will not go through puberty without hormone therapy.

- f. People with Mosaicism have different sets of chromosomes in different cells. Mosaic karyotypes happen as a result of atypical cell division early in embryonic development and could involve various combinations among XX, XY, XO, XXY, and other chromosome patterns. Configuration of gonadal tissue, genitals, and hormone production and response can all vary.
- g. People with ovotestes (sometimes known as Ovotesticular DSD) have gonads that contain both ovarian and testicular tissue. Their chromosomes may be XX, XY, or Mosaic. Genital appearance at birth can be male-typical, female-typical, or something else.
- h. Congenital Adrenal Hyperplasia (CAH) can occur in people with XX or XY chromosomes. People with CAH and 46,XX chromosomes have ovaries, a uterus, and a higher-than-typical production of androgens in utero that can lead to the development of genital differences at birth – such as an enlarged clitoris that may look like a penis, or the lack of a vaginal opening. CAH can also cause the development of typically masculine features like increased muscle mass and body hair.
- i. People with 5-alpha reductase deficiency (5-ARD) have XY chromosomes, but they have an enzyme deficiency that inhibits conversion of testosterone to dihydrotestosterone (the active form of testosterone) to varying degrees. This can impact genital development, and at birth, people with 5-ARD may have

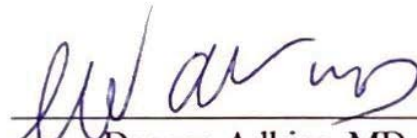
genitals that appear female-typical, neither male-typical nor female-typical, or mostly male-typical with differences like hypospadias (where the urethra is located somewhere other than the tip of the penis). During puberty, hormonal changes allow them to make more dihydrotestosterone, causing the development of some secondary sex characteristics typically associated with males, as well as genital masculinization.

49. As the examples above underscore, from a medical perspective, chromosomes, reproductive anatomy, and endogenous hormones alone do not determine a person's sex, nor does a single sex-related characteristic.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on

1/21/2022


Deanna Adkins, MD

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Non Author publications

1. Turner DA, Curran ML, Myers A, Hsu DC, Kesselheim JC, Carraccio CL and the Steering Committee of the Subspecialty Pediatrics Investigator Network (SPIN). Validity of Level of Supervision Scales for Assessing Pediatric Fellows on the Common Pediatric Subspecialty Entrustable Professional Activities. *Acad Med*. 2017 Jul 11. doi: 10.1097/ACM.0000000000001820. PMID:28700462
2. Mink R, Carraccio C, High P, Dammann C, McGann K, Kesselheim J, Herman B. Creating the Subspecialty Pediatrics Investigator Network (SPIN). Creating the Subspecialty Pediatrics Investigator Network Richard Mink, MD, MACM1, Alan Schwartz, PhD2, Carol Carraccio, MD, MA3, Pamela High, MD4, Christiane Dammann, MD5, Kathleen A. McGann, MD6, Jennifer Kesselheim, MD, EdM7, *J Peds* 2018 Jan;192:3-4.e2. PMID: 29246355 DOI: 10.1016/j.jpeds.2017.09.079
3. Erratum 2018. PMID: 29246355 DOI: [10.1016/j.jpeds.2017.09.079](https://doi.org/10.1016/j.jpeds.2017.09.079)
4. Mink RB¹, Myers AL, Turner DA, Carraccio CL. Competencies, Milestones, and a Level of Supervision Scale for Entrustable Professional Activities for Scholarship. *Acad Med*. 2018 Jul 10. doi: 10.1097/ACM.0000000000002353. [Epub ahead of print] PMID: 29995669 DOI:[10.1097/ACM.0000000000002353](https://doi.org/10.1097/ACM.0000000000002353) Mink RB, Schwartz A, Herman BE,

Editorials

- a. Editorial Charlotte News and Observer-“**NC pediatric specialists say HB2 ‘flawed’ and ‘harmful,’ call for repeal**”; April 18, 2016; authors: Deanna

Adkins, Ali Calikoglu, Nina Jain, Michael Freemark, Nancie MacIver, Robert Benjamin, Beth Sandberg, etc.

- b. Editorial Raleigh News and Observer-**“Beverly Gray: Repeal HB2”** May 2016: authors Beverly Gray, Deanna Adkins, Judy Sidenstein, Jonathan Routh, Haywood Brown, Clayton Afonso, William Meyer, Kristen Russell, Caroline Duke, Nancy Zucker, Kevin Weinfurt, Jennifer St. Claire, Angela Annas, Katherine Keitcher

Chapters in Books

1. Endocrinology Chapter writer and editor in **Fetal and Neonatal Physiology for the Advanced Practice Nurse**; Editors: Amy Jnah DNP, NNP-BC, Andrea Nicole Trembath MD, MPH, FAAP. December 21, 2018 ISBN-10 0826157319
2. Chapter in **Dental Clinics of North America Adolescent Oral Health Edition** Understanding and Caring for LGBTQ+ Youth for the Oral Health Care Provider; Authors Joshua Raisin, DDS, Deanna Adkins MD, Scott B. Schwartz, DDS, MPH. 2021
3. Intersex Identity and Gender Assignment; **Encyclopedia of Adolescent Health**; Editor Brian Eichner, MD; Author Deanna Adkins MD 2021-pending

Selected Abstracts:

1. Redding-Lallinger RC, **Adkins DW**, Gray N: The use of diaries in the study of priapism in sickle cell disease. Poster Abstract in Blood November 2003
2. **Adkins, D.W.** and Calikoglu, A.S.: Delayed puberty due to isolated FSH deficiency in a male. Pediatric Research Suppl. 51: Abstract #690. page 118A, 2004
3. Zeger, M.P.D., **Adkins, D.W.**, White, K., Loechner, K.L.: Opsismodysplasia and Hypophosphatemic Rickets. Pediatric Research Suppl.-from PAS 2005
4. Kellee M. Miller¹, David M. Maahs², **Deanna W. Adkins**³, Sureka Bollepalli⁴, Larry A. Fox⁵, Joanne M. Hathway⁶, Andrea K. Steck², Roy W. Beck¹ and Maria J. Redondo⁷ for the T1D Exchange Clinic Network; Twins Concordant for Type 1 Diabetes in the T1D Exchange -poster at ADA scientific sessions 6/2014
5. Laura Page, MD; Benjamin Mouser, MD; Kelly Mason, MD; Richard L. Auten, MD; **Deanna Adkins, MD** CHOLESTEROL SUPPLEMENTATION IN SMITH-LEMLI-OPITZ: A Case of Treatment During Neonatal Critical Illness; - poster 06/2014
6. Lydia Snyder, MD, **Deanna Adkins, MD**, Ali Calikoglu, MD; Celiac Disease and Type 1 Diabetes: Evening of Scholarship UNC Chapel Hill 3/2015 poster
7. **Deanna W. Adkins, MD**, Kristen Russell, LCSW, Dane Whicker, PhD, Nancy Zucker, Ph. D: Departments of Pediatrics and Psychiatry, Duke University Medical Center; Evaluation of Eating Disturbance and Body Image Disturbance in the Trans Youth Population; WPATH International Scientific Meeting June 2016; Amsterdam, The Netherlands
8. Rohit Tejwani, **Deanna Adkins**, Brian J. Young, Muhammad H. Alkazemi, Steven Wolf³, John S. Wiener, J. Todd Purves, and Jonathan C. Routh; Contemporary Demographic and

- Treatment Patterns for Newborns Diagnosed with Disorders of Sex Development; Poster presentation at AUA meeting 2016
9. S.A. Johnson, **D.W. Adkins**, Case Report: The Co-diagnosis of Hypopituitarism with Klinefelter in a patient with short stature; Pediatric Academic Society Meeting 2018
 10. Lapinski J, Dooley R, Russell K, Whicker D, Gray, B, **Adkins DW**; **Title:** Developing a Pediatric Gender Care Clinic at a Major Medical Setting in the South; Workshop Philadelphia Trans Wellness Conference 2018
 11. Jessica Lapinski, DO, Deanna Adkins, MD, Tiffany Covas, MD, MPH, Kristen Russell, MSW, LCSW; An Interdisciplinary Approach to Full Spectrum Transgender Care; WPATH Conference Buenos Aires, Argentina, November 3, 2018
 12. Leigh Spivey, MS, Nancy Zucker, PhD, Erik Severiede, B.S., Kristen Russell, LCSW, Deanna Adkins, MD; USPATH Washington, DC Sept. 2019. Platform presentation; "Psychological Distress Among Clinically Referred Transgender Adolescents: A latent Profile Analysis"

Non-Refereed Publications

- i. Print
 - i. Editorial Charlotte News and Observer-"**NC pediatric specialists say HB2 'flawed' and 'harmful,' call for repeal**"; April 18, 2016
 - ii. Editorial News and Observer-HB2 May 2016 -"**Beverly Gray: Repeal HB2**" May 2016
- ii. Digital
 - i. Supporting and Caring for Transgender Children-HRC guide 2017
 - ii. Initial endocrine workup and referral guidelines for primary care Providers- Pediatric Endocrine Society Education Committee Website Publication
 - iii. Only Human Podcast August 2, 2016;
<https://www.wnycstudios.org/podcasts/onlyhuman/episodes/id-rather-have-living-son-dead-daughter>
- iii. Media and Community Interviews
 - i. Greensboro News and Record Community Forum October 2017-*Transgender Panel Moderator*
 - ii. Playmakers Repertory Company-Chapel Hill: *Draw the Circle* Transgender Community Panel 2017
 - iii. Duke Alumni Magazine
 - iv. Duke Stories
 - v. DukeMed Alumni Magazine
 - vi. NPR Podcast Only Human piece on caring for transgender youth and follow up piece 1 year later
 - vii. ABC11, WRAL, WNCN News Coverage
 - viii. News and Observer: Charlotte and Raleigh
 - ix. Duke Chronicle and Daily Tarheel Article
 - x. Huffington Post Article
 - xi. <https://www.businessinsider.com/the-olympics-uses-testosterone-to-treat-trans-athletes-like-cheaters-2021-7>

- xii. <https://www.wral.com/top-transgender-doctor-warns-teen-treatment-ban-could-be-deadly/19618762/>
- xiii. <http://www.ncpolicywatch.com/2021/04/07/experts-bills-targeting-trans-people-get-the-science-wrong/>

Published Scientific Reviews for Mass Distribution

Position and Background Papers

Other Publications

Editorial Experience

Editorial Boards

Ad Hoc scientific review journals

Hormone Research, Lancet, NC Medical journal, Journal of Pediatrics, Pediatrics, Transgender Health, International Journal of Pediatric Endocrinology, Journal of Adolescent Health

Consultant Appointments

North Carolina Newborn Screening Committee

Human Rights Campaign Transgender Youth Advisory Board

Scholarly Societies

Professional Awards and Special Recognitions

ESPE Fellows Summer School, 2001

NIH Loan Repayment Program Recipient

Lawson Wilkins AstraZeneca Research Fellow,
2003-2004

HEI 2017 Leaders in LGBTQ Healthcare
Equality

Inside Out Durham Appreciation Award

Duke Health System Diversity and Inclusion
Award January 2018

America's Top Doctor's 2020, 2021

Duke Health System Diversity and Inclusion
Award January 2020- CDHD Course Team

Teaching for Equity Fellow 2021

Organizations and Participation

Organization	Role	Dates
American Academy of Pediatrics	Member Council on Information Technology Member Reviewer COCIT Member Section on Endocrinology	1998 to present 2004 to present
Pediatric Endocrine Society	Member Member Education Committee SIG member-Transgender, DSD, liaison to Advocacy SIG Writer Web Publication for Pediatricians	2000 to present
NC Pediatric Society	Member	1998 to present
Endocrine Society	Member	2000 to present
WPATH-International Transgender Society	Member	2014 to present

External Support

<u>Approximate Duration</u>	<u>PI</u>	<u>% Effort</u>	<u>Purpose</u>	<u>Amount Duration</u>
<u>Past</u>	<u>JAEB Center- Deanna Adkins</u>	0.5%	<u>Type 1 diabetes research</u>	<u>\$ 5yr</u>
<u>Past</u>	<u>Josiah Trent Foundation Grant-Deanna Adkins</u>	0.5%	<u>Transgender and eating disorder research</u>	<u>\$5000 3 yr</u>
<u>Pending: Submitted</u>	<u>NIH-Kate Whetten</u>	0.1%	<u>Analysis of TransgenderHealth in Adolescents in Rural Africa, India, and Thailand</u>	<u>Consultant</u>

<u>Approximate Duration</u>	<u>PI</u>	<u>% Effort</u>	<u>Purpose</u>	<u>Amount Duration</u>
<u>Re-Submitting June 2021</u>	<u>NIH R21 Deanna Adkins</u>	2%	Development of New Gender Dysphoria Measures in Youth	<u>Co PI</u>
<u>ReSubmitting June 2021</u>	<u>NIH R21 Sarah Legrand</u>	2%	Glow and Grow	<u>consultant</u>
<u>Submitted November 2020</u>	<u>CMS-Deanna Adkins and Rob Benjamin</u>	1%	<u>Innovations Grant</u>	<u>Co PI</u>
<u>Submitted Sept 2020</u>	<u>Kate Whetten</u>	2%	SAHMSA Grant for development of multidisciplinary LGBTQ education	<u>Co PI</u>
<u>Gifts</u>	<u>Private Family</u>			

Mentoring Activities

Faculty	
Fellows, Doctoral, Post docs	Nancie MacIver-fellow
	Dorothee Newbern-fellow
	Krystal Irizarry-fellow
	Kelly Mason-fellow
	Laura Page-fellow
	Elizabeth Sandberg fellow UNC
	Dane Whicker-psychology post doc Leigh Spivey-psychology post doc Joey Honeycutt, Chaplain Intern Kathryn Blew-research mentor
Residents	Yung-Ping Chin-mentor
	Kristen Moryan-mentor
	Jessica Lapinski-mentor
	Kathryn Blew-research mentor
	Matthew Pizzuto, Briana Scott-Coach, Laura Hampton Coach

Medical students	Tulsi Patel-continuity clinic mentor Sonali Biswas-research mentor 3rd year project Katha Desai-research mentor 3rd year project
Undergraduates	Erik Severeide-Duke University Lindsay Carey-Dickinson College Jeremy Gottlieb-Duke University Jay Zussman-Duke University Beles Abebe-Duke University
High School Students	Aeryn Colton-Intern Apex High School
Graduate Student MBS program	Nicholas Hastings
UNC Gillings School of Public Health MPH students	Lauren Frey, Emily Dake, Alexandra Carle, Lindsay Woodcock, Hunter McGuire
Nurse Practitioners	ECU, Duke-multiple
DNP candidates	Ethan Cicero-PhD committee member Amanda Lund-PhD committee member
Pediatric Dental Fellow UNC	Joshua Raisin-research associate

Education / Teaching Activities

Didactic classes

High School

- c. Cary Academy: Work Experience Program 2021

Undergraduate

1. Creating Excellence and Ambulatory Nursing 2008
2. Profile in Sexuality Research Series at Duke CGSD 2016
3. Duke School of Nursing BSN Course on Sexual and Gender Health guest lecturer: fall 2017, spring 2018, fall 2018, spring 2019, fall 2019, spring 2020, fall 2020, spring 2021, fall 2021
4. Duke School of Nursing Lecture on Transgender Care-recorded for reuse
5. Duke Physician Assistant Program guest lecturer; fall 2017, spring 2018
6. Duke Global Health Course guest lecturer fall 2016
7. Duke Neuroscience course on Gender and Sex guest lecturer fall 2016
8. Duke Ethics Interest group guest lecturer fall 2018, 2020
9. Duke EMS group lecture fall 2018
10. Duke Physician Assistant Program LGBTQ+ Rotation Educator 2019 to present
11. Global Health Sexual and Gender Minority Seminar Lecturer 2020

UME:

1. Cultural Determinants of Health and Health Disparities Course: Facilitator and developed one class; 2017-18 and 2018-19, 2019-20, 2020-21, 2021-22; Steering Committee member for course development
2. UNC School of Medicine Lecturer for LGBTQ Health series 2016-recorded for reuse
3. Duke Pediatrics Interest Group lecture Nov 2020
4. Duke Med Pediatrics Interest Group lecture fall 2018, 2020
5. Lecturer Body and Disease Course MS1 2019, 2020, 2021 Clinical Correlation Differences of Sex Development
6. Lecturer Body and Disease Course MS1 2020, 2021 Transgender Medicine
7. Lecture on Cancer in Transgender and Intersex Individuals April 14, 2021 Mount Sinai School of Medicine
8. Lecture on Transgender Medicine Univ. of Tenn. Health Science Center School of Medicine May 7, 2021

Graduate School Courses:

1. Master of Biomedical Science Program-guest lecturer on Transgender Medicine fall 2016
2. School of Nursing Graduate Intensive Course Lecturer on Sexual and Gender Health; fall 2017, spring 2018, fall 2018, spring 2019, Fall 2019
3. Fuqua School of Business Med Pride Panel and presentation fall 2017
4. Master of Biomedical Science Program Mentor 2019-2020
5. Endocrinology for Nurse Practitioners Duke Neonatal Nurse Practitioner Program August 2021

DUHS Employee Education

1. Annual Duke Human Resources Lunch and Learn on Gender Diversity 2016, 2017, 2018
2. Over 100 lectures across the institution on gender including CHC front desk/nursing staff, hospital wide social work/case management, radiology, PDC clinic front desk/nursing staff
3. Steering Committee for Sexual and Gender Identity Epic Module development and Educational module development
4. DCRI Pride invited speaker
5. Duke Children's staff update 2021

GME:

1. Adult Endocrinology Fellows every year on growth and/or gender
2. Pediatric Residency Noon conferences on Growth and Gender-yearly
3. Reproductive Endocrinology Noon Conferences every 2 to 3 years
4. Psychiatry Noon Conferences periodically
5. Family Practice Noon Conference periodically
6. Pediatric Endocrine Fellow lectures twice a year or more
7. Pediatrics grand rounds: Vitamin D, Type 2 diabetes, Pubertal Development, Gender Diverse Youth

8. Duke Urology Grand Rounds 2016
9. Duke Ob/Gyn Grand Rounds 2017
10. Webinar for Arkansas Children's Hospital on transgender care 2018
11. Reproductive Challenges for Transgender people-Reproductive Endocrinology-2020
12. Metabolic Bone Disease in Neonates-NICU fellows 2019
13. Duke Psychiatry Grand Rounds 2017
14. Duke Pathology Grand Rounds fall 2020
15. Duke Family Medicine Community Rotation Educator 2019 to present
16. NC NAPNAP Symposium Keynote Speaker October 10, 2020
17. Duke Internal Medicine LEADS program speaker; Transgender Care 8/3/2021
18. Equity and Social Justice Webinar: Clinical Advocacy and Care of Transgender and Gender Diverse Youth October 27, 2021Harvard Equity and Social Justice Webinar

Development of Courses Educational programs

1. Pituitary Day October 2019-full day multispecialty seminar for caregivers of patients with hypopituitarism-Organized and developed the curriculum
2. Development of Gender Diversity Education for Health System education
3. Steering Committee for Cultural Determinants and Health Disparities Course
4. Helping to Adapt Resident Coaching Program to Pediatric Fellowships
5. Developed half day course for Duke Student Health on Care of the Gender Diverse Student with multiple disciplines included
6. Course Director: American Diabetes Association Camp Carolina Trails rotation for fellows and residents: 2009, 2011 – 2019
7. Medical Education for Camp Morris 2019, 2021

Development of Assessment Tools and Methods

1. Currently under development with Population Health Sciences-method to assess gender dysphoria; received Brief High Intensity Production (BHIP) grant for this collaboration; NIH grant Submitted March 2020; I am writing the portion of grant giving background on the population and the need for better measures.
2. Collaborating with the Duke Chaplain group to develop a spiritual assessment tool for gender diverse children and their families. Completed 2019

Educational leadership roles

1. Fellowship Program Director Pediatric Endocrinology 2008-2019
2. Course Director: American Diabetes Association Camp Carolina Trails rotation for fellows and residents: 2009, 2011 to 2019

Educational Research

1. Working with coaching program for residents modified and applied in pediatric fellows
2. Worked with the Council on Pediatric Subspecialties EPA study

Invited Lectures and Presentations

1. NC Peds Conference: Pubertal Development 2016

2. Trent Center for Ethics Lecture May 2017: Transgender Medicine: a Wealth of Ethical Issues
3. Visiting Professorship: ECU Brody School of Medicine Invited Professor October 2017
4. College of Diplomates-pediatric dentistry society-Webinar on transgender care 4/1/2020
5. NAPNAP keynote speaker Annual Meeting October 2020
6. Wake County Duke CME program: Type 2 diabetes treatments in pediatrics 2019
7. Lecture on Cancer in Transgender and Intersex Individuals April 14, 2021 Mount Sinai School of Medicine
8. Lecture on Transgender Medicine Univ. of Tenn. Health Science Center School of Medicine May 7, 2021
9. Equity and Social Justice Webinar: Clinical Advocacy and Care of Transgender and Gender Diverse Youth October 27, 2021 Harvard Equity and Social Justice Webinar

International Meetings

1. WPATH Amsterdam 2016
2. WPATH Buenos Aires 2018

National Scientific Meetings (invited)

1. Transgender SIG Developing a Patient Registry
2. Patient Advocacy for Transgender Youth Philadelphia 2018

Instructional Courses, Workshops, Symposiums (National)

1. Time to Thrive Arkansas Children's Hospital April 2018
2. National Transgender Health Summit UCSF Jan 2018: Providers as Advocates Workshop
3. Magic Foundation-Chicago, IL Annual Speaker on Precocious Puberty, Adrenal Insufficiency, and Growth Hormone at National Conference 2016, 2017, 2019, 2020, 2021
4. The Seminar-Fort Lauderdale, FL Invited Speaker on Care of Transgender Youth 2017

Regional Presentations and Posters

- a. North Carolina Pediatric Society: Pubertal Development Presentation--Pinehurst, NC 2017
- b. North Carolina Psychiatric Association: Caring for Transgender Children Presentation and Workshop on key concepts in care of transgender child-Asheville, NC 2017
- c. ECU Campus Health Presentation Caring for Transgender Patients 2018
- d. Radiology Technology Symposium Presentation on Caring for Transgender Patients 2018
- e. Duke CME in Wake County-Update on Type 2 Diabetes Treatments Feb 2019
- f. Hilton Head Pediatric CME Course-Update on Type 2 Diabetes, Short Stature, and Caring for Transgender Patients June 2019
- g. Wake County Duke Pediatrics CME Type 2 diabetes treatments Feb 2019
- h. NAPNAP Annual Meeting Keynote Speaker 2020

- i. Sexual and Gender Minorities Research Symposium Duke Feb 2020; speaker and organizer

Local Presentations

1. Grand Rounds: 2016 to present-Duke Pediatrics twice, Moses Cones Pediatrics, ECU Ob/Gyn, Duke Ob/Gyn, Duke Psychiatry, Duke Urology, Duke Adult Endocrinology, Duke Pathology
2. Prior to 2016-Rex Grand rounds: Salt and Water balance, New treatments in Pediatric Diabetes, Adrenal Insufficiency, Duke peds grand rounds Bone Health, Type 2 Diabetes Mellitus
3. Duke Women's Weekend 2018 hosted by Duke Alumni Association
4. NCCAN Social Work Training 2016
5. NAPNAP lecture 2016 and 2018 and 2020
6. Profiles in Sexuality Research Presentation at Duke Center for Sexual and Gender Diversity 2017
7. Duke LGBTQ Alumni Weekend Presentation 2017
8. UNC Chapel Hill Campus Health Presentation 2018
9. Duke Student Health Presentation 2017, 2018, 2019 (workshop)

Clinical Activity

1. Duke Consultative Services of Raleigh-2.5 days per week in endocrinology and diabetes
2. Duke Child and Adolescent Gender Care Clinic 1.2 day per week at the CHC
3. Inpatient Consult Service Pediatric Endocrinology 1 week per month

Administrative and Leadership Positions

1. Medical Director Duke Children's and WakeMed Consultative Services of Raleigh
2. Director Duke Child and Adolescent Gender Care Clinic
3. Pediatric Endocrinology Fellowship Program Director 2008-2019

Committees

1. Graduate Medical Education Committee-2008-2019
2. School of Medicine Sexual and Gender Diversity Council 2015 to present
3. Pediatrics Clinical Practice Committee-2015? To present
4. Pediatric Diversity and Inclusion Committee

Community

1. Test proctor local schools
2. Guest lecture GSA multiple years
3. Diabetes Camp over 10 years
4. 100 Women who give a hoot
5. Collaborated to bring "Becoming Johanna" to Duke along with multiple screenings with the director and the lead actor
6. Teddy Bear Hospital volunteer both years

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA

B.P.J. by her next friend and mother,	)	
HEATHER JACKSON,	)	
<i>Plaintiff,</i>	)	Civil Action No. 2:21-cv-00316
v.	)	
	)	Hon. Joseph R. Goodwin
WEST VIRGINIA STATE BOARD OF	)	
EDUCATION, et al.,	)	
	)	
<i>Defendants,</i>	)	
	)	
and	)	
	)	
LAINY ARMISTEAD,	)	
	)	
<i>Defendant-</i>	)	
<i>Intervenor.</i>	)	
	)	
	)	

EXPERT REBUTTAL REPORT AND DECLARATION OF DEANNA ADKINS, M.D.

I, Deanna Adkins, M.D., hereby declare as follows:

1. I have been retained by counsel for Plaintiff as an expert in connection with the above-captioned litigation.
2. I have actual knowledge of the matters stated in this rebuttal report and declaration (“Adkins Rebuttal”) and have collected and cite to relevant literature concerning the issues that arise in this litigation in the body of the report. I refer herein to my initial expert report in this matter as “Adkins Report.”
3. My credentials are set forth in my initial report executed on January 21, 2022.
4. I reviewed the reports of Dr. Stephen Levine and Dr. James M. Cantor (referred to herein as the “Levine Report” and “Cantor Report” respectively). I respond in this report to some of the central points in those disclosures. I do not specifically address each study or article cited

but instead explain the overall problems with some of the conclusions that Dr. Levine and Dr. Cantor draw and provide data showing why such conclusions are in error. I reserve the right to supplement my opinions if necessary as the case proceeds.

5. I have knowledge of the matters stated in this report and have collected and cite to relevant literature concerning the issues that arise in this litigation in the body of this declaration.

6. In preparing this report, I reviewed the text of House Bill 3293 (“H.B. 3293”) at issue in this matter. I also relied on my scientific education and training, my research experience, and my knowledge of the scientific literature in the pertinent fields. The materials I have relied upon in preparing this declaration and expert report are the same types of materials that experts in my field of study regularly rely upon when forming opinions on these subjects. I may wish to supplement these opinions or the bases for them as a result of new scientific research or publications or in response to statements and issues that may arise in my area of expertise.

SEX ASSIGNMENT AND BIOLOGICAL SEX CHARACTERISTICS

7. Dr. Levine does not appear to have any experience with the process of assigning sex to newborns at birth. Despite that lack of experience, he disputes the scientific consensus described in my initial report that the term “biological sex” is imprecise and should be avoided, as the Endocrine Society has advised.¹ Adkins Report ¶ 41; Levine Report ¶¶ 19-20. Dr. Levine

¹ Hembree, Wiley C., et al., Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline, J Clin Endocrinol Metab, Vol. 102, Issue 11, 1 November 2017, 3869–3903.; Berenbaum S., et al., Effects on gender identity of prenatal androgens and genital appearance: Evidence from girls with congenital adrenal hyperplasia. J Clin Endocrinol Metab 2003; 88(3): 1102-6; Dittmann R, et al., Congenital adrenal hyperplasia. I: Gender-related behavior and attitudes in female patients and sisters. Psychoneuroendocrinology 1990; 15(5-6): 401-20; Cohen-Kettenis P. Gender change in 46,XY persons with 5alpha-reductase-2 deficiency and 17beta-hydroxysteroid dehydrogenase-3 deficiency. Arch Sex Behav 2005; 34(4): 399-410; Reiner W, Gearhart J. Discordant sexual identity in some genetic males with cloacal exstrophy assigned to female sex at birth. N Engl J Med 2004; 350(4): 333-41.

instead asserts that sex is “determined at conception.” Levine Report ¶ 20. His only reference for that claim does not support it, but rather is a one-page, undated handout by the National Institutes of Health (“NIH”) Office of Research on Women’s Health on the topic of sex and gender influences on health. *Id.*² Dr. Levine’s repeated assertions that sex is “binary” (*e.g.*, Levine Report ¶ 24) ignore the extensive explanation in my initial report about the many differences of sex development that occur naturally in the population, affecting approximately one out of every 300 births. Adkins Report ¶¶ 47-49. The NIH recognizes “gender minorities” including transgender individuals. Indeed, the NIH has a whole section devoted to research to improve care for these populations as well as to ensure adequate inclusion of these populations in all research. (See NIH policy regarding Sexual and Gender Minorities, <https://dpcpsi.nih.gov/sgmro>.) A paper from Bhargava that Dr. Levine relies on in the Levine Report also goes into great detail about human reproductive development and how many other genes, hormones, and other processes that occur well after conception are necessary for typical male or female reproductive tracts to develop. The paper further supports the conclusion that there is wide variation in presentation of human reproductive organs depending on whether all of these steps occur appropriately. There are scientifically validated tools including the Prader Scale that are used to describe variability in external genitalia of humans at birth. These tools are widely used in endocrinology and urology.

8. In addition, Dr. Levine offers selective references to an NIH requirement to include “sex as a biological variable” in research, Levine Report ¶ 21, and an Endocrine Society statement authored by Bhargava, et al. with observations about applying that requirement. Levine Report ¶¶ 21-22. None of these sources contradict my opinions in this case.

² See *id.* (citing National Institutes of Health, Office of Research on Women’s Health. *How Sex and Gender Influence Health and Disease*, https://orwh.od.nih.gov/sites/orwh/files/docs/SexGenderInfographic_11x17_508.pdf).

9. Dr. Levine also invokes human brain development and “differences between genders in function studies” to support his claim that sex is a binary concept established at birth, Levine Report ¶ 23, but ignores the literature showing that transgender women share some gender-differentiated brain structures with cisgender women, and that transgender men share some gender-differentiated brain structures with cisgender men. (See Bhargava et al. 2021.) Additionally, there are several studies that show an increase in the likelihood of being transgender with certain variations in the androgen receptor, as well as in utero exposure to certain hormones and hormone related medications.

10. Dr. Levine seeks to refute the biological underpinnings for transgender status by reference to supposed changes in incidence of gender dysphoria, changes in the ratio of transgender boys versus girls, alleged “clustering” among friend groups, claims of desistance, and nonscientific labels some individuals use such as gender fluidity. Levine Report ¶¶ 97-102. He also invokes these examples to contest the explanation in my initial report that gender identity is not subject to voluntary change. Adkins Report ¶ 18; *see also* Cantor Report ¶ 13. But the increase in the number of people known to be transgender in no way suggests that people’s gender identity can be changed. We are able to see and treat more transgender people now because of increased societal acceptance and improved medical treatments over the past decade. And that some people describe their gender as fluid does not mean that they can change their gender identity. Gender identity—whether cisgender, transgender, or something that does not fall into a binary male or female category—cannot be changed voluntarily or by external factors and is therefore fixed. That some people have changing understandings of their gender identity or express it differently at different times in no way changes that.

11. It is also not the case that there are high numbers of transgender people who “desist” in their transgender identity once they reach puberty. Adolescents with persistent gender dysphoria after reaching Tanner Stage 2 almost always persist in their gender identity in the long-term, whether or not they were provided gender-affirming care.³ No medical treatment is provided to transgender youth until they have reached Tanner Stage 2. But for pre-pubertal children who may explore transgender identity and later realize that they are not transgender, that does not mean their gender identity is not “fixed” but rather that their understanding of it evolved.

12. Dr. Levine and Dr. Cantor misconstrue my statements in my opening report that differences of sex development help us understand the importance of one’s gender identity. Adkins Report ¶¶ 42-47. As I explained, surgical interventions undertaken on children with differences of sex development to supposedly normalize their genital structures, without adequate information about the child’s gender identity, have sometimes had disastrous results because gender identity cannot be involuntarily altered. Adkins Report ¶ 46. Dr. Levine asserts that it is “an error to conflate the two distinct concepts.” Levine Report ¶¶ 105-107; *see also* Cantor Report ¶¶ 25-26. But my testimony is not that having a difference of sex development and being transgender are the same, but that the similarities in these conditions help demonstrate that gender identity is deeply rooted for people who are transgender or intersex, just as for cisgender people. Dr. Levine suggests that if you identify with a gender other than those that are represented by your chromosomes that you are transgender. Levine Report ¶¶ 109-111. Under that inaccurate premise, all women with complete androgen insensitivity, who have XY chromosomes and cannot sense

³ Turban JL, DeVries ALC, Zucker K. Gender Incongruence & Gender Dysphoria. In Martin A, Bloch MH, Volkmar FR (Editors): *Lewis’s Child and Adolescent Psychiatry: A Comprehensive Textbook*, Fifth Edition. Philadelphia: Wolters Kluwer 2018.

testosterone at all, would also be categorized as transgender. Dr. Levine's theory is erroneous and does not represent my testimony, or the relevant science, on the matter.

13. Although in medicine we endeavor through research and scholarship to learn the causes of various conditions, illness, and diseases, we do not do so to the exclusion of providing decades-long documented safe and efficacious treatment to the patient immediately in front of us. Such is the case with gender-affirming care and patients with gender dysphoria. It is unnecessary for us to know the exact cause of a medical condition before we can provide treatment to alleviate distress and suffering. There are many other conditions in medicine that do not have a known genetic cause, and yet we still provide medical treatments that have been shown for decades to be helpful in treatment as we continue to study and learn more about their precise causes or etiologies. These conditions include autism as well as the multitude of different medical issues that affect people with Down syndrome. For example, I would not hesitate to treat someone with Down syndrome who has hyper- or hypo-thyroidism, which is common in this patient population, simply because I did not know the exact explanation or source for the hyper or hypo-thyroidism. In the medical profession, there are well-documented research and clear treatments for autism and Down syndrome, and I do not need to know the exact reason behind the condition before I would use those treatments to save the lives of my patients.

TREATMENT PROTOCOLS FOR GENDER DYSPHORIA

14. Dr. Levine offers a variety of opinions about treatment models for persons who are transgender, Levine Report ¶¶ 34-54, with an emphasis on treatment for prepubertal children. It is worth clarifying that opinions about this population are irrelevant to this case based on my understanding of H.B. 3293, which does not apply to elementary schools, and therefore generally does not affect prepubertal children. Additionally, while the vast majority of Dr. Levine's opinions

appear focused on the appropriate behavioral and medical care for minors with gender dysphoria, H.B. 3293 (which is about sports participation) does not have any effect on those decisions, which are reserved to parents, their children, and their team of medical and mental health care providers.

15. Dr. Levine and Dr. Cantor repeatedly express concerns about the purported lack of mental health evaluation before medical interventions are determined to be medically indicated for adolescents (*e.g.*, Levine Report ¶¶ 73, 83; Cantor Report ¶¶ 14, 19), but this misunderstands the standards of care and how practitioners administer this care. Both the Endocrine Society Clinical Practice Guideline (the “Endocrine Society Guideline”) and the World Professional Association of Transgender Health Standards of Care (the “WPATH SOC”) require mental health assessments and informed consent processes before any medical treatment is initiated. In my experience treating over 600 youth with gender dysphoria during my tenure at the Duke Center for Child and Adolescent Gender Care (commonly referred to as the Duke Gender Clinic), each patient undergoes a psychological assessment and, if medical interventions are deemed medically appropriate, an extensive informed consent process before such interventions are provided. Any and all decisions about medical care involve not just the adolescent, but also their legal guardians, ensuring that informed consent is provided both by the patient and adults responsible for their care. Additionally, Dr. Cantor’s suggestion that gender dysphoric children should be treated *exclusively* with counseling as opposed to any gender affirming medical care underscores his lack of clinical experience in providing any treatment whatsoever to this population. Cantor Report ¶ 17. Cantor’s assertion that my opinion about possible outcomes of untreated gender dysphoria misrepresents Spack et al.’s views or conclusions from the 2012 article are also unfounded. *Id.* Dr. Cantor cherry-picked various sentences from the Spack article and strung them together to fit his hypothesis, even going so far as to ignore the clear statement from the article that “Our

observations reflect the Dutch finding that psychological functioning improves with medical intervention and suggests that the patients' psychiatric symptoms might be secondary to a medical incongruence between mind and body, not primarily psychiatric." (Spack, *et al.*, 2012, at 422-23). Finally, Dr. Levine incorrectly and without evidence asserts that the role of psychotherapy in the treatment of gender dysphoria was "downgraded" in the WPATH SOC Version 7. Levine Report ¶¶ 70, 73. Dr. Levine's apparent concern is that if patients are not "required" to undergo psychotherapy for an arbitrary amount of time even when it is clear that medical treatment is indicated, advocates of conversion therapy like himself will be unable to "enable[e] a patient to return to or achieve comfort with the gender identity aligned with his or her biology"—in other words, to not be transgender. The medical community has learned a great deal from the harms inflicted on transgender patients by delaying medical intervention because of the faulty assumption that being transgender was an inherent pathology. Levine Report ¶ 5.

16. Contrary to Dr. Levine's suggestions, providers who treat patients do not encourage any patient to initiate gender-affirming care, nor do they rush patients into medical treatment. *See, e.g.*, Levine ¶¶ 123, 126. Nor does gender-affirming care consist of treatment "on-demand" as Dr. Cantor repeatedly suggests. *See, e.g.*, Cantor Report ¶ 45. Consistent with the WPATH SOC and the Endocrine Society Guideline, each patient in my clinic is met first by mental health providers who explore the patient's medical and mental health history and identity. When following the Standards of Care, no provider rushes any patient into any treatment, much less medical treatment, and no treatment is initiated without the mental health evaluations and a thorough informed consent process for patients and their guardians.

17. Dr. Levine and Dr. Cantor express a view that care should be withheld from adolescents so that they can be encouraged to identify with their birth-assigned sex. This view

contravenes the standard of care; encourages “conversion therapy,” which has been widely discredited as unethical and profoundly harmful; and is wholly unsupported by any scientific evidence, as both admit. Levine Report ¶ 49 (admitting that “there is no evidence beyond anecdotal reports that psychotherapy can enable a return” to identifying as one’s birth-assigned sex); Cantor Report ¶ 42 (admitting “there has not yet been any such study” that supports withholding care). Additionally, being deprived of access to medically necessary care for gender dysphoria can impose serious and potentially irreversible harms. Many physiological changes that happen during endogenous puberty cause severe distress for patients with gender dysphoria and can be difficult, if not impossible, to reverse with subsequent treatment. Based on my clinical experience, patients with severe dysphoria who are able to receive medically indicated treatment as adolescents experience substantial mental health improvements.

WPATH IS A PROFESSIONAL MEDICAL ORGANIZATION

18. Dr. Levine critiques WPATH because it is “a voluntary membership organization” and “attendance at its biennial meetings has been open to trans individuals who are not licensed professionals.” Levine Report ¶ 67. This critique is misplaced, as an organization can both advocate for patients and pursue rigorous scientific research, which WPATH and many other medical associations do. This is not an isolated or new phenomenon in medicine. The American Diabetes Association, for example, is a professional association that both advocates for patients with diabetes and is a scientific organization that conducts research, hosts meetings with open attendance, and reports on developments in the field. Similarly, rigorously researched papers are presented at the WPATH biennial meetings and well-funded scientific scholarship is reported on to other attendees. I have attended many of these meetings and have heard open, collegial and cordial debate. I have not had the experience suggested by Dr. Levine in the last decade, nor has

he, as he has admittedly not been a member of WPATH for more than two decades. Levine Report ¶ 66.

19. Dr. Levine additionally critiques WPATH and its members, claiming, “some current members of WPATH have little ongoing experience with the mentally ill” and recognizing and treating psychiatric comorbidities. Levine Report ¶ 73. In my clinic, as is recommended by the Endocrine Society Guideline, every patient is treated by a multidisciplinary team that includes a social worker, psychologist, psychiatrist, and endocrinologist. The mental health providers are all well-trained faculty and clinicians at Duke University Medical School with years of experience diagnosing and treating mental health conditions. For patients who have other mental health diagnoses, they are treated by a team of mental health providers before medical treatment for gender dysphoria is initiated. Clinic protocol requires written confirmation from the patient’s mental health team that any other underlying mental health conditions are well-managed, and the patient is able to begin treatment.

20. Similarly, Dr. Levine asserts that the 2017 Endocrine Society Guidelines are not “standards of care.” Levine Report ¶¶ 85-86. Dr. Levine misinterprets my testimony in that the titles of the clinical care recommendations based in the medical literature published by the Endocrine Society are all titled “clinical care guidelines.” These guidelines are meant to be useful to providers in this field, and are recommendations from the Endocrine Society to improve care for transgender individuals.

SAFETY AND EFFICACY OF TREATMENTS

Safety and Efficacy of Puberty-Delaying Treatment

21. Puberty blockers have been used to treat patients with gender dysphoria since at least 2004 in the United States. We have almost 20 years of data showing the safety and efficacy

of this treatment for patients with gender dysphoria. We have over 30 years of data about the safety of this treatment based on data from treating children with precocious (i.e., early onset) puberty. Even with all of this supporting data, the Duke Gender Clinic still does not treat patients with a “one-size-fits-all approach” that Drs. Levine and Cantor proclaim exists. Not all patients who are experiencing their endogenous puberty when they present for care at our clinic are indicated for treatment with puberty blockers. This avenue of treatment is a case-by-case decision made with the expertise and thoughtful analysis of the entire multidisciplinary team, and with the patient and their family weighing the risks and benefits of each treatment path.

22. Though Dr. Levine warns throughout his report about delaying puberty, pubertal suppression in transgender youth does not delay puberty beyond the typical age range. Pubertal development has a very wide age variation among individuals. Puberty in individuals assigned male at birth typically begins anywhere from age nine to age 14, and sometimes does not complete until a person’s early twenties. For those individuals assigned female at birth, puberty typically occurs sometime within the ages of eight to 17, generally beginning between the ages of eight and 13. Protocols used to treat adolescents with gender dysphoria would tend to put them in the latter third of typical pubertal age ranges but nothing outside of the typical range.⁴ Though some peers of a patient on pubertal suppression may undergo pubertal changes earlier than the gender dysphoric patient, many peers will have comparably timed or even later puberty. There is no data to support Dr. Levine’s assertion that delaying puberty within these normal age ranges will have negative social and developmental consequences, including Dr. Levine’s unsupported claim that

⁴ Hembree, W.C., Cohen-Kettenis, P.T., Gooren, L., et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*. 2017; 102(11): 3869-903; Euling, S.Y., Herman-Giddens, M.E., Lee, P.A., et al. Examination of U.S. Puberty-Timing Data from 1940 to 1994 for Secular Trends: Panel Findings. *Pediatrics*. 2008; 121 (Supplemental 3): S172-S191.

transgender youth will experience psychosocial harms from their purportedly delayed puberty. Levine Report ¶ 192. Contrary to the suggestions by Dr. Cantor and Dr. Levine, my clinical experience has shown that adolescents who access needed gender-affirming medical treatment have improved social and romantic relationships and are able to develop positive peer relationships with cisgender and transgender people alike.

23. Dr. Levine claims that patients treated with puberty-delaying medication will experience a range of health consequences. Levine Report ¶¶ 185-94. For example, he says that patients treated with puberty suppressants will be at an elevated risk of lower bone density. Levine Report ¶ 186. During the course of treatment, patients may have reduced bone mineral density, but after two years on hormone therapy, their bone structure and strength generally matches that of cisgender people who went through the same puberty. This has been shown in research⁵ and has also been my experience with patients. Additionally, studies have shown no changes in bone mineralization among patients with central precocious puberty treated with pubertal suppression for a period of four years.⁶ As with all of the risks of puberty suppression, the risks related to bone mineralization and the state of the evidence are discussed extensively with patients and their parents during the informed consent process.

24. Dr. Levine's claim that brain development occurring during puberty is negatively affected by pubertal suppression is not accurate. Levine Report ¶ 187. Patients with gender dysphoria who are treated with puberty-delaying medication undergo hormonal puberty with all

⁵ van der Loos, M.A., Hellinga, I., Vlot, M.C., et al. Development of Hip Bone Geometry During Gender-Affirming Hormone Therapy in Transgender Adolescents Resembles That of the Experienced Gender When Pubertal Suspension Is Started in Early Puberty. *Journal of Bone and Mineral Research*. 2021; 36(5): 931-41. doi: <https://doi.org/10.1002/jbmr.4262>.

⁶ Park, H.K., Lee, H.S., Ko, J.H., et al. The effect of gonadotrophin-releasing hormone agonist treatment over 3 years on bone mineral density and body composition in girls with central precocious puberty. *Clinical Endocrinology*. 2012; 77(5): 743-48.

the same brain and other bodily system development.⁷ Dr. Levine's claim is inaccurate for the additional reason that some people never go through hormonal puberty, such as patients with Turner Syndrome, and still have normal brain development with respect to cognition and executive function. His claim also seems to imply that youth with gender dysphoria have their puberty delayed beyond the typical age range, but, as I discussed above, this is not accurate. He also implies that gender dysphoric youth treated with pubertal suppression remain on puberty blockers longer than those treated for precocious puberty. Levine Report ¶ 184. This is also not accurate. The longest period of time that my patients with gender dysphoria are treated with pubertal suppression before the introduction of pubertal hormones is approximately three years. By contrast, many patients with precocious puberty are treated with pubertal suppression for five to seven years.

25. As I explained in my initial report, Adkins Report ¶ 30, puberty-delaying medication simply pauses development at the stage it has reached at the time treatment is initiated. On its own, pubertal-delaying medication has no permanent effects on the maturation of sexual organs. For patients treated with puberty blockers who do not go on to gender-affirming hormones, once they stop taking blockers, puberty—including maturation of sexual organs—resumes. Dr. Levine's concerns about potentially diminished sexual response are also misplaced. Levine Report ¶ 199. For transgender women on estrogen who experience sexual side effects from the treatment, these are effectively managed through dosing as well. None of these side effects are inevitable, unmanageable, or unique to this treatment, and all potential side effects are discussed with patients

⁷ Staphorsius, A. S., Kreukels, B. P., Cohen-Kettenis, P. T., et al. Puberty suppression and executive functioning: An fMRI-study in adolescents with gender dysphoria. *Psychoneuroendocrinology*. 2015; 56: 190-99. doi: <https://doi.org/10.1016/j.psyneuen.2015.03.007>.

during the informed consent process required to initiate treatment. And, in my experience, many patients experience no side effects whatsoever from treatment, and instead experience exactly their intended effect: the diminishment of distress caused by untreated gender dysphoria. There is also data that shows that the majority of transgender individuals see an improvement in their sexual satisfaction after gender-affirming care.

26. Dr. Levine’s theories about the unknown impact of puberty blockers on fertility and the supposed “irreversibility” of this treatment are again uninformed. Levine Report ¶¶ 179, 180, 185. In addition to treating precocious puberty and gender dysphoria, puberty blockers are used to *preserve* gonadal function and ensure fertility when patients undergo gonadotoxic treatments. For example, puberty blockers have been shown to protect gonadal function and preserve fertility in patients undergoing cancer and rheumatologic treatment.⁸ Puberty delaying medication is supported as the standard of care to preserve fertility in oncology patients who may undergo gonadal injuring treatments. When patients are no longer undergoing this treatment, their natal gonads resume their normal function and development. It is precisely for this reason, and for the decades of safe and efficient use of these treatments for children with precocious puberty that puberty blockers are relied upon as the least invasive intervention for medical treatment of gender dysphoria.

27. An additional claim by Dr. Levine that lacks evidentiary bases is that an “irreversible” and “inevitable” outcome of the administration of puberty blockers is the later use

⁸ Int J Rheum Dis. 2018 Jun ; 21(6):1287-1292. doi: 10.1111/1756-185X.13318.

Effect of a gonadotropin-releasing hormone analog for ovarian function preservation after intravenous cyclophosphamide therapy in systemic lupus erythematosus patients: a retrospective inception cohort study; nt J Mol Sci 2020 Oct 21;21(20):7792. doi: 10.3390/ijms21207792.

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of hormone therapy. In contrast to Dr. Levine's baselessly imagined world of unethical medical professionals, in actual medical practice in actual medical clinics like mine, no treatment is decided in advance for every single patient, and that is a foremost standard of care. While the majority of my patients who undergo puberty delaying treatment do go on to initiate hormone therapy, some do not. Dr. Levine's imbedded premise is that puberty blockers work as a cause-and-effect mechanism for later use of hormone therapy, but that misses reality entirely, when the cause for any medical treatment is the appropriate management of gender dysphoria with the goal of finding the best treatment possible for each patient, without a predetermined idea of what that will be.

28. Finally, Dr. Levine makes it appear as if the Endocrine Society has significant reservations about puberty-delaying treatment by again misquoting and misrepresenting quoted portions of the 2017 Guidelines. Levine Report ¶¶ 87, 188. To begin with, Dr. Levine asserts that on page 3872, the Guidelines "go no further than 'suggest[ing]' use of puberty blockers." *Id.* ¶ 87. This quote can be found nowhere on page 3872. Instead, in the abstract section labeled "Conclusion" beginning on the first page of the Guidelines (3869) and continuing onto page 3870 is the direct quote "We **recommend** treating gender-dysphoric/gender-incongruent adolescents who have entered puberty at Tanner Stage G2/B2 by suppression with gonadotropin-releasing hormone agonists." (emphasis added). Levine then goes on to quote several disconnected sentences from the Guidelines out of context as support for his wholly unsupported hypothesis that there is a "negative impact" on brain development of adolescents treated with puberty delaying medication. Levine Report ¶¶ 187-88. Notably, while Dr. Levine offers no insight about the impact of the anxiety, depression, and overall distress caused by untreated gender dysphoria on adolescent brain development, he maintains that the Guidelines support his unsubstantiated hypothesis by "acknowledging as much." Levine Report ¶ 188. The Guidelines do no such thing; instead they

merely acknowledge the data existing at the current moment, and like any field of medicine, the need for additional study and information. For example, Dr. Levine's first out of context quote ignores the Guidelines' following statements from the same page that "[i]nitial data in GD/gender-incongruent subjects demonstrated *no change* of absolute areal BMD [bone mineral density] during 2 years of GnRH analog therapy but a decrease in BMD z scores." The Guidelines also note, and Levine omits, that "[r]esearchers reported normal BMD z scores at age 35 years in one individual who used GnRH analogs from age 13.7 until age 18.6 years before initiating sex hormone treatment." Additionally, Dr. Levine leaves out the entire first half of the sentence before his reference to "animal data," from page 3883, which in complete form states that "[a] single cross-sectional study demonstrated no compromise of executive function." Regardless of Dr. Levine's mischaracterizations of the purpose or words of the Endocrine Society Guidelines, in the five years since they were published, additional research has been completed by clinicians and researchers in the area, resulting in findings like those recently included in a study in the Best Practice & Research Clinical Endocrinology and Metabolism: "With more than 30 years of experience, we can affirm that GnRHa treatment is safe. The most frequently documented side effects are headaches and hot flashes."⁹

Safety and Efficacy of Hormone Therapy

29. Dr. Levine expresses concern that the evidence supporting hormone therapy for treatment of gender dysphoria is graded as low quality. Levine Report ¶¶ 144-47. It is common that standard treatments in medicine generally, and endocrinology specifically, receive reviews that the quality of evidence is "low" or "very low" because of the evidence available at the moment

⁹ Leandro Soriano-Guillén, Jesús Argente, Central precocious puberty, functional and tumor-related, Best Practice & Research Clinical Endocrinology & Metabolism, Volume 33, Issue 3, 2019, 101262, ISSN 1521-690X, <https://doi.org/10.1016/j.beem.2019.01.003>.

a review is conducted and because of the limited and rigid definitions of “evidence” used by the reviewing organizations. For example, the Endocrine Society also has a Clinical Practice Guideline for the Treatment of Pediatric Obesity which was released the same year as the Endocrine Society Guideline for the Treatment of Gender Dysphoric Persons. In the Pediatric Obesity Guideline, the Guideline’s strong recommendation for the prevention of obesity is that clinicians prescribe “healthy eating habits”—an obviously time-tested and well-founded recommendation—but this recommendation has a “very low” quality rating of the evidence—just like puberty blockers. Similarly, the Cochrane Database of Systemic Reviews on which Dr. Levine relies has similar levels of evidence for treatments that are standard of care in medicine. For example, in 2021 the Cochrane Database provided a review of “early versus delayed appendectomy for abscess.” Despite appendectomies being one of the oldest and most common surgical procedures completed on children in the United States, the Cochrane Review looked at 66 years’ worth of study and research and found just two studies with 80 total patients that were acceptable for their review and from that data deemed that the evidence is “of very low quality.” (Cochrane Database 2017).

30. Finally, Dr. Levine’s assertion that random control trials are necessary in order to establish any worthwhile science on the safe and effective medical treatment for gender dysphoria is unethical. When withholding treatment is more dangerous (likely to result in death or injury) than providing that treatment, clinicians will, with informed consent and appropriate screening mechanisms, use that treatment even if the amount of evidence supporting the treatment is not vast. In the case of gender-affirming hormone therapy, available data supports that these treatments lower suicide attempts and suicidal ideation as much as four-fold. When combined with the fact that the second leading cause of death in all adolescents is suicide, there are ample

reasons to utilize this treatment pathway even if evidence does not meet the stringent levels of the Cochrane Review. Significantly, there are no reported deaths in youth from receiving puberty blockers or hormone therapy. Given that withholding this care increases the likelihood of death, it is unethical to do so in order to perform a randomized control trial (“RCT”). RCTs are only ethically performed between treatments that are at equal in treating a condition. Providing gender-affirming care to transgender young people and not providing it are not equal in treating the condition, as decades of evidence of the death of transgender individuals before gender-affirming hormone treatments were available demonstrate.

31. Dr. Levine warns of risks of infertility related to gender-affirming hormone therapy, Levine Report ¶ 197, but many transgender individuals conceive children both during and after undergoing hormone therapy.¹⁰ Pregnancy among trans men after undergoing testosterone therapy is very common.¹¹ A recent eight-year study found that four months after stopping testosterone treatment, transgender men had comparable egg yields to non-transgender women.¹² Going directly from pubertal suppression to gender-affirming hormones does affect fertility. For these patients, and any patients treated with estrogen, who are concerned about the impact of estrogen

¹⁰ Light A.D., Obedin-Maliver J., Sevelius J.M., et al. Transgender men who experienced pregnancy after female-to-male gender transitioning. *Obstetrics Gynecology*. 2014; 124(6): 1120-27; Maxwell S., Noyes N., Keefe D., Berkeley A.S., et al. Pregnancy Outcomes After Fertility Preservation in Transgender Men. *Obstetrics Gynecology*. 2017; 129(6):1031-34; Neblett M.F. & Hipp H.S. Fertility Considerations in Transgender Persons. *Endocrinology and Metabolism Clinics*. 2019; 48(2): 391-402.

¹¹ See, e.g., Moseson, H., Fix, L., Hastings, J., et al. Pregnancy intentions and outcomes among transgender, nonbinary, and gender-expansive people assigned female or intersex at birth in the United States: Results from a national, quantitative survey. *International Journal of Transgender Health*. 2020; 22(1-2): 30-41. doi: .

¹² Leung, A., Sakkas, D., Pang, S., et al. Assisted reproductive technology outcomes in female-to-male transgender patients compared with cisgender patients: a new frontier in reproductive medicine. *Fertility and Sterility*. 2019; 112(5): 858-65.

on fertility, fertility preservation remains a viable option we communicate to patients. More generally, many medical interventions necessary to preserve a person's health and well-being can impact an individual's fertility, but as with virtually every decision in medicine, we carefully weigh the risks and the benefits of treatment and proceed with the treatment after informed consent.

32. Dr. Levine asserts that transgender people “most likely [] require regular administration of hormones for the rest of their lives.” Levine Report ¶ 129. Some patients may take hormones for some number of years and then decide to discontinue the treatment if dysphoria is well-managed. For those who do remain on maintenance doses of hormone therapy for their lifetime, the risks of ongoing hormone therapy can be well-managed and are not unlike risks associated with those present for other patients who undergo long-term hormone therapy for different conditions like hypothyroidism, Klinefelter's Syndrome, Turner Syndrome, or hypopituitarism. Generally, in endocrinology, our treatment goals for all patients are to maintain hormone levels at the range of normal human physiology, regardless of a person's chromosomes, reproductive anatomy, or gender identity. When this is done, the body knows no difference in the source of the hormones and functions in normal physiologic fashion, regardless of whether the patient is cisgender or transgender.

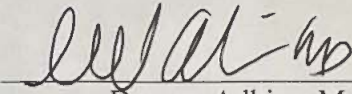
33. Ultimately, Dr. Levine's and Dr. Cantor's reports reveal a central opinion is that it is not healthy to be transgender and that government policies and medical practice should undertake efforts to make people not transgender (*i.e.*, use endless psychotherapy to encourage people to live in accordance with their assigned sex at birth rather than their gender identity, deny them medical treatment when it is indicated, ignore their distress unless science and medicine is 100 percent certain there is no possible risk to any intervention). This approach to the management of any condition is counter to medicine and science overall. And attempts to “treat” transgender

people in this manner is historically well-known to be not only entirely ineffective, but to be extremely harmful and is considered unethical by every major medical association.¹³ My clinical experience and the peer-reviewed literature overwhelmingly demonstrate that gender-affirming medical care drastically improves the health and well-being of adolescents with gender dysphoria for whom the care is medically indicated.

¹³ American Academy of Child & Adolescent Psychiatry. Conversion Therapy. 2018. https://www.aacap.org/AACAP/Policy_Statements/2018/Conversion_Therapy.aspx; American Medical Association. Health care needs of lesbian, gay, bisexual and transgender populations. H-160.991. 2017. <https://policysearch.ama-assn.org/policyfinder/detail/H-160.991%20?uri=%2FAMADoc%2FHOD.xml-0-805.xml/>

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on this 10th day of March 2022.



Deanna Adkins, M.D.

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6. Mann, Courtney M., Kristen Russell, Alexy Hernandez, Nicole Lucas, Erik Savereide, Dane R. Whicker, **Deanna W. Adkins**, Nancy L. Zucker, Raye Dooley, and Bryce B. Reeve. "Concept elicitation for the development of quality measures in transgender health." In *Quality of Life Research*, 28:S104–S104. SPRINGER, 2019.

7. M. Hassan Alkazemi, MD, MS, Leigh Nicholl, MS, Ashley W. Johnston, MD, Steven Wolf, MS, Gina-Maria Pomann, PhD, Diane Meglin, MSW, **Deanna Adkins, MD**, Jonathan C. Routh, MD, MPH; Community Perspectives on Difference of Sex Development (DSD) Diagnoses: a Crowdsourced Survey, 2020 Jun;16(3):384.e1-384.e8. doi: 10.1016/j.jpuro.2020.03.023. Epub 2020 Apr 27. PMID: 32409277
8. McGuire H, Frey L, Woodcock LR, Dake E, Carl A, Matthews D, Russell K, **Adkins DA** "Differences in Patient and Parent Informant Reports of Depression and Anxiety Symptoms in a Clinical Sample of Transgender and Gender Diverse Youth" *LGBT Health* 2021-LGBT Health. Aug-Sep 2021;8(6):404-411. doi: 10.1089/lgbt.2020.0478. Epub 2021 Aug 12
9. Lund A, **Adkins DA**, Simmons C, "Simulation-Based Teaching to Improve Perioperative Care of Transgender Patients". In press. *Clinical Simulation in Nursing*

Non Author publications

1. Turner DA, Curran ML, Myers A, Hsu DC, Kesselheim JC, Carraccio CL and the Steering Committee of the Subspecialty Pediatrics Investigator Network (SPIN). Validity of Level of Supervision Scales for Assessing Pediatric Fellows on the Common Pediatric Subspecialty Entrustable Professional Activities. *Acad Med*. 2017 Jul 11. doi: 10.1097/ACM.0000000000001820. PMID:28700462
2. Mink R, Carraccio C, High P, Dammann C, McGann K, Kesselheim J, Herman B. Creating the Subspecialty Pediatrics Investigator Network (SPIN). Creating the Subspecialty Pediatrics Investigator Network Richard Mink, MD, MACM1, Alan Schwartz, PhD2, Carol Carraccio, MD, MA3, Pamela High, MD4, Christiane Dammann, MD5, Kathleen A. McGann, MD6, Jennifer Kesselheim, MD, EdM7, *J Peds* 2018 Jan;192:3-4.e2. PMID: 29246355 DOI: 10.1016/j.jpeds.2017.09.079
3. Erratum 2018. PMID: 29246355 DOI: [10.1016/j.jpeds.2017.09.079](https://doi.org/10.1016/j.jpeds.2017.09.079)
4. Mink RB¹, Myers AL, Turner DA, Carraccio CL. Competencies, Milestones, and a Level of Supervision Scale for Entrustable Professional Activities for Scholarship. *Acad Med*. 2018 Jul 10. doi: 10.1097/ACM.0000000000002353. [Epub ahead of print] PMID: 29995669 DOI:[10.1097/ACM.0000000000002353](https://doi.org/10.1097/ACM.0000000000002353) Mink RB, Schwartz A, Herman BE,

Editorials

- a. Editorial Charlotte News and Observer-“**NC pediatric specialists say HB2 ‘flawed’ and ‘harmful,’ call for repeal**”; April 18, 2016; authors: Deanna Adkins, Ali Calikoglu, Nina Jain, Michael Freemark, Nancie MacIver, Robert Benjamin, Beth Sandberg, etc.
- b. Editorial Raleigh News and Observer-“**Beverly Gray: Repeal HB2**” May 2016: authors Beverly Gray, Deanna Adkins, Judy Sidenstein, Jonathan Routh, Haywood Brown, Clayton Afonso, William Meyer, Kristen Russell, Caroline Duke, Nancy Zucker, Kevin Weinfurt, Jennifer St. Claire, Angela Annas, Katherine Keitcher

Chapters in Books

1. Endocrinology Chapter writer and editor in **Fetal and Neonatal Physiology for the Advanced Practice Nurse**; Editors: Amy Jnah DNP, NNP-BC, Andrea Nicole Trembath MD, MPH, FAAP. December 21, 2018 ISBN-10 0826157319
2. Chapter in **Dental Clinics of North America Adolescent Oral Health Edition** Understanding and Caring for LGBTQ+ Youth for the Oral Health Care Provider; Authors Joshua Raisin, DDS, Deanna Adkins MD, Scott B. Schwartz, DDS, MPH. 2021
3. Intersex Identity and Gender Assignment; **Encyclopedia of Adolescent Health**; Editor Brian Eichner, MD; Author Deanna Adkins MD 2021-pending

Selected Abstracts:

1. Redding-Lallinger RC, **Adkins DW**, Gray N: The use of diaries in the study of priapism in sickle cell disease. Poster Abstract in Blood November 2003
2. **Adkins, D.W.** and Calikoglu, A.S.: Delayed puberty due to isolated FSH deficiency in a male. Pediatric Research Suppl. 51: Abstract #690. page 118A, 2004
3. Zeger, M.P.D., **Adkins, D.W.**, White, K., Loechner, K.L.: Opsismodysplasia and Hypophosphatemic Rickets. Pediatric Research Suppl.-from PAS 2005
4. Kellee M. Miller¹, David M. Maahs², **Deanna W. Adkins**³, Sureka Bollepalli⁴, Larry A. Fox⁵, Joanne M. Hathway⁶, Andrea K. Steck², Roy W. Beck¹ and Maria J. Redondo⁷ for the T1D Exchange Clinic Network; Twins Concordant for Type 1 Diabetes in the T1D Exchange -poster at ADA scientific sessions 6/2014
5. Laura Page, MD; Benjamin Mouser, MD; Kelly Mason, MD; Richard L. Auten, MD; **Deanna Adkins, MD** CHOLESTEROL SUPPLEMENTATION IN SMITH-LEMLI-OPITZ: A Case of Treatment During Neonatal Critical Illness; - poster 06/2014
6. Lydia Snyder, **MD, Deanna Adkins, MD**, Ali Calikoglu, MD; Celiac Disease and Type 1 Diabetes: Evening of Scholarship UNC Chapel Hill 3/2015 poster
7. **Deanna W. Adkins, MD**, Kristen Russell, LCSW, Dane Whicker, PhD, Nancy Zucker, Ph. D: Departments of Pediatrics and Psychiatry, Duke University Medical Center; Evaluation of Eating Disturbance and Body Image Disturbance in the Trans Youth Population; WPATH International Scientific Meeting June 2016; Amsterdam, The Netherlands

8. Rohit Tejawani, **Deanna Adkins**, Brian J. Young, Muhammad H. Alkazemi, Steven Wolf³, John S. Wiener, J. Todd Purves, and Jonathan C. Routh; Contemporary Demographic and Treatment Patterns for Newborns Diagnosed with Disorders of Sex Development; Poster presentation at AUA meeting 2016
9. S.A. Johnson, **D.W. Adkins**, Case Report: The Co-diagnosis of Hypopituitarism with Klinefelter in a patient with short stature; Pediatric Academic Society Meeting 2018
10. Lapinski J, Dooley R, Russell K, Whicker D, Gray, B, **Adkins DW**; **Title:** Developing a Pediatric Gender Care Clinic at a Major Medical Setting in the South; Workshop Philadelphia Trans Wellness Conference 2018
11. Jessica Lapinski, DO, Deanna Adkins, MD, Tiffany Covas, MD, MPH, Kristen Russell, MSW, LCSW; An Interdisciplinary Approach to Full Spectrum Transgender Care; WPATH Conference Buenos Aires, Argentina, November 3, 2018
12. Leigh Spivey, MS, Nancy Zucker, PhD, Erik Severiede, B.S., Kristen Russell, LCSW, Deanna Adkins, MD; USPATH Washington, DC Sept. 2019. Platform presentation; "Psychological Distress Among Clinically Referred Transgender Adolescents: A latent Profile Analysis"

Non-Refereed Publications

- i. Print
 - i. Editorial Charlotte News and Observer-"**NC pediatric specialists say HB2 'flawed' and 'harmful,' call for repeal**"; April 18, 2016
 - ii. Editorial News and Observer-HB2 May 2016 -"**Beverly Gray: Repeal HB2**" May 2016
- ii. Digital
 - i. Supporting and Caring for Transgender Children-HRC guide 2017
 - ii. Initial endocrine workup and referral guidelines for primary care Providers- Pediatric Endocrine Society Education Committee Website Publication
 - iii. Only Human Podcast August 2, 2016;
<https://www.wnycstudios.org/podcasts/onlyhuman/episodes/id-rather-have-living-son-dead-daughter>
- iii. Media and Community Interviews
 - i. Greensboro News and Record Community Forum October 2017-*Transgender Panel Moderator*
 - ii. Playmakers Repertory Company-Chapel Hill: *Draw the Circle* Transgender Community Panel 2017
 - iii. Duke Alumni Magazine
 - iv. Duke Stories
 - v. DukeMed Alumni Magazine
 - vi. NPR Podcast Only Human piece on caring for transgender youth and follow up piece 1 year later
 - vii. ABC11, WRAL, WNCN News Coverage
 - viii. News and Observer: Charlotte and Raleigh
 - ix. Duke Chronicle and Daily Tarheel Article
 - x. Huffington Post Article

- xi. <https://www.businessinsider.com/the-olympics-uses-testosterone-to-treat-trans-athletes-like-cheaters-2021-7>
- xii. <https://www.wral.com/top-transgender-doctor-warns-teen-treatment-ban-could-be-deadly/19618762/>
- xiii. <http://www.ncpolicywatch.com/2021/04/07/experts-bills-targeting-trans-people-get-the-science-wrong/>

Published Scientific Reviews for Mass Distribution

Position and Background Papers

Other Publications

Editorial Experience

Editorial Boards

Ad Hoc scientific review journals

Hormone Research, Lancet, NC Medical journal, Journal of Pediatrics, Pediatrics, Transgender Health, International Journal of Pediatric Endocrinology, Journal of Adolescent Health

Consultant Appointments

North Carolina Newborn Screening Committee

Human Rights Campaign Transgender Youth Advisory Board

Scholarly Societies

Professional Awards and Special Recognitions

ESPE Fellows Summer School, 2001

NIH Loan Repayment Program Recipient

Lawson Wilkins AstraZeneca Research Fellow,
2003-2004

HEI 2017 Leaders in LGBTQ Healthcare
Equality

Inside Out Durham Appreciation Award

Duke Health System Diversity and Inclusion
Award January 2018

America's Top Doctor's 2020, 2021

Duke Health System Diversity and Inclusion
Award January 2020- CDHD Course Team

Teaching for Equity Fellow 2021

Organizations and Participation

Organization	Role	Dates
American Academy of Pediatrics	Member Council on Information Technology Member Reviewer COCIT Member Section on Endocrinology	1998 to present 2004 to present
Pediatric Endocrine Society	Member Member Education Committee SIG member-Transgender, DSD, liaison to Advocacy SIG Writer Web Publication for Pediatricians	2000 to present
NC Pediatric Society	Member	1998 to present
Endocrine Society	Member	2000 to present
WPATH-International Transgender Society	Member	2014 to present

External Support

<u>Approximate Duration</u>	<u>PI</u>	<u>% Effort</u>	<u>Purpose</u>	<u>Amount Duration</u>
<u>Past</u>	<u>JAEB Center- Deanna Adkins</u>	0.5%	<u>Type 1 diabetes research</u>	<u>\$ 5yr</u>
<u>Past</u>	<u>Josiah Trent Foundation Grant-Deanna Adkins</u>	0.5%	<u>Transgender and eating disorder research</u>	<u>\$5000 3 yr</u>
<u>Pending: Submitted</u>	<u>NIH-Kate Whetten</u>	0.1%	<u>Analysis of TransgenderHealth in Adolescents in Rural Africa, India, and Thailand</u>	<u>Consultant</u>

<u>Approximate Duration</u>	<u>PI</u>	<u>% Effort</u>	<u>Purpose</u>	<u>Amount Duration</u>
<u>Re-Submitting June 2022</u>	<u>NIH R21 Deanna Adkins</u>	2%	Development of New Gender Dysphoria Measures in Youth	<u>Co PI</u>
<u>ReSubmitting February 2022</u>	<u>NIH R21 Sarah Legrand</u>	2%	Glow and Grow	<u>consultant</u>
<u>Submitted November 2020</u>	<u>CMS-Deanna Adkins and Rob Benjamin</u>	1%	<u>Innovations Grant</u>	<u>Co PI 3 yrs</u>
<u>Gifts</u>	<u>Private Family</u>		Multiple including leadership training initiatives as well as other LGBTQ work	<u>Approx. \$18,000 Unlimited duration</u>

Mentoring Activities

Faculty	
Fellows, Doctoral, Post docs	Nancie MacIver-fellow
	Dorothee Newbern-fellow
	Krystal Irizarry-fellow
	Kelly Mason-fellow
	Laura Page-fellow
	Elizabeth Sandberg fellow UNC
	Dane Whicker-psychology post doc Leigh Spivey-psychology post doc Joey Honeycutt, Chaplain Intern Kathryn Blew-research mentor
Residents	Yung-Ping Chin-mentor
	Kristen Moryan-mentor
	Jessica Lapinski-mentor
	Kathryn Blew-research mentor
	Matthew Pizzuto, Briana Scott-Coach, Laura Hampton Coach

Medical students	Tulsi Patel-continuity clinic mentor Ernest Barrel-continuity clinic mentor Sonali Biswas-research mentor 3rd year project Katha Desai-research mentor 3rd year project
Undergraduates	Erik Severeide-Duke University Lindsay Carey-Dickinson College Jeremy Gottlieb-Duke University Jay Zussman-Duke University
High School Students	Aeryn Colton-Intern Apex High School
Graduate Student MBS program	Nicholas Hastings
UNC Gillings School of Public Health MPH students	Lauren Frey, Emily Dake, Alexandra Carle, Lindsay Woodcock, Hunter McGuire
Nurse Practitioners	ECU, Duke-multiple
DNP candidates	Ethan Cicero-PhD committee member Amanda Lund-PhD committee member
Pediatric Dental Fellow UNC	Joshua Raisin-research associate

Education / Teaching Activities

Didactic classes

High School

- c. Cary Academy: Work Experience Program 2021

Undergraduate

1. Creating Excellence and Ambulatory Nursing 2008
2. Profile in Sexuality Research Series at Duke CGSD 2016
3. Duke School of Nursing BSN Course on Sexual and Gender Health guest lecturer: fall 2017, spring 2018, fall 2018, spring 2019, fall 2019, spring 2020, fall 2020, spring 2021, fall 2021
4. Duke School of Nursing Lecture on Transgender Care-recorded for reuse
5. Duke Physician Assistant Program guest lecturer; fall 2017, spring 2018
6. Duke Global Health Course guest lecturer fall 2016
7. Duke Neuroscience course on Gender and Sex guest lecturer fall 2016
8. Duke Ethics Interest group guest lecturer fall 2018, 2020
9. Duke EMS group lecture fall 2018
10. Duke Physician Assistant Program LGBTQ+ Rotation Educator 2019 to present
11. Global Health Sexual and Gender Minority Seminar Lecturer 2020

UME:

1. Cultural Determinants of Health and Health Disparities Course: Facilitator and developed one class; 2017-18 and 2018-19, 2019-20, 2020-21, 2021-22; Steering Committee member for course development
2. UNC School of Medicine Lecturer for LGBTQ Health series 2016-recorded for reuse
3. Duke Pediatrics Interest Group lecture Nov 2020
4. Duke Med Pediatrics Interest Group lecture fall 2018, 2020
5. Lecturer Body and Disease Course MS1 2019, 2020, 2021 Clinical Correlation Differences of Sex Development
6. Lecturer Body and Disease Course MS1 2020, 2021 Transgender Medicine
7. Lecture on Cancer in Transgender and Intersex Individuals April 14, 2021 Mount Sinai School of Medicine
8. Lecture on Transgender Medicine Univ. of Tenn. Health Science Center School of Medicine May 7, 2021

Graduate School Courses:

1. Master of Biomedical Science Program-guest lecturer on Transgender Medicine fall 2016
2. School of Nursing Graduate Intensive Course Lecturer on Sexual and Gender Health; fall 2017, spring 2018, fall 2018, spring 2019, Fall 2019
3. Fuqua School of Business Med Pride Panel and presentation fall 2017
4. Master of Biomedical Science Program Mentor 2019-2020
5. Endocrinology for Nurse Practitioners Duke Neonatal Nurse Practitioner Program August 2021

DUHS Employee Education

1. Annual Duke Human Resources Lunch and Learn on Gender Diversity 2016, 2017, 2018
2. Over 100 lectures across the institution on gender including CHC front desk/nursing staff, hospital wide social work/case management, radiology, PDC clinic front desk/nursing staff
3. Steering Committee for Sexual and Gender Identity Epic Module development and Educational module development
4. DCRI Pride invited speaker
5. Duke Children's staff update 2021

GME:

1. Adult Endocrinology Fellows every year on growth and/or gender
2. Pediatric Residency Noon conferences on Growth and Gender-yearly
3. Reproductive Endocrinology Noon Conferences every 2 to 3 years
4. Psychiatry Noon Conferences periodically
5. Family Practice Noon Conference periodically
6. Pediatric Endocrine Fellow lectures twice a year or more

7. Pediatrics grand rounds: Vitamin D, Type 2 diabetes, Pubertal Development, Gender Diverse Youth
8. Duke Urology Grand Rounds 2016
9. Duke Ob/Gyn Grand Rounds 2017
10. Webinar for Arkansas Children's Hospital on transgender care 2018
11. Reproductive Challenges for Transgender people-Reproductive Endocrinology-2020
12. Metabolic Bone Disease in Neonates-NICU fellows 2019
13. Duke Psychiatry Grand Rounds 2017
14. Duke Pathology Grand Rounds fall 2020
15. Duke Family Medicine Community Rotation Educator 2019 to present
16. NC NAPNAP Symposium Keynote Speaker October 10, 2020
17. Duke Internal Medicine LEADS program speaker; Transgender Care 8/3/2021
18. Equity and Social Justice Webinar: Clinical Advocacy and Care of Transgender and Gender Diverse Youth October 27, 2021Harvard Equity and Social Justice Webinar

Development of Courses Educational programs

1. Pituitary Day October 2019-full day multispecialty seminar for caregivers of patients with hypopituitarism-Organized and developed the curriculum
2. Development of Gender Diversity Education for Health System education
3. Steering Committee for Cultural Determinants and Health Disparities Course
4. Helping to Adapt Resident Coaching Program to Pediatric Fellowships
5. Developed half day course for Duke Student Health on Care of the Gender Diverse Student with multiple disciplines included
6. Course Director: American Diabetes Association Camp Carolina Trails rotation for fellows and residents: 2009, 2011 – 2019
7. Medical Education for Camp Morris 2019, 2021

Development of Assessment Tools and Methods

1. Currently under development with Population Health Sciences-method to assess gender dysphoria; received Brief High Intensity Production (BHIP) grant for this collaboration; NIH grant Submitted March 2020; I am writing the portion of grant giving background on the population and the need for better measures.
2. Collaborating with the Duke Chaplain group to develop a spiritual assessment tool for gender diverse children and their families. Completed 2019

Educational leadership roles

1. Fellowship Program Director Pediatric Endocrinology 2008-2019
2. Course Director: American Diabetes Association Camp Carolina Trails rotation for fellows and residents: 2009, 2011 to 2019

Educational Research

1. Working with coaching program for residents modified and applied in pediatric fellows
2. Worked with the Council on Pediatric Subspecialties EPA study

Invited Lectures and Presentations

1. NC Peds Conference: Pubertal Development 2016
2. Trent Center for Ethics Lecture May 2017: Transgender Medicine: a Wealth of Ethical Issues
3. Visiting Professorship: ECU Brody School of Medicine Invited Professor October 2017
4. College of Diplomates-pediatric dentistry society-Webinar on transgender care 4/1/2020
5. NAPNAP keynote speaker Annual Meeting October 2020
6. Wake County Duke CME program: Type 2 diabetes treatments in pediatrics 2019
7. Lecture on Cancer in Transgender and Intersex Individuals April 14, 2021 Mount Sinai School of Medicine
8. Lecture on Transgender Medicine Univ. of Tenn. Health Science Center School of Medicine May 7, 2021
9. Equity and Social Justice Webinar: Clinical Advocacy and Care of Transgender and Gender Diverse Youth October 27, 2021 Harvard Equity and Social Justice Webinar

International Meetings

1. WPATH Amsterdam 2016
2. WPATH Buenos Aires 2018

National Scientific Meetings (invited)

1. Transgender SIG Developing a Patient Registry
2. Patient Advocacy for Transgender Youth Philadelphia 2018

Instructional Courses, Workshops, Symposiums (National)

1. Time to Thrive Arkansas Children's Hospital April 2018
2. National Transgender Health Summit UCSF Jan 2018: Providers as Advocates Workshop
3. Magic Foundation-Chicago, IL Annual Speaker on Precocious Puberty, Adrenal Insufficiency, and Growth Hormone at National Conference 2016, 2017, 2019, 2020, 2021
4. The Seminar-Fort Lauderdale, FL Invited Speaker on Care of Transgender Youth 2017

Regional Presentations and Posters

- a. North Carolina Pediatric Society: Pubertal Development Presentation–Pinehurst, NC 2017
- b. North Carolina Psychiatric Association: Caring for Transgender Children Presentation and Workshop on key concepts in care of transgender child-Asheville, NC 2017
- c. ECU Campus Health Presentation Caring for Transgender Patients 2018
- d. Radiology Technology Symposium Presentation on Caring for Transgender Patients 2018
- e. Duke CME in Wake County-Update on Type 2 Diabetes Treatments Feb 2019
- f. Hilton Head Pediatric CME Course-Update on Type 2 Diabetes, Short Stature, and Caring for Transgender Patients June 2019

- g. Wake County Duke Pediatrics CME Type 2 diabetes treatments Feb 2019
- h. NAPNAP Annual Meeting Keynote Speaker 2020
- i. Sexual and Gender Minorities Research Symposium Duke Feb 2020; speaker and organizer

Local Presentations

- 1. Grand Rounds: 2016 to present-Duke Pediatrics twice, Moses Cones Pediatrics, ECU Ob/Gyn, Duke Ob/Gyn, Duke Psychiatry, Duke Urology, Duke Adult Endocrinology, Duke Pathology
- 2. Prior to 2016-Rex Grand rounds: Salt and Water balance, New treatments in Pediatric Diabetes, Adrenal Insufficiency, Duke peds grand rounds Bone Health, Type 2 Diabetes Mellitus
- 3. Duke Women's Weekend 2018 hosted by Duke Alumni Association
- 4. NCCAN Social Work Training 2016
- 5. NAPNAP lecture 2016 and 2018 and 2020
- 6. Profiles in Sexuality Research Presentation at Duke Center for Sexual and Gender Diversity 2017
- 7. Duke LGBTQ Alumni Weekend Presentation 2017
- 8. UNC Chapel Hill Campus Health Presentation 2018
- 9. Duke Student Health Presentation 2017, 2018, 2019 (workshop)

Clinical Activity

- 1. Duke Consultative Services of Raleigh-2.5 days per week in endocrinology and diabetes
- 2. Duke Child and Adolescent Gender Care Clinic 1.2 day per week at the CHC
- 3. Inpatient Consult Service Pediatric Endocrinology 1 week per month

Administrative and Leadership Positions

- 1. Medical Director Duke Children's and WakeMed Consultative Services of Raleigh
- 2. Director Duke Child and Adolescent Gender Care Clinic
- 3. Pediatric Endocrinology Fellowship Program Director 2008-2019

Committees

- 1. Graduate Medical Education Committee-2008-2019
- 2. School of Medicine Sexual and Gender Diversity Council 2015 to present
- 3. Pediatrics Clinical Practice Committee-2015? To present
- 4. Pediatric Diversity and Inclusion Committee

Community

- 1. Test proctor local schools
- 2. Guest lecture GSA multiple years
- 3. Diabetes Camp over 10 years
- 4. 100 Women who give a hoot
- 5. Collaborated to bring "Becoming Johanna" to Duke along with multiple screenings with the director and the lead actor
- 6. Teddy Bear Hospital volunteer both years

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

B.P.J. by her next friend and mother, HEATHER JACKSON,

Plaintiff,

v.

WEST VIRGINIA STATE BOARD OF EDUCATION, HARRISON COUNTY BOARD OF EDUCATION, WEST VIRGINIA SECONDARY SCHOOL ACTIVITIES COMMISSION, W. CLAYTON BURCH in his official capacity as State Superintendent, DORA STUTLER in her official capacity as Harrison County Superintendent, and THE STATE OF WEST VIRGINIA,

Defendants,

and

LAINY ARMISTEAD,

Defendant-Intervenor.

Civil Action No. 2:21-cv-00316

Hon. Joseph R. Goodwin

EXPERT REPORT AND DECLARATION OF PROFESSOR MARY D. FRY, PHD

1. I have been retained by counsel for Plaintiff as an expert in connection with the above-captioned litigation.

2. The purpose of this expert report and declaration is to offer my expert opinion on: (1) the psychological and behavioral benefits of sports for youth and young adults (including collegiate athletes); and (2) the conditions that lend themselves to youth and young adults participating in athletics and accessing those benefits when they do participate.

3. I have knowledge of the matters stated in this expert report and declaration. I have collected and cite to relevant literature concerning the issues that arise in this litigation in the body of this expert report and declaration and in the attached bibliography.

4. In preparing this expert report and declaration, I reviewed West Virginia H.B. 3293, the bill at issue in this litigation.

5. In preparing this expert report and declaration, I relied on my education and training, my professional and research experience, and my knowledge of the literature in the pertinent fields. The materials I have relied upon in preparing this expert report and declaration are the same types of materials that experts in my field of study regularly rely upon when forming opinions on the subject. I may wish to supplement these opinions or the bases for them as a result of new research or publications or in response to statements and issues that may arise in my area of expertise.

PROFESSIONAL BACKGROUND

6. I am a Professor in the Department of Health, Sport & Exercise Sciences at the University of Kansas in Lawrence, Kansas. A true and correct copy of my Curriculum Vitae is attached hereto as Exhibit A.

7. In 1984, I graduated from Texas Wesleyan University in Fort Worth, Texas with a Bachelor of Science in Physical Education. After graduating, I spent about five years teaching physical education and coaching tennis at schools and summer camps in Texas and North Carolina.

8. I graduated with a Master of Science in Sport Psychology/Pedagogy from the University of North Carolina in Greensboro, North Carolina in 1990. Then, in 1994, I graduated with a doctorate in Sport & Exercise Psychology from Purdue University in West Lafayette, Indiana. From 1994 to 1999, I served as an Assistant Professor in the University of Memphis's

Department of Human Movement Sciences and Education. I continued at the same institution from 1999 to 2007 as an Associate Professor in the Department of Human & Sport Sciences. I joined the faculty of the University of Kansas in 2007, where I continue to teach and research as a Professor today.

9. I have authored or coauthored 69 papers in peer-reviewed journals, including many studies in sport psychology and youth athlete motivation. I have coauthored seven book chapters and one book, titled *A Coach's Guide to Maximizing the Youth Sport Experience: Work Hard and Be Kind*. I have also given 118 presentations on my research at both international and national conferences, as well as dozens of local and regional presentations.

10. I have taught and/or developed six undergraduate level courses and 12 graduate level courses in sport and exercise psychology. The courses I developed include Psychosocial Aspects of Sport, Applied Sport Psychology, Developmental Perspectives in Youth Sport, and Special Course: Sport Psychology Within Youth Sport.

11. On a national level, I have served with the Association of Applied Sport Psychology ("AASP") as a member of the Program Review Committee (2008-present), a Subject Matter Expert for the Certification Exam Committee (2018), and a member of the Ad-Hoc Future of AASP Committee (2012-2015). For the AASP, I have served as an Executive Board Member (2004-2006), two three-year terms as a member of the Social Psychology Section Committee (1996-99; 2001-2003), and as a member of the Dissertation Award Committee (1998; 2002). I have also served on the Editorial Board for *Physical Activity Today* (1997-2001) and on the Program Review Committee for the American Alliance of Health, Physical Education, Recreation & Dance (2009-2017), in addition to chairing the Committee in 2010. I also serve on the National Advisory Board for the Positive Coaching Alliance.

12. I have undertaken editorial roles on professional journals within my field, including as Associate Editor (2009-2012) and Editorial Board Member (2000-2009; 2013-present) for the *Journal of Applied Sport Psychology*; Associate Editor (2008-present) for the *Journal of Sport Psychology in Action*; Section Editor (2003-2006) and Reviewer (1994-present) for the *Research Quarterly for Exercise and Sport*; and Editorial Board Member (2011-present) for *Sport, Exercise, and Performance Psychology*.

13. I have served on the Kansas University Certificate in Sport Committee (2017-2018), and the Kansas University Center for Undergraduate Research, Advisory Board (2016-2018), among other roles at the University.

14. I am, or have been, a member of several professional organizations, including the American Psychological Association (2017-present), the Kansas Alliance for Health, Physical Education, Recreation, & Dance (2008-present), the American Alliance for Health, Physical Education, Recreation, and Dance (1988-2017), and the North American Society for the Psychology of Sport and Physical Activity (1988-2000).

15. I also have experience applying sport psychology in the field, which include mental skills interventions for various athletes and teams, including with high school and university athletes (2000-present), a high school baseball team (2013-2018), a youth baseball team (2009-2011), a Division I collegiate volleyball team (2008-2010), a high school basketball team (2006-2007), and a Division I cross-country team (2006).

16. I have not previously testified as an expert witness in either deposition or at trial.

17. I am being compensated at an hourly rate of \$250 per hour. My compensation does not depend on the outcome of this litigation, the opinions I express, or the testimony I provide.

**FOCUSING SOLELY ON PERFORMANCE OUTCOMES UNDERMINES THE
BENEFITS OF SPORT FOR YOUTH AND YOUNG ADULT ATHLETES**

18. For youth and young adult student-athletes, athletics serve a different purpose than for athletes who participate in professional athletics or world elite competition. A myopic focus on winning in youth and young adult athletics ignores the other important benefits that school athletics offer young athletes, such as teamwork and camaraderie, which are advanced when all athletes have the opportunity to play the sport they love and reap the benefits of such participation.

19. The National Collegiate Athletic Association (NCAA) estimates that there are eight million high school student-athletes in the United States.¹ Of those millions of athletes, only about 6% go on to compete at the college level in any division (with only about 2% earning an athletic scholarship).² By the numbers alone, the primary purpose of high school sports is not about preparing youth for college sports. For the 93% of high school athletes who do not compete in college as well as for those who do, youth sport creates a myriad of benefits unrelated to preparing athletes to compete in college.

20. Then for collegiate athletics, most athletes do not go on to have athletic careers beyond college in an elite sports context. According to the NCAA: “Fewer than two percent of NCAA student-athletes go on to be professional athletes.”³ That percentage does not include National Association of Intercollegiate Athletics (for small college sports) and junior college student-athletes, who are less likely to have professional sports careers. Accordingly, among total numbers of collegiate athletes in the United States, the total percentage of athletes who go on to participate in elite, professional athletics after college is even lower than two percent.

¹ <https://www.ncaa.org/about/resources/research/estimated-probability-competing-college-athletics>

² *Id.*; <https://www.ncaa.org/student-athletes/future/scholarships>

³ <https://www.nfhs.org/media/886012/recruiting-fact-sheet-web.pdf>

21. There are many benefits to young people from participating in athletic activities, discussed further herein. But understanding what motivates youth and young adults to participate in athletics in the first place is essential for understanding how they can access these benefits. One critical way to increase participation in athletics is to understand the factors that motivate individuals to stay engaged at different ages and in different contexts. Understanding motivation also helps to explain how the benefits youth and young adults derive from participating in sport translate to other aspects of their lives.

22. In simple terms, motivation is the desire to do activities. More formally, it is defined as “the process that influences initiation, direction, magnitude, perseverance, continuation, and quality of goal-directed behavior” (Maehr & Zusho, 2009). Motivation is about why, how, when, and in what circumstances people employ their resources.

23. One of the most-researched motivational theories in the field of sport psychology is achievement goal perspective theory, which was developed to address how motivation could be heightened and sustained over time (Nicholls 1984, 1989). Achievement goal perspective theory includes three components that together can work to optimize motivation among all individuals, including youth and young adults participating in sports.

24. First is the developmental component of achievement goal perspective theory. Young children are incapable of accurately comparing their ability to others, overestimate their ability, and are naturally focused on their effort as a marker of success. By the time they enter adolescence, however, they are able to distinguish the concepts of effort, luck, and ability.

25. Second, around 12 years of age, children achieve a mature understanding of the concept of ability and at that time adopt their own personal definitions of success, or “goal orientations.” The primary goal orientations are task and ego. Individuals with a “high task

orientation” define success based on their effort, improvement, and mastery of tasks over time. In contrast, a high ego orientation occurs when individuals define success in normative terms, only feeling successful when they outperform others. Individuals are to some degree both task- and ego-oriented; in fact, they can be high and/or low in both orientations.

26. Third, motivations are shaped by outside factors, which can reinforce a task orientation as opposed to an ego orientation. Specifically, athletes can perceive the environment that is created by coaches (but can also be influenced by parents and teammates) (Ames, 1992a, 1992b; Nicholls, 1984, 1989) as a task-involving or ego-involving climate. When the environment created by coaches and others is a caring environment, athletes are more likely to perceive the overall climate as task-involving. A caring environment is one where athletes feel safe, welcome, comfortable, and valued, and are treated with kindness and respect by all in the sport setting (Newton et al., 2007). A climate that is both task-involving and caring is one in which coaches do the following: recognize and reward effort and improvement; foster cooperation among teammates; make everyone feel they play an important role on the team; treat mistakes as part of the learning process; and encourage an atmosphere where everyone is treated with mutual kindness and respect.

27. A high task orientation, described above in Paragraph 25 is the key to optimizing motivation over time because effort and improvement – the keys to task orientation – are variables that individuals can more easily control. High task orientation results in athletes being more likely to seek challenge, exert high effort, and persist over time (Maehr & Zusho, 2009).

28. Perhaps the strongest finding within the goal orientation research links task orientation with high enjoyment. Throughout childhood and adolescence, and across a range of sports, athletes who define success based on their personal effort and improvement have more fun

playing their sport than those high in ego orientation (Schneider, Harrington, & Tobar, 2017; Seifriz, Duda, & Chi, 1992; Stephens, 1998; Stuntz & Weiss, 2009; van de Pol & Kavussanu, 2011). Importantly, goal orientations are also associated with the sources of enjoyment athletes identify. For example, youth athletes with a high task orientation more often report experiencing enjoyment from learning and having positive team interactions. In contrast, athletes high in ego orientation more often report experiencing enjoyment as a result of winning and having high perceived competence (Lochbaum & Roberts, 1993).

29. Another benefit of high task orientation in youth athletes is the strong and positive association with interpersonal and team dynamics (Balaguer, Duda, & Crespo, 1999; Ommundsen, Roberts, Lemyre, & Miller, 2005). Task orientation is positively correlated with peer acceptance, less conflict with peers, and greater satisfaction with the coach.

30. Athletes high in task orientation also report greater confidence and perceived ability, and task orientation has been correlated with both self and team efficacy and greater perceived competence (Magyar & Feltz, 2003; Seifriz et al., 1992; Stuntz & Weiss, 2009). Further, athletes high in task orientation report utilizing more adaptive coping strategies (Kim, Duda, & Gano-Overway, 2011; McCarthy, 2011). These adaptive outcomes have been found for middle school, high school, and collegiate athletes.

31. By contrast, ego orientation (i.e., the non-pejorative, descriptive term for defining success based on ability and performance outcomes), is not correlated with perceived ability in general. Confidence of athletes high in ego orientation was more often based on their perceptions of ability and having a strong physical presence, whereas athletes high in task orientation based their perceptions of confidence on their sense of feeling well prepared and mentally strong (Magyar and Feltz, 2003).

32. Athletes high in ego orientation report lower companionship and greater conflict with teammates (Balaguer et al., 1999), and there is no evidence to suggest they reap the benefits of enhanced social relationships that athletes with high task orientation do (Ommundsen et al., 2005). Despite the ego-involving climate's emphasis on performance outcomes, results across studies suggest that the benefits of a task-involving climate may have a direct impact on athletic performance and ultimately improve performance outcomes (Jackson & Roberts, 1992; McDonald, Cote, & Deakin, 2011). By contrast, no evidence currently points to an ego-involving climate leading to greater performance outcomes with young athletes.

33. There is also a consistently significant relationship between ego orientation and anxiety (Lochbaum et al., 2016). Young athletes with high ego orientation participating in a variety of sports have reported higher trait and state cognitive and somatic anxiety, as well as greater concentration disruption, maladaptive perfectionism, and concern over making mistakes (Grossbard, Cumming, Standage, Smith, & Smoll, 2007; Hall, Kerr, & Matthews, 1998; Ommundsen & Pedersen, 1999; Ommundsen et al., 2005; White & Zellner, 1996).

34. Even for athletes who are themselves highly ego-oriented, and who prioritize winning and external rewards, a task-involving and caring climate is preferable. Such a climate encourages young athletes to orient themselves toward a task-involved model for motivation and away from the stress-inducing ego-orientation, which will in turn garner the young person the benefits associated with a task-orientation. For example, Division I college athletes who perceived a task-involving climate on their teams reported having stronger mental skills including their use of goal setting, ability to concentrate, remain worry free, cope with adversity and peak under pressure, act with confidence, and be open to receiving feedback from coaches (Fry, Iwasaki, & Hogue, 2021). These findings would suggest that athletes with strong mental skills might also

perform better. Further, perceptions of an ego-involving climate have been linked to higher salivary cortisol responses (Hogue, Fry, & Fry, 2017). Cortisol is an important and necessary hormone, but in excess it can break down muscle tissue and interfere with the immune system.

35. Thus, the benefits associated with youth and young adult sport are not limited to whether athletes are winning competitions, where they are ranked in their sport, or what level of publicity they are getting. In fact, a focus exclusively on those things not only undermines an athlete's success in those areas but can compromise the holistic range of benefits derived from youth and young adult sport. Ultimately, athletes are more likely to reap the positive benefits associated with youth and young adult sports if they are task-involved, which places greater emphasis on effort, than if they are ego-involved, which would put greater emphasis on trappings of individual success.

36. It should be noted that the research findings described above, which highlight the relationships between goal orientations and numerous outcome variables, have been consistent for both boys and girls. In other words, within the body of research on athletes' goal orientations, results across studies reveal that task orientation is more often positively correlated with adaptive outcomes (e.g., intrinsic motivation), and ego orientation is more often negatively associated with maladaptive outcomes (e.g., worry) for both boys and girls (Fry & Moore, 2019; Roberts, 2012; Roberts, Nerstad, & Lemyre, 2018).

**EXCLUDING TRANSGENDER STUDENTS FROM PARTICIPATING IN
YOUTH AND YOUNG ADULT ATHLETICS WOULD DEPRIVE THEM AND THEIR
TEAMMATES OF A WIDE RANGE OF BENEFITS**

37. A goal of youth sport is to help young athletes have positive experiences across sport. This includes creating space for athletes to have fun, develop skills, make friends, increase their levels of physical activity, continue their participation over time, and learn valuable life

lessons (Thompson, 2010). If transgender students are arbitrarily excluded from youth sports, they are, in turn, deprived of those positive experiences and outcomes and their teammates are deprived of a genuinely optimal sport experience.

38. Athletes who participate in high school sport are more likely to finish college, and more likely to be actively engaged in planning for their future after their sport career ends (Chamberlin & Fry, 2020; Troutman & Defur, 2007). Many of the benefits to youth who participate in athletics are documented throughout life. For example, women who participated in high school sport see greater success in the business world (ESPNW & EY, 2017; Sasaki, 2020). When athletes are excluded from participating in sport, or are in a climate where they do not feel accepted or respected, they do not have the opportunity to reap these benefits.

39. In addition, arbitrarily excluding transgender students from teams undermines a task-involving climate, which, in turn, diminishes the positive outcomes for all youth and collegiate athletes. (Balaguer, Duda, & Crespo, 1999; Ommundsen, Roberts, Lemyre, & Miller, 2005). Fostering task orientation positively correlates with peer acceptance, less conflict with peers, and greater satisfaction with the coach. These outcomes help athletes have a sport experience that make them want to keep playing sport. Because these positive benefits are fostered in a task-involving environment, arbitrary exclusions can cause harm not only to the athletes who are excluded, but also to the other athletes on the team.

40. When a team, league, or organization adopts an ego-promoting philosophy, and cares only about performance outcomes, the broader benefits of sport are diminished for all involved (both with regard to their future athletic careers and lives outside of sport). As noted above, the overwhelming majority of high school athletes will never go on to compete in college, and the overwhelming majority of college athletes will never go on to compete on professional

teams. Focusing only on the highest-performing athletes or post-graduate elite athletics compromises the other critical benefits of sports for youth and young adults.

41. The climate of youth sport must be geared to include all participants, so that teams are more likely to help every athlete maximize their potential. From an educational perspective, it is optimal to encourage all athletes to do the best that they can, and to help all athletes enjoy the sport that they love.

42. For coaches of youth and young adult athletes, one important message is that, for the overwhelming majority of people, the period of time that a person participates in organized athletics is short and maximizing the benefits of that participation is essential. As Jim Thompson, Founder and former-CEO of the Positive Coaching Alliance notes: “Here’s the bottom line for parents. Your child’s experience with youth sports will come to an end, and it may happen suddenly. If you are like me, you will look back and think, ‘I wish I had enjoyed it more. I wish I hadn’t obsessed so much about how well my child was performing, or the team’s record, or whether he or she was playing as much as I wanted, or why the coach didn’t play him or her in the right position. I wish I had just enjoyed the experience more.’ Because the youth sports experience is so intense, we tend to forget how short it is and what a small amount of time parents and children get to spend together over the course of life.”

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Dated: January 24, 2022



Professor Mary D. Fry, PhD

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EXHIBIT A

CURRICULUM VITAE

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EDUCATION

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MS	Sport Psychology/Pedagogy	University of North Carolina- Greensboro	1990
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EXPERIENCE

RANK/POSITION	DEPARTMENT/DIVISION	INSTITUTION/ORG.	PERIOD
Professor	Health, Sport & Exercise Sci	University of Kansas	2019
Associate Professor	Health, Sport & Exercise Sci	University of Kansas	2007-2019
Associate Professor	Human & Sport Sciences	University of Memphis	1999-2007
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Editorial Assistant	Journal of Applied Sport Psychology		1992-1994
Associate Investigator	Indiana Youth Risk Behavior Study for Disease Control	Indiana Dept. of Education/Centers	1992
Research Consultant	Grant to Study Youth Sports	National Institute for Fitness & Sport Indianapolis, IN	1991
Teaching Assistant	Health, Kinesiology & Leisure Studies	Purdue University	1990-1992
Teaching Assistant	Sport & Exercise Science	U. North Carolina-Greensboro	1989-1990

RANK/POSITION	DEPARTMENT/DIVISION.	INSTITUTION/ORG.	PERIOD
Middle School Teacher	Physical Education	Allen Middle School Greensboro, NC	1988-89
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Certification. Secondary Teacher Certification in English and Physical Education in the State of Texas, 1984.

HONORS/AWARDS:

Coleman Griffith Lecture, Association of Applied Sport Psychology (2021)
 Del Shankel Teaching Excellence Award (Recipient 2021; Finalist 2018, 2019)
 Budig Teaching Professorship, University of Kansas (2018)
 Outstanding Mentor, McNair Scholars Program (2017)
 KU Woman of Distinction, (2014-2015)
 Joyce Elaine Pauls Morgan HSES Teaching Award (2013)
 Budig Teaching Professorship, Nominee (2012)
 Bird Outstanding Mentor Award, Nominee (2011)
 Service Award, School of Education, University of Kansas, Nominee (2011)
 KU Keeler Professorship, University of Kansas (2010).
 Fellow, Association of Applied Sport Psychology (2009).
 Outstanding Research Article published in *Research Quarterly for Exercise & Sport* (1997).
 Presented by the Research Consortium of the American Alliance of Health, Physical
 Education, Recreation, & Dance.
 Outstanding Doctoral Dissertation, North American Society for the Psychology of Physical
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RESEARCH PUBLICATIONS

Refereed Journal Publications

Easton, L., **Fry, M. D.**, Hogue, C. M., & Iwasaki, S. (in press). Goal orientations predict exercisers' effort and enjoyment while engaged in exercise and reasons for using a fitness tracker. *Acta Facultatis Educationis Physicae Universitatis Comenianae*.

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Invited Book Chapters

- Gano-Overway, L., & **Fry, M. D.** (in press). Caring climates. In L. Davis, R. Keegan, & S. Jowett (Eds.), *Social Psychology of Sport* (Second Edition). Champaign, IL: Human Kinetics.
- Fry, M. D.**, & Fontana, M. (in press). Did you hear the one about the hilarious professor? Yeah, me neither: Incorporating humor in sport psychology to enhance motivation and relieve stress. In K. Vaidya (Ed.), *Teach Exercise & Sport With a Sense of Humor: Why and How to Be a Funnier and More Effective Exercise & Sport Teacher and Laugh All the Way to Your Classroom?* Curious Academic Publishing.

- Fry, M. D., & Hogue, C. M.** (2021). Foundational psychological theories, models, and constructs. *Certified Mental Performance Consultant Essentials Resource Guide*. Association for Applied Sport Psychology.
- Fry, M. D., & Moore, E. W. G.** (2019). *Motivation in sport: Theory to application*. In M. H. Anshel (Ed.), T. Petrie, E. Labbe, S. Petruzello, & J. Steinfeldt (Assoc. Eds.), *APA handbook of sport and exercise psychology: Vol. 1. Sport psychology*. Washington DC: American Psychological Association.
- Fry, M. D., & Hogue, C. M.** (2018). Psychological considerations for children in sport and performance. In Oliver Braddick (Ed.), *Oxford Research Encyclopedia of Psychology*. New York: Oxford University Press.
- Fry, M. D.** (2014). Sport and Exercise Psychology as a Venue to Develop “Difference Makers”. In K. Vaidya (Ed.), *Exercise and Sports for the Curious: Why Study Exercise and Sports*. Curious Academic Publishing.
- Fry, M. D.** (2001). The development of motivation in children. In G. Roberts (Ed.), *Motivation in sport and exercise (2nd Ed.)*, pp. 51-78, Champaign, IL: Human Kinetics.

Book

- Fry, M. D., Gano-Overway, L., Guivernau, M., Kim, M., & Newton, M.** (2020). *A Coach’s Guide to Maximizing the Youth Sport Experience: Work Hard and Be Kind*. NY: Routledge.

PRESENTATIONS

Invited International Presentations

- Fry, M. D.** (2019). *Achievement goal perspective theory as a framework for interventions in sport and physical activity*. Autonomous University of Baja California; Ensenada, Mexico.
- Fry, M. D.** (2019). *Utilizing goal orientations as a lens to optimize athletes’ motivation*. Autonomous University of Baja California; Ensenada, Mexico.
- Fry, M. D.** (2019). *Building a caring and task-involving climate in sport through words, activities, and core values*. Autonomous University of Baja California; Ensenada, Mexico.
- Fry, M. D.** (2019). *Team building to foster positive relationships on sport teams*. Autonomous University of Baja California; Ensenada, Mexico.
- Fry, M. D.** (2016). *The power of a caring and task-involving climate in sport*. Children International; Guatemala City, Guatemala/.
- Fry, M. D.** (2005, March). *Creating a positive motivational climate in physical activity settings*. Sao Paulo, Brazil.
- Duda, J. L., & Walling, M. D.** (1993, November). *Toward a developmental theory of motivation in sport*. University of Barcelona, Barcelona, Spain.
- Walling, M. D.** (1993, November). *The examination of Nicholls’ developmental theory of motivation in the physical domain*. University of Valencia, Valencia, Spain.
- Walling, M. D.** (1993, November). *Motivational aspects in physical education for school-age Children*. National Physical Education Institute, Lleida, Spain.
- Duda, J. L., & Walling, M. D.** (1993, November). *A conceptual and empirical examination of the motivational climate created by coaches*. University of Barcelona, Barcelona, Spain.

Refereed Presentations at National Conferences

- Scott, C., **Fry, M. D.**, Wineinger, T. O., & Iwasaki, S. (2021). *Staying positive during the COVID-19 Pandemic: The impact of collegiate team climate*. Association for Applied Sport Psychology, Virtual.
- Wineinger, T. O., Rosen, D., & **Fry, M. D.** (2021). *The influence of a motivational intervention on participants' physiological measures of effort and muscle performance*. Association for Applied Sport Psychology, Virtual.
- Scott, C., **Fry, M. D.**, Wineinger, T., & Weingartner, H. (2020). *Collegiate sport club athletes' perceptions of the climate on their teams and indices of their psychological well-being*. Association for Applied Sport Psychology, Virtual.
- Wineinger, T. O., & **Fry, M. D.** (2020). *A sport psychology lab partners with the Women's Intersport Network (WIN) to optimize young girls' sport camp experiences*. Association for Applied Sport Psychology, Virtual.
- Fry, M. D.**, Claunch, J., Hogue, C. M., Iwasaki, S., & Peynetsa, I. (2019). *A coaching education collaboration for American Indian Youth Sport Coaches on the Zuni Reservation*. Association for Applied Sport Psychology. Portland, OR.
- Moore, E. W. G., & **Fry, M. D.** (2018). *Elementary physical education students' motivational climate perceptions predict goal orientations and physical education satisfaction*. International Society of Behavioral Nutrition and Physical Activity. Hong Kong.
- Pan, T. Y., Davis, A. M., Atchley, R. A., Forbush, K. T., Wallace, D. P., Savage, C. R., & **Fry, M.D.** (2018). *The longitudinal relationship between obesity and depression in children*. American Psychological Association, San Francisco, CA.
- Warlick, C., Krieschok, T., Frey, B., Kerr, B., . . . & **Fry, M. D.** (2018). *Does hope matter? Examining a popular positive psychology construct in a DBT intensive-outpatient community health population*. Association for Behavioral and Cognitive Therapies.
- Breske, M., **Fry, M. D.**, A., & Hogue, C. M. (2017). *The effects of goal priming on cortisol responses in an ego-involving climate*. Association for Applied Sport Psychology, Orlando, FL.
- Chamberlin, J., **Fry, M. D.**, & Iwasaki, S. (2017). *The influence of high school athletes' perceptions of the motivational climate on athletic identity and academic endeavors*. Association for Applied Sport Psychology, Orlando, FL.
- Easton, L., **Fry, M. D.**, & Iwasaki, S. (2017). *The relationship of fitness center members' goal orientations and perceptions of the motivational climate to variables related to well-being and motivational responses*. Association for Applied Sport Psychology, Orlando, FL.
- Fontana, M. & **Fry, M. D.** (2017). *Exploring the relationship between motivational climate and shame*. Association for Applied Sport Psychology, Orlando, FL.
- Fry, M. D.**, Thompson, J., Iwasaki, S., & Reid, C. (2017). *Bridging theory, research, and practice in youth sports: sport psychology's partnership with positive coaching alliance to enhance youth sport*. Association for Applied Sport Psychology, Orlando, FL.
- Glover, K., **Fry, M. D.**, & Weingartner, H. (2017). *Helping a women's intersport network provide a winning experience for girls in their summer sport camps*, Association for Applied Sport Psychology, Orlando, FL.

- Iwasaki, S., & **Fry, M. D.** (2017). *An exploration of the relationship among female adolescent athletes' perceptions of the motivational climate, goal orientation, refocusing, and peak ability*. International Society of Sport Psychology 14th World Congress, Sevilla, Spain.
- Tyler, E., Warlick, C., Cole, B., & **Fry, M. D.** (2017). *Collegiate student-athletes' perceptions of their sport team climate and level of hope*. Association for Applied Sport Psychology, Orlando, FL.
- Tyler, E., Warlick, C., Cole, B., & **Fry, M. D.** (2017). *Relationship among student-athletes' perceptions of the climate, locker room talk, and sexual behaviors*. Association for Applied Sport Psychology, Orlando, FL.
- Hogue, C. M., **Fry, M. D.**, & Fry, A. C. (2017). *Adolescents' Physiological Stress Responses to Motivational Climate in a Physical Education Setting*. Society for Physical Education and Health, Boston, MA.
- Claunch, J. & **Fry, M. D.** (2016). *Setting the stage for a motivational climate collaboration*. Association for Applied Sport Psychology, Phoenix, AZ.
- Chamberlin, J., **Fry, M. D.**, & Iwasaki, S. (2016). *High school athletes' perceptions of the motivational climate in their off-season Training Programs*. Association for Applied Sport Psychology, Phoenix, AZ.
- Easton, L., Iwasaki, S., & **Fry, M. D.** (2016). *The relationship of members' perceptions of the motivational climate to their Psychological well-being at a university medical center fitness facility*. Association for Applied Sport Psychology, Phoenix, AZ.
- Fry, M. D.**, Iwasaki, S., Vanorsby, H., & Breske, M. (2016). *Masters' swimmers' perceptions of the climate in their training facilities and their motivational responses*. Association for Applied Sport Psychology, Phoenix, AZ.
- Fry, M. D.**, Solomon, G., Iwasaki, S., Madeson, M., Vanorsby, H., Meisinger, R., & Haberer, J. (2016). *Division I athletes' perceptions of their team climate, mental skills, and mindfulness*. Association for Applied Sport Psychology, Phoenix, AZ.
- Hogue, C. M., **Fry, M. D.**, & Fry, A. C. (2016). *Physiological and psychological stress responses to a motivational climate intervention*. Association for Applied Sport Psychology, Phoenix, AZ.
- Fontana, M., & **Fry, M. D.** (2016). *Creating and validating the Shame in Sport Questionnaire*. Association for Applied Sport Psychology, Phoenix, AZ.
- Hogue, C. M., & **Fry, M. D.** (2016). *Leader observations of participant behaviors during a motivational climate intervention: A qualitative investigation*. Association for Applied Sport Psychology, Phoenix, AZ.
- Iwasaki, S., & **Fry, M. D.** (2016). *Male High School Athletes' Perceptions of Their Team Climate and Mindful Engagement*. Association for Applied Sport Psychology, Phoenix, AZ.
- Iwasaki, S., **Fry, M. D.**, Vanorsby, H., Breske, M. (2016). *Master swimmers' perceptions of the climate in their training facilities and their motivational responses*. Association for Applied Sport Psychology, Phoenix, AZ.
- Brown, T. C., M. S., **Fry, M. D.**, Breske, M., Iwasaki, S., & Wilkinson, T. (2015). *High school athletes' perceptions of their sport team climate and their willingness to report concussion symptoms*. Association for Applied Sport Psychology, Indianapolis, IN.
- Fry, M. D.**, Brown, T. C., Iwasaki, S., Breske, M., & Wilkinson, T. (2015). *Middle school athletes' perceptions of their sport team climate and their willingness to report concussion symptoms*. Association for Applied Sport Psychology, Indianapolis, IN.

- Fry, M. D., & Easton, L.** (2015). *Health in Action: Helping students design creative interventions onsite*. Kansas Alliance for Physical Education, Health, Recreation, & Dance, Wichita, KS.
- Fontana, M. S., Iwasaki, S., Hogue, C., Claunch, J., Poux, K., & **Fry, M. D.** (2014). *Initiating mental skills training with a high school freshman baseball*. Association for Applied Sport Psychology, Las Vegas, NE.
- Fry, A.C., **Fry, M. D.**, Sterczala, A. J., Chiu, L. Z. F., Schilling, B., & Weiss, L. W. (2014). *High power resistance exercise overreaching can be monitored with a training questionnaire*. National Strength and Conditioning Association, Las Vegas, NE.
- Medina, R, **Fry, M. D.**, & Iwasaki, S. (2014). *Youngsters' perceptions of the climate and their experiences in recreational exercise classes*. Association for Applied Sport Psychology, Las Vegas, NE.
- Rosen, D., & **Fry, M. D.** (2014). *Motivational climate and seniors' experiences in group exercise classes*. Association for Applied Sport Psychology, Las Vegas, NE.
- Hogue, C. M., & **Fry, M. D.** (2013). *A qualitative examination of participant reactions to a motivational climate intervention*. Association for Applied Sport Psychology, New Orleans, LA.
- Kwon, S., & **Fry, M. D.** (2013). *Mediational role of interest and intrinsic motivation between perceived caring climate and satisfaction and attitudes among physical education students*. Association for Applied Sport Psychology, New Orleans, LA.
- Moore, E. W. G., & **Fry, M. D.** (2013). *PE teachers' perspective on a motivational climate professional development session*. Association for Applied Sport Psychology, New Orleans, LA.
- Claunch, J. & **Fry, M. D.** (2013). *Transformative learning experience: Collegiate football coaches' perceptions of participating in a motivational climate intervention*. Association for Applied Sport Psychology, New Orleans, LA.
- Moore, E. W. G., & **Fry, M. D.** (2012). *Goal orientations, motivational climate, and outcomes in physical education across one semester*. Association for Applied Sport Psychology to held in Atlanta, GA.
- Kwon, S., & **Fry, M. D.** (2012). *The change of physical educators' enjoyment and intrinsic motivation of track and field through PST*. Association for Applied Sport Psychology, Atlanta, GA.
- Iwasaki, S., & **Fry, M. D.** (2012). *Physical education students' perceptions of the climate and their psychological well-being*. Association for Applied Sport Psychology, Atlanta, GA.
- Hogue, CM., **Fry, M.D.**, Fry, A.C., & Pressman, S. D. (2012). *Participant salivary cortisol and psychological responses to a motivational climate intervention*. Association for Applied Sport Psychology, Atlanta, GA.
- Fry, M. D.**, Brown, T. C., & Iwasaki, S. (2012). *Girls' self perceptions after participating in a positive life skills/physical activity program*. Association for Applied Sport Psychology, Atlanta, GA.
- Brown, T. C., & **Fry, M. D.** (2012). *Results of a caring, task-involving climate intervention at a recreation center*. Association for Applied Sport Psychology, Atlanta, GA.
- Kwon, S., & **Fry, M. D.** (2011). *The effects of athletes' self-management on their self-confidence*. Association for Applied Sport Psychology, Honolulu, HI.
- Andre, M. J., Fry, A.C., Gallagher, P. M., Vardiman, P., **Fry, M. D.** Kudrna, B., Gandy-Moody,

- N., & McCartney, M. (2011). *The effects of a pre-workout caffeine supplement on endogenous growth hormone levels*. A presentation made at the meeting of the National Strength and Conditioning Association, Las Vegas, NE.
- Hogue, C. M., Iwasaki, S., & **Fry, M. D.** (2011). *A case study of a physical activity/mental skills training intervention with a young athlete*. Association for Applied Sport Psychology, Honolulu, HI.
- Iwasaki, S., & **Fry, M. D.** (2011). *The exploration of motivational climate in a youth sport basketball camp*. Association for Applied Sport Psychology, Honolulu, HI.
- Fry, M. D.** (2011). *From the Strong Girls' viewpoints: Research results from semester 1*. Association for Applied Sport Psychology, Honolulu, HI.
- Fry, M. D.** (2011). *The exercise climate: An introduction to the research on examining task-involving and caring climates in the exercise domain*. Association for Applied Sport Psychology, Honolulu, HI.
- Fry, M. D.,** Hogue, C. M., Sauer, S. (2011). *Using digital storytelling as a creative tool in health*. American Alliance of Health, Physical Education, Recreation, & Dance, San Diego, CA.
- Kwon, S., & **Fry, M. D.** (2010). *Relationship of exercisers' perceptions of the motivational climate to their flow experience*. Association of Applied Sport Psychology, Providence, RI.
- Iwasaki, S., Merczek, K., & **Fry, M. D.** (2010). *Young athletes' experiences in a volleyball camp*. Association of Applied Sport Psychology, Providence, RI.
- Iwasaki, S., Sogabe, A., **Fry, M. D.,** & Christensen, E. (2010, June). *Differences in aggression and social skills among judo and non-judo practitioners*. American College of Sports Medicine, Baltimore, MD.
- Hogue, C. M., **Fry, M. D.,** & Brown, T. C. (2010). *Incorporating team building activities in a summer day camp for children: Lessons learned*. Association of Applied Sport Psychology, Providence, RI.
- Brown, T. C., & **Fry, M. D.** (2010). *Caring climate intervention for sport skills and fitness camp leaders*. Association of Applied Sport Psychology, Providence, RI.
- Brown, T. C., & **Fry, M. D.** (2010). *Teaching life skills in a physical activity after-school program*. American School Health Association, Kansas City, MO.
- Moore, E. W., & **Fry, M. D.** (2009). *The effect of a caring and task-involving climate on student empowerment and ownership in physical activity classes*. Association for Applied Sport Psychology, Salt Lake City, UT.
- Kwon, S., & **Fry, M. D.** (2009). *Members' perceptions of their fitness club climate and their exercise flow*. Association for Applied Sport Psychology, Salt Lake City, UT.
- Hogue, C. M., **Fry, M. D.,** & Dodd, R. (2009). *Athletes' perceptions of the climate at their training centers and their motivational responses*. Association for Applied Sport Psychology, Salt Lake City, UT.
- Fry, M. D.** (2009). *From theory to practice: Creating positive and caring environments in the real world*. Association for Applied Sport Psychology, Salt Lake City, UT.
- Brown, T. C., & **Fry, M. D.** (2009). *Students' perceptions of their exercise class environment and their psychological well-being*. Association for Applied Sport Psychology, Salt Lake City, UT.
- Marshall, K., Stephens, L., Grindle, V., **Fry, M. D.,** & Li, Y. (2009). *Mental imagery and EEG*

- activity in elite and novice collegiate soccer players.* Association for Applied Sport Psychology to be, Tampa, FL.
- Brown, T. C., & **Fry, M. D.** (2009). *Participants' perceptions of a caring and positive climate in their exercise classes.* American Alliance of Health, Physical Education, Recreation, & Dance, Tampa, FL.
- Fry, M. D.**, Dodd, R. K., & Brown, T. C. (2008). *Young athletes' perceptions of their coaches' and teammates' caring and uncaring behaviors.* Association for Applied Sport Psychology, St. Louis, MO.
- Binkley, S.E., & **Fry, M. D.** (2007). *The relationship of college students' perceptions of their BMI and weight status to their physical self-concept.* Association for Applied Sport Psychology, Louisville, KY.
- Smith, H., **Fry, M.D.**, Li, Y., & Weiss, L. (2006). *The relationship of anxiety and self-confidence to treadmill exercise tolerance tests performance by sedentary obese women.* Association for the Advancement of Applied Sport Psychology, Miami, FL.
- McCarty, L., **Fry, M.D.**, & Curly, C. (2006). *The relationship of a caring climate to motivational responses and psychological well-being in youth baseball.* Association for the Advancement of Applied Sport Psychology, Miami, FL.
- Gano-Overway, L. A., Newton, M., Magyar, AM., **Fry, M. D.**, Kim, M., & Guivernau, M. (2006). *Caring, self-regulatory efficacy, empathic efficacy, and prosocial/antisocial behaviors in a physical activity setting.* Association for the Advancement of Applied Sport Psychology, Miami, FL.
- Fry, A.C., Haneishi, K., Moore, C.A., Schilling, B.K., Li, Y., & **Fry, M.D.** (2006). *Cortisol and stress responses during a game and practice in female collegiate soccer players.* National Conference on Student Assessment, Washington, D.C.
- Bricker, J. B., & **Fry, M. D.** (2005). *The influence of injured athletes' perceptions of social support from their certified athletic trainers on athletes' beliefs about rehabilitation.* Association for the Advancement of Applied Sport Psychology, Vancouver, British Columbia, Canada.
- Magyar, M., Guivernau, M., Gano-Overway, L., Newton, M., **Fry, M.D.**, Kim, M., & Watson, D. (2005). *Exploring the relationship between the caring climate and achievement goal theory among underserved youth in physical activity.* American Alliance of Health, Physical Education, Recreation & Dance, Chicago, IL.
- Fry, M.D.**, & Newton, M. (2004, September). *The development of the Caring Climate Questionnaire.* Association for the Advancement of Applied Sport Psychology, Minneapolis, MN.
- Smith, S., **Fry, M.D.**, & Ethington, C. (2004, September). *The effect of female athletes' perceptions of their coaches' behaviors on their perceptions of the motivational climate.* Association for the Advancement of Applied Sport Psychology, Minneapolis, MN.
- McCay, K., & **Fry, MD.** (2004, September). *The examination of goal perspective theory in relationship to measures of psychological well-being.* Association for the Advancement of Applied Sport Psychology, Minneapolis, MN.
- McCay, K., & **Fry, M.D.** (2004, March). *Predictors of adolescent depression: The role of physical activity and body image.* Society of Behavioral Medicine, Baltimore, MD.
- Henry, H., & **Fry, M.D.** (2003, October). *Corporate fitness members' perceptions of the*

- motivational climate, their intrinsic motivation, and perceptions of being valued by their employer.* Association for the Advancement of Applied Sport Psychology, Philadelphia, PA.
- Fry, M.D.,** Pittman, L., McCay, K., & Wendell, M. (2003, October). *A qualitative examination of underserved 4th grade girls' views about physical education.* Association for the Advancement of Applied Sport Psychology, Philadelphia, PA.
- Fry, M. D.,** Abma, C., Wood, J., & Melland, B. (2002, October). *The effects of an after-school physical activity and life skills program on 4th graders' self concept, motivational perspectives, and fitness levels.* Association for the Advancement of Applied Sport Psychology, Tucson, AZ.
- Abma, C., & **Fry, M. D.** (2002, October). *The effects of an imagery intervention on the trait confidence levels of female college volleyball players.* Association for the Advancement of Applied Sport Psychology, Tucson, AZ.
- Duda, J.L., Smith, M., & **Fry, M. D.** (2002, June). *An examination of learned helpless responses among young children engaged in physical tasks.* North American Society for the Psychology of Sport and Physical Activity, Baltimore, MD.
- Newton, M., **Fry, M.D.,** & Bernhardt, P. (2001, October). *Examination of the interactive relationship of goal orientations, perceptions of the motivational climate, and perceived ability in youth tennis players.* Association for the Advancement of Applied Sport Psychology, Orlando, FL.
- Abma, C. & **Fry, M. D.** (2001, May). *A qualitative examination of underserved 8th grade female students' attitudes about physical education.* 10th World Congress of Sport Psychology held in Skiathos, Greece.
- Lattimore, D., **Fry, M. D.,** & Balas, C. (2000, October). *Students' perceptions of the motivational climate and their motivational responses in physical education.* Association for the Advancement of Applied Sport Psychology, Nashville, TN.
- Fry, M. D.,** Lattimore, D., & Balas, C. (2000, October). *A developmental examination of children's accuracy in judging their physical ability in physical education.* Association for the Advancement of Applied Sport Psychology, Nashville, TN.
- Fry, M.D.,** & Newton, M. (1999, September). *Goal orientations, perceptions of the motivational climate, and motivational responses of urban youth tennis players.* Association for the Advancement of Applied Sport Psychology, Banff, Canada.
- Fry, M. D.,** Lattimore, D., & Balas, C. (1999, September). *A developmental analysis of conceptions of effort and physical ability among underserved youth.* Association for the Advancement of Applied Sport Psychology, Banff, Canada.
- Harber, M. P., **Fry, M. D.,** & Fry, A. C. (1998). *Sources of stress identified by elite collegiate weightlifters.* A paper presented at the annual meeting of the National Strength and Conditioning Association, Nashville, TN.
- Fry, M. D.,** Fry, A. C., & Newton, M. (1997, September). *Sources of stress identified by elite junior weightlifters.* Association for the Advancement of Applied Sport Psychology, San Diego, CA.
- Newton, M., **Fry, M. D.,** & Sandberg, J. (1997). *Goal orientations and purposes of sport and beliefs concerning success among senior Olympians.* North American Society for the Psychology of Sport and Physical Activity, Denver, CO.
- Fry, M. D.** (1997, March). *Symposium: Goal perspectives in physical education and sport:*

- Theory into practice*. American Alliance for Health, Physical Education, Recreation, and Dance, St. Louis, MO.
- Fry, M. D.** (1996, October). *Children's understanding of luck and ability: A developmental analysis*. Association for the Advancement of Applied Sport Psychology, Williamsburg, VA.
- Fry, M. D.** (1996, October). *The motivational climate in sport and physical education: An introduction to theory and research*. Association for the Advancement of Applied Sport Psychology, Williamsburg, VA.
- Fry, M. D., & Fry, A. C.** (1996, June). *Goal perspectives and motivational responses of elite junior weightlifters*. National Strength and Conditioning Association, Atlanta, GA.
- Fry, M. D., & Alexander, C.** (1996, June). *Children's understanding of task difficulty: A developmental analysis*. North American Society for the Psychology of Sport and Physical Activity, Cleveland's House, Canada.
- Duda, J. L., & Walling, M. D.** (1995, October). *Views about the Motivational climate and their self perceptions/affective correlates: The case for young elite female gymnasts*. Association for the Advancement of Applied Sport Psychology, New Orleans, LA.
- Newton, M. L., & Walling, M. D.** (1995, October). Goal orientations and beliefs about the causes of success among senior Olympic games participants. North American Society for the Psychology of Sport and Physical Activity, Asilomar, CA.
- Walling, M. D.** (1994, October). *Developmental differences in children's views regarding physical competence*. Association for the Advancement of Applied Sport Psychology, Lake Tahoe, NV.
- Walling, M. D., & Duda, J. L.** (1994, June). *Children's understanding of effort and ability in the physical domain*. North American Society for the Psychology of Sport and Physical Activity, Clearwater Beach, FL.
- Walling, M. D., Duda, J. L., Newton, M., & White, S.** (1993, October). *The Task and Ego Orientation in Sport Questionnaire: Further analysis with youth sport participants*. Association for the Advancement of Applied Sport Psychology, Montreal, CANADA.
- Walling, M. D., & Duda, J. L.** (1993, March). *Goals and their associations with beliefs about success in and perceptions of the purpose of physical education*. American Alliance for Health, Physical Education, Recreation, and Dance, Washington, DC.
- Walling, M. D.** (1993, February). *Children's conceptions of effort and ability in the physical domain: A dissertation in progress*. Midwest Sport Psychology Symposium, Miami University, Oxford, OH.
- Walling, M. D., Duda, J. L., & Crawford, T.** (1992, October). *The relationship between goal orientations and positive attitudes toward sport and exercise among young athletes*. Association for the Advancement of Applied Sport Psychology, Colorado Springs, CO.
- Walling, M. D., Duda, J. L., & Crawford, T.** (1992, June). *The psychometric properties of the perceived motivational climate in sport questionnaire: Further investigation*. North American Society for the Psychology of Sport and Physical Activity, Pittsburgh, PA.
- Walling, M. D., Crawford, T., Duda, J. L., & Wigglesworth, J.** (1992, April). *Are we having fun yet and will we want to play again?: The interrelationships between goal perspectives and other motivational variables in youth sport athletes*. American Alliance for Health, Physical Education, Recreation, and Dance, Indianapolis, IN.
- Walling, M. D., & Catley, D.** (1992, April). *Jack and Jill in physical education class: Do they*

think their instructor treats them differently? American Alliance for Health, Physical Education, Recreation, and Dance, Indianapolis, IN.

Walling, M. D., & Catley, D. (1992, February). *Sex role stereotyping among college instructors and students' perceptions of instructor gender bias*. Midwest Sport Psychology Symposium, Purdue University, West Lafayette, IN.

Walling, M. D., Catley, D., & Taylor, A. (1991, June). *The interrelationships between goal perspectives, perceived competence, and indices of intrinsic motivation*. North American Society for the Psychology of Sport and Physical Activity, Asilomar, CA.

Walling, M. D. (1991, April). *Learned helplessness: A case study of a sixth-grade physical education student*. American Alliance for Health, Physical Education, Recreation and Dance, San Francisco, CA.

Webinar

Fry, M. D., & Hogue, C. M. (2019). *Theories and Models in Sport Psychology: A Review*. Association for the Advancement of Applied Sport Psychology.

State/Regional Presentations

Gray, R., & Fry, M. D. (2020). *Employing a buddy system to foster physical activity among college students with a physical disability*. Midwest Sport Psychology Symposium, Illinois State University.

Wineinger, T., & Fry, M. D. (2020). A collaboration between a sport psychology lab with a youth sport organization: Helping WIN create an optimal sport experience. Midwest Sport Psychology Symposium, Illinois State University.

Fry, M. D. (2018). *Three ideas for incorporating sport psychology into practice and competition*. Greenbush Coaches' Workshop.

Fry, M. D. (2018). *Three more ideas for incorporating sport psychology into practice and competition*. Greenbush Coaches' Workshop.

Fry, M. D. (2017). *Sport Psychology: Setting a Positive Tone for the Team* (Sessions A & B, repeated). Greenbush Fall Coaches' Workshop.

Fry, M. D. (2016). *KU Graduate Programs in Health, Sport & Exercise Science*. Morehouse College Graduate Program Fair (February, 2016).

Fry, M. D. (2016, Fall). *Keys to Helping Athletes Develop Strong Mental Skills: The Role of Sport Psychology*. Keynote for Greenbush Coaching Conference, Eudora, KS.

Fry, M. D. (2016, Spring). *Working with and bringing out the best in difficult athletes*. Greenbush Coaching Conference, Eudora, KS.

Fry, M. D. (2015). *Bringing out the Best in Every Swimmer: The Contribution of Sport Psychology*. Keynote delivered to US Master Swim at their National Conference; Kansas City, KS.

Fry, M. D. (2015). *Caring Climates for Physical Activity Settings*. University of Milwaukee, Wisconsin.

Fry, M. D. (2015). *Creating a Caring Climate to Maximize Athletes' Potential On and Off the Field*. Keynote presented at the Positive Coaching Alliance Trainers' Institute.

Fry, M. D. (2015). *Maximizing Athletes' Potential On and Off the Field*. Keynote delivered to X's and O's Coaching Education Workshop, Emporia State University, Emporia, KS.

Fry, M. D. (2015). *Setting the Stage for Coaches to Optimize Athletes' Motivation*. Big XII invited lecture at Texas Christian University; Fort Worth, TX.

- Fry, M. D.,** Moore, E., W., G., Iwasaki, S., Fontana, M., Hogue, C., Claunch, J., & McGhee, R. (2012). *Building Mentally Strong Athletes: Ideas for Incorporating Mental Skills Training with Sport Teams*. Kansas Alliance for Health, Physical Education, Recreation, & Dance in Lawrence, KS.
- Fry, M. D.** (2012). *Strong Girls: Hearing About the Benefits of a Physical Activity/Positive Life Skills Program from the Leaders and Kids*. Kansas Alliance for Health, Physical Education, Recreation, & Dance in Lawrence, KS.
- Moore, E. W., & **Fry, M. D.** (2010). *Kids don't care what you know until they know that you care: Tips for building caring environments*. Kansas Alliance for Health, Physical Education, Recreation & Dance, Wichita, KS.
- Brown, T., **Fry, M. D.**, & Hogue, C. (2010). *Positive life skills for every walk of life*. Kansas Alliance for Health, Physical Education, Recreation & Dance, Wichita, KS.
- Fry, M. D.**, Brown, T., Moore, E. W., Hogue, C., Sauer, S., & Beyer, J. (2010). *Team time: Team building activities for any group to use and process*. Kansas Alliance for Health, Physical Education, Recreation & Dance, Wichita, KS.
- Williamson, K., & **Fry, M. D.** (2009). *Bringing out the best in your athletes: Making sport fun again while enhancing your team's competitive edge*. Kansas Alliance for Health, Physical Education, Recreation & Dance, Pittsburg, KS.
- Moore, W. E., & **Fry, M. D.** (2009). *Are we building character or characters?: Strategies for promoting integrity among young athletes*. Kansas Alliance for Health, Physical Education, Recreation & Dance held in Pittsburg, KS.
- Brown, T. C., & **Fry, M. D.** (2009). *Ideas to implement in a youth physical activity life skills program*. Kansas Alliance for Health, Physical Education, Recreation and Dance held in Pittsburg, KS.
- Fry, M. D.**, Dodd, R., Brown, T. C. (2008). *Getting them interested and coming back: Creating a positive and caring environment in exercise settings*. Kansas Association of Health, Physical Education, Recreation and Dance, Emporia, KS.
- Fry, M. D.** (2005). *Creating a Positive Climate and Optimizing Motivation in Physical Education & on Sport Teams*. An invited presentation for the Lutheran Schools Midsouthern Regional Conference held in Memphis, TN.

SUPPORT

EXTERNAL FUNDING	AGENCY/SOURCE	AMOUNT	PERIOD
Creating Optimal Climate for Youth With Congenital Heart Disease	American Council on Exercise	\$2400	2021-2022
Climate Free Throw Intervention	Association for Applied Sport Psychology	\$4980	2021-2022
Strong Girls	Association for Applied Sport Psychology	\$4625	2019-2020
Rock Chalk, Zuni	Running Strong for American Indian Youth	\$5000	2017-2018
KU PCA Initiative	Positive Coaching Alliance/	\$75,000	2017-2020

David and Margaret Shirk Physical Education Programs Fund			
Strong Girls: A positive life skills intervention for 3 rd -5 th girls	Kohl's Cares for Kids	\$4000	2011
Students' salivary stress responses when juggling in two distinct motivational climates	Association of Applied Sport Psychology	\$2800	2010-11
Effects of resistance exercise and a Pre-workout dietary supplement on Physiological adaptations	Labrada	\$5000	2010
Strong Girls: A positive life skills physical activity intervention for elementary school girls	Association of Applied Sport Psychology	\$3220	2009-10
Fostering & maintaining motivation among urban youth tennis players	United States Tennis Association	\$10,000	1997-98
EXTERNAL PROPOSALS NOT FUNDED	AGENCY/SOURCE	AMOUNT	PERIOD
Children's International Guatemala & US Collaboration	ASportsUnited: International Sports Programming Initiative	\$224,953	2012
Dare to Care: Tackling Childhood Obesity	Albert Foundation	\$46,000	2013
Strong Girls: A positive life skills/physical activity program	Live-Well Lawrence-Kansas Health Foundation	\$5000	2011
Strong Girls: A positive life skills/physical activity program for girls	Payless Foundation	\$15, 000	2011
Strong Girls: A positive life skills/Physical activity program for children	Sprint Foundation	\$168, 000	2011
SUPPORT			
INTERNAL FUNDING	AGENCY/SOURCE	AMOUNT	PERIOD
Research Excellence Initiative" A Collaboration to Train Biology Lab Instructors to Create a Caring & Task Involving Climate	University of Kansas; College of Liberal Arts & Sciences	\$30, 000	2019-2020 (under review)

Strong Girls: A community life skills/physical activity research and service project for elementary girls in Lawrence.	University of Kansas KU SOE Academic Year Research Support	\$8000	2011
Examining the motivational climate in a national fitness company.	University of Kansas Faculty Research Grant	\$5000	2010
Strong Girls: A physical activity and life skills intervention for faculty adolescent girls.	University of Kansas Research Grant	\$6000	2009
A team building/mental skills intervention for children enrolled in a summer camp.	University of Kansas New Faculty Research Grant	\$8000	2008
The relationship between young athletes' perceptions of a caring climate on their sport teams to their motivational responses	University of Memphis Faculty Research Grant	\$6000	2005
Effect of a strength training intervention for underserved elementary students	University of Memphis Faculty Research Grant	\$4000	2000-02
An examination of black females' perceptions of physical activity	Center for Research on Educational Policy, University of Memphis	\$5000	2000
Children's perceptions of ability and their motivational responses in physical education class.	Center for Research on Educational Policy, University of Memphis	\$3800	1999
The motivational implications of students' understanding of effort and ability in the physical domain.	University of Memphis Faculty Research Grant	\$4000	1995
Children's understanding of luck and ability, and task difficulty.	University of Memphis Faculty Research Grant	\$3000	1994
Developmental differences in children's conceptions of ability, effort, and task difficulty in the physical domain.	Purdue Foundation Grant	\$9,900 (per year for 2 years)	1992-94

Memberships in Professional Organizations

American Psychological Association (2017-present)

American Alliance for Health, Physical Education, Recreation, and Dance (1988-2017).

Association for Applied Sport Psychology, Member (1991-present).

Kansas Alliance for Health, Physical Education, Recreation, & Dance (2008-present).

North American Society for the Psychology of Sport and Physical Activity, Member (1988-2000).

Indiana Association for Health, Physical Education, Recreation, and Dance, Member (1993-1994).

Tennessee Association for Health, Physical Education, Recreation, and Dance, Member (1994-2000).

Teaching Responsibilities:**Undergraduate**

EXSS 3307 Psychosocial Aspects of Sport [UMemphis]

EXSS 3450 Psychological Aspects of Exercise [UMemphis]*

EXSS 4605 Internship in Exercise & Sport Science [UMemphis]

EXSS 4999 Senior Project in Health, Physical Education, & Recreation [UMemphis]*

HSES 385 Psychological Aspects of Exercise [KansasU]*

HSES 440 Applied Sport Psychology [KansasU]*

Graduate

EXSS 7173 Sport and Exercise Psychology [UMemphis]*

EXSS 6903 Developmental Perspectives in Youth Sport [UMemphis]*

EXSS 7133 Current Readings: Motivation in Physical Activity Settings [UMemphis]*

EXSS 7907 Special Topics: Applied Sport Psychology [UMemphis]*

HSES 798 Special Course: Creating a Positive Environment in Physical Activity Settings [KansasU]*

HSES 798 Special Course: Sport Psychology Within Youth Sport [KansasU]*

HSES 798 Special Course: Advanced Sport Psychology [KansasU]**

HSES 804 Sport Psychology [KansasU]**

HSES 806 Stress Management [KansasU]*

HSES 823 Behavior Modification [KansasU]

HSES 892 Psychological Foundations of Sport and Physical Activity [KansasU] *

HSES 982 Research Ethics [KansasU]

*Courses I developed.

Community Presentations

Fry, M. D. (November, 2017). *Lead campus participation in celebration of World Kindness Day.*

Fry, M. D. (June, 2016). *Mental Skills: A Key Ingredient for Excellence in Cross Country.* Workshop for Eudora High School Cross Country Team; Eudora, KS.

Fry, M. D. (2016). *Creating a Caring and Task-Involving Climate in CI's Game On Program.* A presentation for CI Employees at the International Headquarters Office in Kansas City, KS.

Fry, M. D. (2016). *Team Building: The Potential for Children International.* Workshop for Children International Employees at the National Headquarters office in

Kansas City, KS.

- Fry, M. D.** (2015). *Activities and Strategies to Help Children and Adolescents Thrive in Physical Activity Settings*. Topeka Parks and Recreation Conference; Topeka, KS.
- Fry, M. D.** (2015). *Fostering Wellness at the Worksites*. Live Well Lawrence; Lawrence, KS.
- Fry, M. D.** (2011, Nov.). Guest panelist for KU Alternative Breaks, University of KS
- Fry, M. D.** (2011, Nov.). Guest speaker for Multicultural Education, University of KS.
- Fry, M. D.** (2011, Nov.). Guest speaker for Coaching Football Class, University of KS.
- Fry, M. D.** (2011, Oct.). Guest speaker for KU Bowling Team, University of KS.
- Fry, M. D.** (2011, April). Guest speaker for Positive Psychology Class, University of KS.
- Fry, M. D.** (2011, March). Guest speaker for Coaching Softball Class, University of KS.
- Fry, M. D.** (2011, Feb.). Guest speaker for Coaches Meeting for Sunflower Soccer Association, Topeka, KS.
- Fry, M. D.** (2010). Guest speaker for Healthy Musicians Class (2-hour workshop), University of KS.
- Fry, M. D.** (2009). Guest speaker for Life Skills Class at Atchison Community High School, KS.
- Fry, M. D.** (2005, Feb.). Caring communities within physical activity settings. An invited presentation to a Memphis Chapter of the Philanthropic Educational Organization.
- Fry, M. D.** (2001-present). Coordinate mental skills and physical activities for youngsters (i.e., cancer patients & their siblings) at Target House in Memphis, TN. Have conducted approximately 12 1.5-2 hour sessions.
- Fry, M. D.** (2002, July 17th). The role of sport psychology in the prevention of and rehabilitation after injury. A presentation for coaches attending the Memphis Interscholastic Athletic Association Conference.
- Fry, M. D.** (May, 2002). Presented stress management session for Cancer Support Group at Pentecostal Church in Memphis, TN.
- Fry, M. D.** (2001-present). Coordinate mental skills and physical activities for youngsters (i.e., cancer patients & their siblings).
- Fry, M. D.** (2000 & 2001, March-April). Coordinator for Short Putts to Spring Workshops for the MidSouth Junior Golf Association. Presenter for 2 of the 5 workshops on team building skills.
- Fry, M. D.** (1996). Optimizing arousal levels in tennis. A presentation to the Women's tennis team at The University of Memphis.
- Fry, M. D.** (1995, October). *Mental skills training in track and field*. A presentation to the Women's track and cross country teams at The University of Memphis.
- Walling, M. D.** (1995, February). *Maximizing your children's motivation in swimming: An educational sport psychology perspective*. A presentation to the Booster Club parents of the University of Memphis Swim Club.
- Walling, M. D.** (1995, February). *Fostering effort and enjoyment with your tennis players: A sport psychology perspective*. An invited talk which was part of a workshop sponsored by the USTA, the National Umpires Association and the Memphis City Schools for high school tennis coaches.
- Walling, M. D.** (1994). *Sport psychology with a developmental twist*. An invited presentation to the Sport Psychology Colloquium, Department of Psychology, University of Memphis.
- Walling, M. D.** (1993, October). *The influence of parents on young gymnasts' levels of stress and motivation*. An invited presentation sponsored by the United States Gymnastics Federation, Indianapolis, IN.

Walling, M. D.(1992, October). *The mechanics of sport psychology: What we do and how it impacts you and your family.* Presentation to the Purdue Mechanical Engineering Advisory Board Spouses.

Walling, M. D. (1991, July). *Stress Management.* Invited presentation sponsored by the National Institute for Fitness and Sport.

Walling, M. D., & Newton, M. (1991, October). *Sport Psychology for the Weekend Athlete.* Invited presentation sponsored by the Eli Lilly Corporation, Indianapolis, IN.

Departmental/University Service

KU Faculty Research Grant Review Committee (2021-2023)

Wolfe Teaching Award, School of Education (2021)

KU Title IX Committee (2020)

Kansas Women's Leadership Institute, Net-Walk Mentor Participant (2016-2017).

KU Certificate in Sport Committee (2017-2018).

KU Center for Undergraduate Research, Advisory Board (2016-2018).

KU Calendar Committee (2016-2018; Chair, 2017-2019).

SOE Scholarship & Awards Committee (2013-2019).

SOE Convocation Volunteer (2009-present).

HSES Faculty Search Committees (2009, 2010, 2012, 2013, 2014, 2015).

HSES Scholarship & Awards Committee (2010-2013), University of Kansas.

HSES Personnel Committee (2011-present), University of Kansas.

HSES Graduate Curriculum Committee (2008-2014), University of Kansas.

SOE Diversity Committee (2013-2016), University of Kansas.

SOE Technology Committee (2011-2013), University of Kansas.

SOE Governance Committee (2011-2013), University of Kansas.

SOE Personnel Committee (2007-2010), University of Kansas.

University of Kansas, Dean of the School of Education 5-year Review Committee (2014).

President's Tenure & Promotions Appeal Committee. (2007-2009). The University of Memphis.

HSS Community Affairs Committee (2004-2006). The University of Memphis.

Coordinator of Achievement Motivation Seminar (2003). The University of Memphis, Dept. HMSE.

PETE Unit Head, Dept. of HMSE, University of Memphis (2001-2003).

HMSE Tenure and Promotion Committee (1999-2000; Chair 2000-2001), The University of Memphis.

HMSE Coordinator for the Science Olympiad sponsored by The University of Memphis for high school honor science students in the Western portion of TN (1995-1999).

Dean's Council for Teacher Education (1994-1995), University of Memphis.

HMSE Material Resources Committee (1994-1995; 1998-2000, 2002; 2000-2001, Chair), University of Memphis.

HMSE Ad Hoc Committee on Internships (1994-1995), University of Memphis.

HMSE Recruitment Committee (1995-1996).

HMSE Physical Education Teacher Education Unit (1994-present; Unit Head-2001-2002), University of Memphis.

HMSE Ad Hoc Committee on Proposing a PhD Program (1995-1997).

HMSE Undergraduate Council (1994-95 & 1997-1998)

HMSE Academic Council (1996-1998).

HMSE Graduate Studies and Research Council (1995-2001; chair from 1996-1998)

College of Education Graduate Council (1996-1998).

Graduate Coordinator for the Department of Human Movement Sciences and Education, (1996-1998).

Service to National Organizations

Creating a Caring Climate Within and Across an Athletic Program, Positive Coaching Alliance Workshop (2020).

Subject Matter Expert for the Certification Exam Committee, Association of Applied Sport Psychology (2018).

Member of Ad-Hoc Committee to Study Future of AASP, Association of Applied Sport Psychology (2012-2015).

Member of the Social Psychology Section Committee, Association for the Advancement of Applied Sport Psychology (AAASP). Appointed for a 3-year-term, 1996-99; 2001-2003.

Member of AAASP Dissertation Award Committee (1998 & 2002).

Member of Editorial Board for *Physical Activity Today* (American Alliance for Health, Physical Education, Recreation and Dance publication), 1997-2001.

Member of Sport Psychology Program Area Review Committee for the 1996 Annual Meeting of the North American Society for the Psychology of Sport and Physical Activity (NASPSA).

Executive Board Member, Association for the Advancement of Applied Sport Psychology, (2004-2006).

Member of Program Review Committee, American Alliance of Health, Physical Education, Recreation & Dance (2009- 2017); Chaired committee in 2010.

Member of Program Review Committee, Association for Applied Sport Psychology (2008-present).

Reviewing/Editing Responsibilities

Associate Editor (2009-2012); Editorial Board Member (2000-2009; 2013-present) and Reviewer (1992-1999). *Journal of Applied Sport Psychology*.

Associate Editor. *Sport Psychology in Action* (2008-present).

Editorial Board Member. *Sport, Exercise, and Performance Psychology* (2011-present; American Psychological Association Journal).

Sport & Exercise Psychology Section Editor (2003-2006) and Reviewer (1994-present). *Research Quarterly for Exercise and Sport*.

Co-editor with David R. Black of Abstracts Column. *Peer Facilitator Quarterly* (1993-1994).

Reviewer. *Education and Treatment of Children* (1993-1995).

Reviewer. *Journal of Health Education* (1993-1995).

Reviewer. *The Sports Psychologist* (1997-present).

Reviewer. *International Journal of Sport Psychology*. (1997-present).

Reviewer. *Journal of Sport and Exercise Psychology* (1993-present).

Reviewer. *Journal of Strength and Conditioning* (1998-present).

Reviewer & Editorial Board Member. *Journal of Strength and Conditioning Research* (Reviewer, 1996-present; Editorial Board Member, 1996-1998).

Contributor to Community/National Forum

- Fry, M. D., & Brown, T. C.** (2021-present). Co-Directors of Strong Girls, an after-school physical activity and lifeskill program for adolescent girls. University of Kansas.
- Fry, M. D.** (Fall, 2017). *Participating in a Positive Sport Climate Reaps Many Benefits for Young People*. Column written for the National Dropout Prevention Coalition-Newsletter.
- Fry, M. D.** (2017). *The Power of the Positive*. Contributor to the Positive Coaching Alliance Video.
- DeAngelis, T.** (2016) *Psychologists' research points ways to keep youth athletes in sports*. American Psychological Association Monitor Newsletter [KU Sport & Exercise Psychology Lab featured]
- Fry, M.D.** (2003). *Coaches' rant can bench kids for life*. Invited guest column in the Viewpoint Section of the Commercial Appeal, April 7, 2003.
- Fry, M.D.** (2003, March). *Strategies for creating a task-involving climate with underserved youth*. An invited presentation to the Dept. of EXSS at the University of Mississippi.
- Fry, M.D.** (2002). Presenter of workshop entitled: *The Climate Counts: Techniques and Strategies for Fostering a Task-Involving Motivational Climate*.
- Fry, M. D., & Newton, M. L.** (1997, December). *TARGETing success in volleyball: Creating a positive motivational climate*. Invited speaker at the American Volleyball Coaches Association (AVCA) National Convention preceding the NCAA Final Four Tournament in Spokane, WA.
- Fry, M. D.** (1996, April). Invited speaker at Colonial Junior High's Career Day.
- Fry, M. D.** (February, 1995 & October, 1996). Invited guest on Eddie Cantler's talk-show, "The Trainer's Corner" seen on the Library Channel, Memphis, TN.
- Walling, M. D.** (1995). Choosing quality youth sport programs for children: The critical role of parents. *Journal of Kinetic Arts*, 1 (5).

Applied Sport Psychology Experiences

- Fry, M. D.** (2008-present). Mental Skills Interventions with high school & university athletes.
- Fry, M. D.** (2013-2018). Mental Skills Intervention with a high school baseball team.
- Fry, M. D.** (2009-2011). Mental Skills Intervention with a youth baseball team.
- Fry, M. D.** (2008-2010). Mental Skills Intervention with a Division 1 collegiate volleyball team.
- Fry, M.D.** (2006-2007). Mental Skills Intervention with a high school basketball team.
- Fry, M. D.** (2006). Mental Skills Intervention with a Division 1 cross country team.
- Fry, M.D.** (2005-2006). Mental Skills activities with a high school golfer.
- Fry, M.D.** (2003). Mental Skills Activities provided to the Dolphins, a youth synchronized swim program in Memphis.
- Fry, M.D.** (2001-2007). Mental Skills Games and Activities Sessions provided to residents of Target House (i.e., long-term treatment patients at St. Jude Hospital).
- Fry, M. D.** (2001, Spring). The Strength Club. An after-school mental skills training program for elementary-aged children.
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Walling, M. D. (1992). Consultation with High School Tennis Player Over a Season.

Chair, Graduate Student Advisory Council, Department of Health, Kinesiology, and Leisure Studies at Purdue University, 1991-1992.

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

B.P.J. by her next friend and mother, HEATHER JACKSON,

Plaintiff,

v.

WEST VIRGINIA STATE BOARD OF EDUCATION, HARRISON COUNTY BOARD OF EDUCATION, WEST VIRGINIA SECONDARY SCHOOL ACTIVITIES COMMISSION, W. CLAYTON BURCH in his official capacity as State Superintendent, DORA STUTLER in her official capacity as Harrison County Superintendent, and THE STATE OF WEST VIRGINIA,

Defendants,

and

LAINY ARMISTEAD,

Defendant-Intervenor.

Civil Action No. 2:21-cv-00316

Hon. Joseph R. Goodwin

**REBUTTAL EXPERT REPORT AND DECLARATION OF
ARON JANSSEN, M.D.**

I, Aron Janssen, M.D., hereby declare as follows:

1. I have been retained by counsel for Plaintiffs as an expert in connection with the above-captioned litigation. I submit this expert declaration based on my personal knowledge.
2. The purpose of this declaration is to respond to the expert reports of Dr. Stephen Levine, MD and Dr. Stephen Cantor, Ph.D., submitted by Defendants in this case, which misrepresent current standards of care for treating gender dysphoria in children and adolescents, the practices commonly known as gender-affirming care, and the scientific data supporting those practices.

3. I have knowledge of the matters stated in this declaration and have collected and cite to relevant literature concerning the issues that arise in this litigation in the body of this declaration.

4. In preparing this declaration, I reviewed: the Complaint in this action, the expert reports of Dr. Joshua D. Safer, M.D., and Dr. Deanna Adkins, M.D., submitted by Plaintiff, and the expert reports of Dr. Levine and Dr. Cantor submitted by Defendants. I also relied on my scientific education and training, my research experience, my knowledge of the scientific literature in the pertinent fields, and my clinical experience treating children, adolescents, and adults with gender dysphoria. A true and accurate copy of my curriculum vitae is attached hereto as Exhibit A. It documents my education, training, research, and years of experience in this field and includes a list of my publications from the last 10 years, which I also rely upon to support my opinions.

5. The materials I have relied upon in preparing this declaration are the same types of materials that experts in my field regularly rely upon when forming opinions on these subjects. I may wish to supplement these opinions or the bases for them as a result of new scientific research or publications or in response to statements and issues that may arise in my area of expertise.

BACKGROUND QUALIFICATIONS

6. I am the Vice Chair of the Pritzker Department of Psychiatry and Behavioral Health at the Ann and Robert H. Lurie Children's Hospital of Chicago ("Children's Hospital"), where I also serve as Clinical Associate Professor of Child and Adolescent Psychiatry and Medical Director for Outpatient Psychiatric Services.

7. I previously served as Co-Director of the New York University Pediatric Consultation Liaison Service for the New York University Department of Child and Adolescent Psychiatry. I also was the Founder and Clinical Director of the New York University Gender and Sexuality Service, which I founded in 2011.

8. I am Board Certified in Child, Adolescent, and Adult Psychiatry. In my clinical practice, I have seen approximately 500 transgender patients.

9. I am an Associate Editor of the peer-reviewed publication *Transgender Health*. I am also a reviewer for *LGBT Health* and *Journal of the American Academy of Child and Adolescent Psychiatry*, both of which are peer-reviewed journals.

10. I am the author or co-author of 16 articles on care for transgender patients and am the co-author of *Affirmative Mental Health Care for Transgender and Gender Diverse Youth: A Clinical Casebook*, Springer Publishing, 2018. I have also authored or co-authored numerous book chapters on treatment for transgender adults and youth.

11. I have been a member of the World Professional Association for Transgender Health (“WPATH”) since 2011. I have been actively involved in WPATH’s revision of its Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People (“Standards of Care”), serving as a member of revision committees for both the child and adult mental health chapters of the forthcoming eighth edition of WPATH’s Standards of Care.

12. I am involved in a number of international, national, and regional committees that contribute to the scholarship and provision of care to transgender people. I am the Chair of the American Academy of Child and Adolescent Psychiatry’s Sexual Orientation and Gender Identity Committee. I serve as a member of the Transgender Health Committee for the Association of Gay and Lesbian Psychiatrists. I also am the Founder and Director of the Gender Variant Youth and Family Network.

13. I have not testified as an expert at trial or by deposition in the last four years.

14. I am being compensated for my work on this matter at a rate of \$400 per hour for preparation of this report and for time spent preparing for and giving local deposition or trial testimony. In addition, I would be compensated \$2,500 per day for deposition or trial testimony.

requiring travel and \$300 per hour for time spent travelling, plus reasonable expenses. My compensation does not depend on the outcome of this litigation, the opinions I express, or the testimony I may provide.

SUMMARY OF OPINIONS

15. My understanding is that this case is a legal challenge to a West Virginia law (“H.B. 3293”) that prohibits girls and women who are transgender from participating on girls’ and women’s sports teams in “[i]nterscholastic, intercollegiate, intramural, or club athletic teams or sports that are sponsored by any public secondary school or a state institution of higher education.” W. Va. Code § 18-2-25d(c)(1). In their expert reports, Dr. Levine and Dr. Cantor do not offer any expert opinions directly relating to H.B. 3293 or the participation of transgender athletes. Instead, Dr. Levine and Dr. Cantor launch a broadside attack against the prevailing model of gender-affirming care for transgender youth that has been endorsed by the American Academy of Child and Adolescent Psychiatry, the American Academy of Pediatrics, the American Psychological Association, the American Psychiatric Association, and the American Medical Association, among many other mainstream medical organizations.

16. As an initial matter, it is important to note that Dr. Levine and Dr. Cantor’s litany of criticisms are largely irrelevant to the population of people affected by H.B. 3293. Most of Dr. Levine and Dr. Cantor’s arguments relate to (a) prepubertal children who “desist” from expressing a transgender identity once they reach puberty and (b) transgender boys who first seek treatment for gender dysphoria during adolescence. But H.B. 3293 does not affect elementary school students or transgender boys. It affects transgender girls and women in middle school, high school, and college.

17. As I explain in this report, Dr. Levine and Dr. Cantor’s criticisms are also utterly unfounded. First, Dr. Levine and Dr. Cantor lack experience with gender dysphoria in children and adolescents—the groups whom their reports discuss.

18. Second, with respect to prepubertal children, Dr. Levine and Dr. Cantor present a caricatured description of prevailing standards of care that reflects a profound misunderstanding of the subject. Gender-affirming care for prepubertal children is not synonymous with “transition on demand” (Cantor Rep. ¶ 45) or a rubber-stamp recommendation that every prepubertal child expressing feelings of gender dysphoria be encouraged to socially transition. Treatment is individualized based on the needs of the child and the family and other psychosocial considerations and is decided upon only after a discussion of possible benefits and risks. For prepubertal transgender children with intense, persistent gender dysphoria, there is substantial evidence that, in appropriate cases, socially transitioning can have significant mental health benefits.

19. Third, Dr. Levine and Dr. Cantor’s criticisms of gender-affirming care for adolescents—like their criticisms of gender-affirming care for prepubertal children—also reflect a distorted interpretation of the relevant scientific literature and a caricatured understanding of what gender-affirming care is. Studies have repeatedly documented that puberty-blocking medication and gender-affirming hormone therapy are associated with mental health benefits in both the short and long term. Contrary to the portrayal in Dr. Levine and Dr. Cantor’s reports, gender-affirming treatment also requires a careful and thorough assessment of a patient’s mental health, including co-occurring conditions, history of trauma, and substance use, among many other factors.

20. Finally, while purporting to offer expert opinions on mental health care for transgender youth, Dr. Levine and Dr. Cantor do not appear to offer any expert opinions on the mental health impact of H.B. 3293 itself. Excluding transgender adolescent girls and women from

female sports teams will not cure their gender dysphoria or improve their mental health. To the contrary, stigma and discrimination have been shown to have a profoundly harmful impact on the mental health of transgender people and other minority groups.

DISCUSSION

Dr. Levine and Dr. Cantor Lack Experience with Gender Dysphoria in Children and Adolescents

21. According to his CV, Dr. Levine is not board certified in child and adolescent psychiatry, which requires specialized training in child development that is essential for working with transgender young people and their families. His declaration and CV also indicate that he does not have significant clinical experience working with adolescents experiencing gender dysphoria, the patient population at the heart of this case.

22. Moreover, Dr. Levine repeatedly acknowledges in his report that he has no first-hand knowledge of how gender-affirming mental health care is actually provided to children and adolescents. His descriptions are based on second-hand conversations and often sensationalized media reports. (*See, e.g.*, Levine Rep. ¶¶ 49, 118 (offering opinions based on anecdotal reports from the internet).)

23. Dr. Cantor appears to have no experience in child or adolescent psychology and no relevant experience with respect to gender dysphoria in childhood and adolescence. His academic career has focused on pedophilia and sexual paraphilias in adults.

Gender-Affirming Care for Prepubertal Children

24. Dr. Levine and Dr. Cantor devote substantial portions of their expert reports to criticizing the positions of mainstream medical organizations with respect to gender-affirming care for prepubertal transgender children. (*See, e.g.*, Levine Rep. ¶¶ 42-43, 114-17, 130-34; Cantor Rep. ¶¶ 36-45, 82-87.) According to Dr. Levine and Dr. Cantor, studies have indicated that gender dysphoria in prepubertal children may desist by the time the children reach puberty, and thus

medical professionals should adopt a “watchful waiting” approach and avoid affirming a prepubertal child’s gender identity.

25. Before addressing Dr. Levine and Dr. Cantor’s arguments about prepubertal children, it is important to emphasize that those arguments are irrelevant to what I understand to be the issues in this case. H.B. 3293 does not apply to elementary schools, and the plaintiff in this case is an 11-year-old middle school student. The relevant population affected by H.B. 3293 is composed of transgender adolescents and young adults, not prepubertal children.

26. With respect to prepubertal children, Dr. Levine and Dr. Cantor present a caricatured description of prevailing standards of care that reflects a profound misunderstanding of the subject. Mental health providers cannot change a prepubertal child’s gender identity or prevent them from being transgender, just as mental health providers cannot change a cisgender child’s gender identity. Prepubertal children who “desist” are children with non-conforming gender expression who realize with the onset of puberty that their gender identity is consistent with their sex assigned at birth. Their understanding of their gender identity changes with the onset of puberty, but their gender identity does not. We cannot definitively determine which prepubertal children will go on to identify as transgender when they reach adolescence, but we know that children with gender dysphoria who persist into puberty are more likely to have expressed a consistent, persistent, and insistent understanding of their gender identity from a young age.¹

27. Gender-affirming care for prepubertal children is not synonymous with “transition on demand” (Cantor Rep. ¶ 45) or a rubber-stamp recommendation that every prepubertal child expressing feelings of gender dysphoria be encouraged to socially transition. Treatment is

¹ Steensma, T.D., *et al.* (2013). *Factors Associated with Desistence and Persistence of Childhood Gender Dysphoria: A Quantitative Follow-Up Study*. J. AM. ACAD. CHILD ADOLESC. PSYCHIATRY. 52(6):582-90 (“Steensma 2013”).

individualized based on the needs of the child and the family and other psychosocial considerations, and is decided upon only after a discussion of possible benefits and risks.² As part of those discussions, the child and their family are advised that prepubertal children do not always go on to identify as transgender when they reach adolescence, and that children are encouraged to continue developing an understanding of their gender identity without expectation of a specific outcome even after social transition takes place.³

28. The focus of gender-affirming care is supporting overall health and wellbeing, regardless of whether the young person continues to identify as transgender. In this manner, the primary goal of gender-affirming care is to help a child understand their own gender identity and build resilience and mental wellness in a child and family, without privileging any one outcome over another.

29. Important considerations in deciding whether social transition is in a child's best interest include: whether there is a consistent, stable articulation of a gender different from the child's sex assigned at birth, which should be distinguished from merely dressing or acting in a gender non-conforming manner; whether the child is expressing a strong desire or need to transition; the degree of distress the child is experiencing as a result of the gender dysphoria; and whether the child will be emotionally and physically safe during and following transition.⁴

² See Hidalgo, M.A., et al. (2013). *The Gender Affirmative Model: What We Know and What We Aim to Learn*. HUMAN DEV. 56(5):285-90.

³ See American Psychological Association. (2015). *Guidelines for Psychological Practice with Transgender and Gender Nonconforming People*. AM. PSYCHOLOGIST. 70(9):832-64 ("APA 2015"); Edwards-Leeper, L., & Spack, N.P. (2012). *Psychological evaluation and medical treatment of transgender youth in an interdisciplinary "Gender Management Service" (GeMS) in a major pediatric center*. J. HOMOSEXUALITY. 59(3):321-36 ("Edwards-Leeper 2012").

⁴ APA 2015.

30. A treatment plan is informed by a psychosocial assessment, which may vary greatly depending on the patient's presentation and the complexity of the issues the patient is navigating. Further, in conducting that assessment, the mental health provider is drawing from their professional training and experience in working with transgender young people, exercising professional judgment, and tailoring the assessment to each individual patient.

31. There is also no requirement that prepubertal children who socially transition receive mental health therapy. Many prepubertal children who express a gender identity different from their sex assigned at birth do not experience any co-occurring conditions or other psychological distress requiring treatment.⁵ Mental health therapy may be useful for some prepubertal children but is not necessary or appropriate for everyone. Forcing children to undergo therapy when it is not medically indicated is both harmful and unethical.

32. What makes gender-affirming care "gender affirming" is that it does not presume that being transgender is incompatible with a young person's short- and long-term health and wellbeing. Simply being transgender or gender nonconforming is not a medical condition or pathology to be treated. As the DSM-5 recognizes, diagnosis and treatment are "focus[ed] on dysphoria as the clinical problem, not identity per se." American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, 451 (2013). The DSM-5 unequivocally repudiated the outdated view that being transgender is a pathology by revising the diagnostic criteria (and name) of gender dysphoria to recognize the clinical distress as the focus of the treatment, not the patient's transgender status.

⁵ See Levine Rep. ¶ 30 (acknowledging that "[y]oung children who are living a transgender identity commonly suffer materially fewer symptoms of concurrent mental distress than do older patients."); de Vries, A.L.C, *et al.* (2011). *Psychiatric comorbidity in gender dysphoric adolescents*. J. CHILD PSYCHOLOGY & PSYCHIATRY. 52(11):1195-202 (noting that 67.6% had no concurrent psychiatric disorder).

33. In criticizing what they imagine to be gender-affirming care, Dr. Levine and Dr. Cantor do not merely advocate for “watchful waiting” to see whether dysphoria persists into adolescence before any treatment is provided. Instead, they offer wild speculation that mental health professionals can and should intervene and provide therapy to encourage the patient to identify with their sex assigned at birth, which they believe will reduce the likelihood that gender dysphoria will persist. Both Dr. Levine and Dr. Cantor candidly admit that there is no credible scientific research indicating that such practices are either possible or ethical. (See Levine Rep. ¶ 49 (“To my knowledge, there is no evidence beyond anecdotal reports that psychotherapy can enable a return to male identification for genetically male boys, adolescents, and men, or return to female identification for genetically female girls, adolescents, and women.”); Cantor Rep. ¶ 42 (speculating that “therapeutic intervention [could] facilitate or speed desistance” while admitting “there has not yet been any such study”).)

34. Although Dr. Levine refers to his preferred modality as the “psychotherapy model” (Levine Rep. ¶¶ 46-48), this approach is more appropriately characterized as the “gender identity conversion model” because its goal is to bring the patient’s gender identity into alignment with their assigned sex and foreclose gender transition as a treatment for gender dysphoria. A recent study found that people who reported experiencing those conversion efforts were more likely to have reported attempting suicide, especially those who reported receiving such therapy in childhood.⁶ That conclusion is further supported by the extensive evidence that rejection of a young person’s gender identity by family and peers is the strongest predictor for adverse mental

⁶ Turban, J.L., *et al.* (2020). *Association Between Recalled Exposure to Gender Identity Conversion Efforts and Psychological Distress and Suicide Attempts Among Transgender Adults*. JAMA PSYCHIATRY. 77(1):68-76.

health outcomes.⁷ Attempting to change a person's gender identity is not an appropriate therapeutic modality, and such practices have been widely recognized as discredited, harmful, and ineffective.⁸

35. In contrast, for prepubertal transgender children with intense, persistent gender dysphoria, there is substantial evidence that, in appropriate cases, socially transitioning can have significant mental health benefits. While not true for every transgender child, transgender children as a group have higher rates of depression, anxiety, and suicidal thoughts and behaviors. Research indicates that social transition significantly improves the mental health of transgender young people, bringing their mental health profiles into close alignment with their non-transgender peers, finding only slightly higher levels of anxiety and no elevated levels of depression.⁹

36. Dr. Levine and Dr. Cantor criticize research demonstrating the benefits of social transition and argue that even after socially transitioning, transgender youth as a group can

⁷ Ryan, C., et al. (2010). *Family Acceptance in Adolescence and the Health of LGBT Young Adults*. J. CHILD ADOLESC. PSYCHIATRIC NURSING. 23(4):205-13; Klein, A., & Golub, S.A. (2016). *Family Rejection as a Predictor of Suicide Attempts and Substance Misuse Among Transgender and Gender Nonconforming Adults*. LGBT HEALTH. 3(3):193-99.

⁸ See American Academy of Child & Adolescent Psychiatry Policy Statement: Conversion Therapy (2018); American Psychiatric Association Position Statement on Conversion Therapy and LGBTQ Patients (2018); American Psychological Association Resolution on Gender Identity Change Efforts (2021).

⁹ See Gibson, D.J., et al. (2021). *Evaluation of Anxiety and Depression in a Community Sample of Transgender Youth*. JAMA NETWORK OPEN. 4(4):e214739; Durwood, L., et al. (2017). *Mental Health and Self-Worth in Socially Transitioned Transgender Youth*. J. AM. ACAD. CHILD ADOLESC. PSYCHIATRY. 56(2):116-23; Olson, K.R., et al. (2016). *Mental Health of Transgender Children Who Are Supported in Their Identities*. PEDIATRICS. 137(3):e20153223 ("Olson 2016").

Dr. Cantor points to a critique of Olson 2016 which attempted—unsuccessfully—to show statistical errors in the paper. (Cantor Rep. ¶¶ 15-16, 100 (citing Schumm, W. R., & Crawford, D.W. (2020). *Is Research on Transgender Children What It Seems? Comments on Recent Research on Transgender Children with High Levels of Parental Support*. THE LINACRE QUARTERLY. 87(1):9–24).) The small statistical errors in Olson 2016 had already been corrected in 2018 and did not alter any of the study's findings. See Olson, K.R., et al. (2018). *Mental Health of Transgender Children Who Are Supported in Their Identities* (Errata). PEDIATRICS. 142(2):e20181436.

experience higher rates of anxiety and depression than cisgender children of the same age. To be sure, stigma and discrimination have been shown to have a profoundly harmful impact on mental health of transgender people and other minority groups.¹⁰ But preventing a child from socially transitioning does not prevent the child from being transgender, and social transition is a treatment for gender dysphoria, not a panacea for all co-occurring mental health concerns. Dr. Levine and Dr. Cantor offer no support whatsoever for their apparent assumption that mental health outcomes would be improved by preventing social transition from occurring.

37. There is also no evidence supporting Dr. Levine's speculation that allowing prepubertal children to socially transition puts children on a "conveyor belt" path to becoming transgender adolescents and adults. (See Levine Rep. ¶¶ 131-34.) Rather, the evidence shows that the same prepubertal children who are likely to have a stable transgender identity into adolescence are the children who are most likely to articulate a strong and consistent need to socially transition.¹¹ For example, a recent study found that a group of transgender children who transitioned before puberty and a group of transgender children who waited to transition until after puberty both showed the same intensity of cross-gender identification. In other words, socially transitioning before puberty did not increase children's cross-gender identification, and deferring transition did not decrease cross-gender identification.¹² Intense cross-gender identification and a strong, persistent desire to transition is simply an indicator that a child is more likely to be transgender and not merely gender nonconforming.

¹⁰ White Hughto, J.M., et al. (2015). *Transgender stigma and health: A critical review of stigma determinants, mechanisms, and interventions*. SOC. SCI. MED. 147:222-31 ("White Hughto 2015").

¹¹ Steensma 2013.

¹² Rae, J.R., et al. (2019). *Predicting Early-Childhood Gender Transitions*. PSYCHOLOGICAL SCI. 30(5):669-81.

Gender-Affirming Care for Adolescents

38. Dr. Levine and Dr. Cantor also devote much of their reports to criticizing the provision of gender-affirming care for adolescents, arguing that the benefits of puberty-blocking medication are overstated and that adolescents should have more rigorous mental health screening. As with their criticisms of gender-affirming care for prepubertal children, Dr. Levine and Dr. Cantor do not explain how any of their criticisms are relevant to the issue of whether girls and women who are transgender should be able to participate on female sports teams in secondary school and college.

39. Dr. Levine and Dr. Cantor's criticisms of gender-affirming care for adolescents—like their criticisms of gender-affirming care for prepubertal children—also reflect a distorted interpretation of the relevant scientific literature and a caricatured understanding of what gender-affirming care is. Despite Dr. Levine's suggestion to the contrary, there is no "watchful waiting" approach for transgender adolescents. Even practitioners who oppose social transition in childhood provide gender-affirming care for transgender adolescents, including puberty-blocking medication and gender-affirming hormone treatments for gender dysphoria.¹³ As with their criticism of care for prepubertal children, Dr. Levine and Dr. Cantor criticize the methodology of studies supporting gender-affirming care while proposing a "therapy only" treatment without any empirical or scientific support whatsoever.

40. Studies have repeatedly documented that puberty blocking medication and gender-affirming hormone therapy are associated with mental health benefits in both the short and long

¹³ Jack Turban, Annelou DeVries & Kenneth Zucker, "Gender Incongruence & Gender Dysphoria," in Lewis's *Child and Adolescent Psychiatry: A Comprehensive Textbook* (A Martin, et al., eds., 5th ed., 2018).

term.¹⁴ In addition to forestalling increased distress and dysphoria resulting from the physical changes accompanying puberty, puberty-delaying medication followed by gender-affirming hormones brings a transgender person's body into greater alignment with their identity over the long term and reduces the number of surgeries a transgender person may need as an adult. The benefits of puberty-blocking medication thus increase over the long term as the person progresses into adulthood.¹⁵

¹⁴ See Tordoff, D.M., *et al.* (2022). *Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care*. JAMA NETWORK OPEN. 5(2):e220978 at 1 (finding that receipt of gender-affirming care, including puberty blockers and gender-affirming hormones, was associated with 60% lower odds of moderate or severe depression and 73% lower odds of suicidality over a 12-month follow-up); Green, A.E., *et al.* (2021). *Association of Gender-Affirming Hormone Therapy with Depression, Thoughts of Suicide, and Attempted Suicide Among Transgender and Nonbinary Youth*. J. ADOLESC. HEALTH [ePublication ahead of print] at 1 (finding that access to gender-affirming hormones during adolescence was associated with lower odds of recent depression and having attempted suicide in the past year); Turban, J.L., *et al.* (2020) *Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation*. PEDIATRICS. 145(2):e20191725 at 1 (finding that access to puberty blockers during adolescence is associated with a decreased lifetime incidence of suicidal ideation among adults); Achille, C., *et al.* (2020). *Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: Preliminary results*. INT'L J. PEDIATRIC ENDOCRINOLOGY. 2020:8 at 1 (finding that endocrine intervention was associated with decreased depression and suicidal ideation and improved quality of life for transgender youth); Kuper, L.E., *et al.* (2020). *Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy*. PEDIATRICS. 145(4):e20193006 at 1 (showing hormone therapy in youth is associated with reducing body dissatisfaction and modest improvements in mental health); van der Miesen, A.I.R., *et al.* (2020). *Psychological Functioning in Transgender Adolescents Before and After Gender-Affirmative Care Compared with Cisgender General Population Peers*. J. ADOLESC. HEALTH. 66(6):699-704 at 699 (showing fewer emotional and behavioral problems after puberty suppression, and similar or fewer problems compared to same-age cisgender peers) (“van der Miesen 2020”); Costa, R., *et al.* (2015). *Psychological Support, Puberty Suppression, and Psychosocial Functioning in Adolescents with Gender Dysphoria*. J. SEXUAL MEDICINE. 12(11):2206-14 at 2206 (finding increased psychological function after six months of puberty suppression); de Vries, A.L.C., *et al.* (2014). *Young Adult Psychological Outcome After Puberty Suppression and Gender Reassignment*. PEDIATRICS. 134(4):696-704 (following a cohort of transgender young people in the Netherlands from puberty suppression through surgical treatment and finding that the cohort had global functioning that was equivalent to the Dutch population) (“de Vries 2014”).

¹⁵ de Vries 2014.

41. Dr. Cantor fails to discuss many of the studies documenting the benefits of puberty-blocking medication. For the studies he does discuss, Dr. Cantor's primary criticism is that many of the prospective cohort studies offered psychosocial support in addition to puberty blockers and hormones, which prevented the study from isolating whether the benefit is associated with the puberty blocker, the gender-affirming hormones, or some combination. (Cantor Rep. ¶¶ 64, 66.) But, as Dr. Cantor himself notes, elsewhere "in medical research, where we cannot manipulate people in ways that would clear up difficult questions, all studies will have a fault. In science, we do not, however, reject every study with any identifiable short-coming—rather, we gather a diversity of observations, made with their diversity of compromises to safety and ethics (and time and cost, etc.)." (Cantor Rep. ¶ 87.) When viewed as a comprehensive body of research, the weight of the evidence and the experience of clinicians has demonstrated that puberty-blocking medication and hormones have been associated with a variety of mental health benefits across different contexts.

42. There is also no credible basis for Dr. Levine's assertion that an adolescent's decision to begin puberty-blocking medication "act[s] as a psychosocial 'switch,' decisively shifting many children to a persistent transgender identity." (Levine Rep. ¶ 137.) Studies showing that a high percentage of transgender adolescents who receive puberty blockers ultimately decide to move forward with gender-affirming hormone therapy more likely reflect the fact that participants were rigorously screened and had demonstrated sustained, persistent gender dysphoria before receiving medical treatment.

43. Instead of addressing the proper treatment for transgender adolescents in need of care, Dr. Levine and Dr. Cantor devote most of their attention to the possibility that a person could be misdiagnosed with gender dysphoria and then later regret their medical transition. For example, Dr. Levine and Dr. Cantor devote a great deal of space to discussing a theory that an increasing

number of people who are assigned female at birth are suddenly identifying as males in mid-to-late adolescence as a result of peer pressure and social contagion. (Levine Rep. ¶¶ 38, 118-20; Cantor Rep. ¶¶ 73-74.) The theory that some adolescents experience “rapid-onset gender dysphoria” (Levine Rep. ¶ 118; Cantor Rep. ¶¶ 73-74) as a result of social influences is based almost exclusively on one highly controversial study.¹⁶ Although purporting to provide a basis for Dr. Levine’s speculations, the study was based on an anonymous survey, allegedly of parents, about the etiology of their child’s gender dysphoria. Participants were recruited from websites promoting this social contagion theory, and the children were not surveyed or assessed by a clinician. Those serious methodological flaws render the study meaningless. The only conclusion that can be drawn from that study is that a self-selected sample of anonymous people recruited through websites that predisposed participants to believe transgender identity can be influenced by social factors do, in fact, believe those social factors influence children to identify as transgender.¹⁷

44. Some transgender people who do not come forward until adolescence may have experienced symptoms of gender dysphoria for long periods of time but been uncomfortable disclosing those feelings to parents. Other transgender people do not experience distress until they experience the physical changes accompanying puberty. In either case, gender-affirming care requires a comprehensive assessment and persistent, sustained gender dysphoria before medical treatment is prescribed.

¹⁶ See Littman, L. (2018). *Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria*. PLOS ONE. 13(8):e0202330.

¹⁷ Aside from these serious methodological flaws, Littman’s hypothesis of “rapid onset gender dysphoria” focuses specifically on gender dysphoria in boys who are transgender and were assigned a female sex at birth. By contrast, the restrictions in H.B. 3293 are limited to girls and women who are transgender and were assigned a male sex at birth. As with their arguments about prepubertal children, Dr. Levine and Dr. Cantor’s arguments about boys who are transgender are not relevant to the population actually affected by H.B. 3293.

45. Contrary to the portrayal in Dr. Levine and Dr. Cantor's reports, gender-affirming treatment also requires a careful and thorough assessment of a patient's mental health, including co-occurring conditions, history of trauma, and substance use, among many other factors.¹⁸ As a result, I have had patients who presented with some symptoms of gender dysphoria, but who ultimately did not meet the diagnostic criteria for a variety of reasons, and therefore I recommended treatments other than transition to alleviate their psychological distress.

46. Dr. Levine and Dr. Cantor also devote substantial space to discussing the possibility that a person could be misdiagnosed with gender dysphoria instead of another mental health condition. (See, e.g. Levine Rep. ¶¶ 118-26; Cantor Rep. ¶¶ 73-74, 76-80.) Studies on transgender young people have long reported data on co-occurring conditions. Indeed, Dr. Cantor specifically cites to one of my own articles on the topic. (Cantor Rep. ¶ 76 (citing Janssen, A., *et al.* (2019). *The Complexities of Treatment Planning for Transgender Youth with Co-Occurring Severe Mental Illness: A Literature Review and Case Study*. ARCHIVES OF SEXUAL BEHAVIOR. 48(7):2003-09).)

47. The existence—and prevalence—of co-occurring conditions among transgender young people is unsurprising. Transgender young people must cope with many stressors, from the fear of rejection by family and peers to pervasive societal discrimination. Not to mention, their underlying gender dysphoria can cause significant psychological distress which, if left untreated, can result in or exacerbate the co-occurring conditions identified in studies on transgender young people.¹⁹ And, given that transgender young people typically delay disclosing their transgender status or initially experience family rejection following disclosure, it is not uncommon for

¹⁸ Olson-Kennedy, J., *et al.* (2019). *Creating the Trans Youth Research Network: A Collaborative Research Endeavor*. TRANSGENDER HEALTH. 4(1):304-12; Edwards-Leeper 2012.

¹⁹ van der Miesen 2020; Turban, J.L., *et al.* (2021). *Timing of Social Transition for Transgender and Gender Diverse Youth, K-12 Harassment, and Adult Mental Health Outcomes*. J. ADOLESC. HEALTH. 69(6):991-98.

transgender young people to engage with psychological or psychiatric care for other reasons prior to being diagnosed with gender dysphoria.

48. Requiring that a transgender patient resolve all co-occurring conditions, many of which are chronic with no reasonable expectation that they be “resolved,” prior to receiving gender-affirming care—as suggested by Dr. Cantor—is not possible, nor is it ethical. (Cantor Rep. ¶¶ 14, 35, 69, 92, 110.) No relevant organizations cite the need for co-occurring mental health conditions to be resolved before a patient may receive gender-affirming care. Rather, such conditions should be reasonably well-controlled and not impair the ability of the patient to make an informed decision or interfere with the accuracy of the diagnosis of gender dysphoria. Indeed, some co-occurring conditions (for example, Attention Deficit Hyperactivity Disorder and Autism Spectrum Disorder, to name a few) could be chronic disorders where complete resolution is impossible and the goal of treatment is mitigating harm and improving functioning,

49. It is important to note that distress associated with untreated gender dysphoria can also amplify co-occurring conditions that developed independently of the gender dysphoria. Thus, treating the underlying gender dysphoria is essential to alleviating the psychological distress associated with co-occurring conditions.

Discriminating Against Transgender Students Does Not Improve Their Mental Health

50. The overarching theme of Dr. Levine and Dr. Cantor’s reports is that transgender people as a group have greater rates of a variety of negative social outcomes and co-occurring conditions over the course of their lives and that, to avoid those negative outcomes and conditions, mental health providers should withhold gender-affirming care to discourage transgender youth from growing into transgender adults.²⁰

²⁰ Dr. Levine bizarrely speculates that once a transgender person’s siblings “marry and have children,” they will not “wish the transgender individual to be in contact with those children,” and

51. Discriminating against transgender people, or withholding gender-affirming care, will not prevent those people from being transgender. And excluding transgender adolescent girls and women from female sports teams will not cure their gender dysphoria or improve their mental health. To the contrary, as noted previously, stigma and discrimination have been shown to have a profoundly harmful impact on the mental health of transgender people and other minority groups.²¹

52. No reasonable mental health professional with relevant experience treating children and adolescents could conclude that H.B. 3293 is anything but harmful to the mental health of transgender youth. Exclusion and isolation are harmful for all adolescents, but particularly so for transgender youth who face the additional burden of societal stigma. Preventing transgender youth from participating in the same activities as their peers—or forcing transgender youth to be treated inconsistent with their gender identity—undermines their ability to socially transition and prevents transgender youth from accessing important educational and social benefits of the school environment.²²

that transgender people will be less likely to find “individuals willing to develop a romantic and intimate relationship with them.” (Levine Rep. ¶¶ 202-03.) Dr. Levine offers no statistical support for these assertions and, in my experience, clinical practice has shown the opposite to be true.

²¹ White Hughto 2015.

²² American Psychological Association Resolution on Supporting Sexual/Gender Diverse Children and Adolescents in Schools (2020) at 5 (supporting inclusion of transgender youth in school activities and sports consistent with their gender identity); Clark, C.M., & Kosciw, J.G. (2022). *Engaged or excluded: LGBTQ youth’s participation in school sports and their relationship to psychological well-being*. PSYCHOLOGY IN THE SCHOOLS. 59:95-114 (finding transgender youth who participated in sports had increased well-being and greater school belonging).

CONCLUSION

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on 3/10/2022

A handwritten signature in black ink, appearing to read 'Aron Janssen', written over a horizontal line.

Aron Janssen, MD

Curriculum Vitae

Aron Janssen, M.D.
 312-227-7783
 aronjans@gmail.com

Personal Data

Born Papillion, Nebraska
 Citizenship USA

Academic Appointments

2011-2017 Clinical Assistant Professor of Child and Adolescent Psychiatry
 2011-2019 Founder & Clinical Director, NYU Gender and Sexuality Service
 Director, LGBT Mental Health Elective, NYULMC
 2015-2019 Co-Director, NYU Pediatric Consultation Liaison Service
 New York University Department of Child and Adolescent Psychiatry
 2017-present Clinical Associate Professor of Child and Adolescent Psychiatry
 2019-present Vice Chair, Pritzker Department of Psychiatry and Behavioral Health
 Ann and Robert H. Lurie Children's Hospital of Chicago
 2020-present Medical Director, Outpatient Psychiatric Services
 Ann and Robert H. Lurie Children's Hospital of Chicago

Education

Year	Degree	Field	Institution
6/97	Diploma		Liberty High School
5/01	B.A.	Biochemistry	University of Colorado
5/06	M.D.	Medicine	University of Colorado

Postdoctoral Training

2006-2009 Psychiatry Residency Ze'ev Levin, M.D. NYU Department of Psychiatry
 2009-2011 Child and Adolescent Psychiatry Fellowship – Fellow and Clinical Instructor
 Jess Shatkin, M.D. NYU Dept of Child/Adolescent Psychiatry

Licensure and Certification

2007-present New York State Medical License
 2011-present Certification in Adult Psychiatry, American Board of Psychiatry and Neurology
 2013-present Certification in Child and Adolescent Psychiatry, ABPN

Academic Appointments

2009-2011 Clinical Instructor, NYU Department of Child and Adolescent Psychiatry
 2011-2017 Clinical Asst Professor, NYU Dept of Child and Adolescent Psychiatry
 2017-2019 Clinical Assoc Professor, NYU Dept of Child and Adolescent Psychiatry
 2011-present Clinical Director, NYU Gender and Sexuality Service
 2015-2019 Co-Director, NYU Pediatric Consultation-Liaison Service
 2019-present Associate Professor of Child and Adolescent Psychiatry, Northwestern University
 2019-present Vice Chair of Clinical Affairs, Pritzker Department of Psychiatry and Behavioral Health, Lurie Children's Hospital of Chicago

Major Committee Assignments**International, National and Regional**

2021-present	Sexual Orientation and Gender Identity Committee, Chair, AACAP
2019-present	WPATH Standards of Care Revision Committee, Children
2019-present	WPATH Standards of Care Revision Committee, Adult Mental Health
2015-2019	Department of Child Psychiatry Diversity Ambassador
2013-2021	Sexual Orientation and Gender Identity Committee Member, AACAP
2012-present	Founder and Director, Gender Variant Youth and Family Network
2012-present	Association of Gay and Lesbian Psychiatrists, Transgender Health Committee
2012-2019	NYULMC, Chair LGBTQ Advisory Council
2012-2019	NYULMC, Child Abuse and Protection Committee
2013-2015	NYULMC, Pediatric Palliative Care Team
2003-2004	American Association of Medical Colleges (AAMC), Medical Education Delegate
2004-2006	AAMC, Western Regional Chair

Psychiatry Residency

2006-2009	Resident Member, Education Committee
2007-2008	Resident Member, Veterans Affairs (VA) Committee

Medical School

2002-2006	Chair, Diversity Curriculum Development Committee
2002-2006	AAMC, Student Representative
2003-2004	American Medical Student Assoc. (AMSA) World AIDS Day Coordinator
2003-2004	AMSA, Primary Care Week Coordinator
2004-2006	Chair, Humanism in Medicine Committee

Memberships, Offices, and Committee Assignments in Professional Societies

2006-present	American Psychiatric Association (APA)
2009-present	American Academy of Child and Adolescent Psychiatry (AACAP)
2011-present	World Professional Association for Transgender Health (WPATH)
2011-present	Director, Gender Variant Youth and Family Network, NYC
2013-2019	Chair, NYU Langone Medical Center LGBTQ Council
2015-present	Clinical Associate Editor, <i>Transgender Health</i>

Editorial Positions

2016-present	Clinical Assistant Editor, <i>Transgender Health</i>
2014-present	Ad Hoc Reviewer, <i>LGBT Health</i> .
2016-present	Ad Hoc Reviewer, <i>JAACAP</i>
2018-present	Associate Editor, <i>Transgender Health</i>

Principal Clinical and Hospital Service Responsibilities

2011-2019	Staff Psychiatrist, Pediatric Consultation Liaison Service
2011-2019	Faculty Physician, NYU Child Study Center
2011-2019	Founder and Clinical Director, NYU Gender & Sexuality Service
2015-2019	Co-Director, Pediatric Consultation Liaison Service
2019-present	Vice Chair, Pritzker Dept of Psychiatry and Behavioral Health
2019-present	Chief Psychiatrist, Gender Development Program

2020-present

Medical Director, Outpatient Psychiatry Services

Relevant Program Development

Gender and Sexuality Service

- founded by Aron Janssen in 2011, who continues to direct the service
- first mental health service dedicated to transgender youth in NYC
- served over 200 families in consultation, with 2-3 referrals to the gender clinic per week
- trained over 500 mental health practitioners in transgender mental health – 1 or 2 full day trainings in partnership with the Ackerman Institute's Gender and Family Project (GFP) and with WPATH Global Educational Initiative (GEI)
- New hires in Adolescent Medicine, Psychology, Plastic Surgery, Urology, Gynecology, Endocrinology, Social Work, Department of Population Health with focus on transgender care has led to expansion of available services for transgender youth at NYULMC in partnership with the Gender and Sexuality Service
- development of partnerships with Ackerman Institute, Callen-Lorde Health Center – both institutions have been granted access to our IRB and have agreed to develop shared research and clinical priorities with the Gender and Sexuality Service. Two active projects are already underway
- multiple IRB research projects underway, including in partnership with national and international clinics
- model has been internationally recognized

Clinical Specialties/Interests

Gender and Sexual Identity Development

Co-Occurring Mental Health Disorders in Transgender children, adolescents and adults

Pediatric Consultation/Liaison Psychiatry

Psychotherapy

- Gender Affirmative Therapy, Supportive Psychotherapy, CBT, MI

Teaching Experience

- 2002-2006 Course Developer and Instructor, LGBT Health (University of Colorado School of Medicine)
- 2011-2019 Instructor, Cultural Competency in Child Psychiatry (NYU Department of Child and Adolescent Psychiatry) – 4 hours per year
- 2011-2019 Course Director, Instructor “Sex Matters: Identity, Behavior and Development” – 100 hours per year
- 2011-2019 Course Director, LGBT Mental Health Elective (NYU Department of Psychiatry) - 50 hours of direct supervision/instruction per year
- 2011-2019 Course Director, Transgender Mental Health (NYU Department of Child and Adolescent Psychiatry – course to begin in Spring 2018.
- 2015-2019 Instructor, Gender & Health Selective (NYU School of Medicine) – 4 hours per year.

Academic Assignments/Course Development

New York University Department of Child and Adolescent Mental Health Studies

- Teacher and Course Director: “Sex Matters: Identity, Behavior and Development.”
A full semester 4 credit course, taught to approximately 50 student per year since

2011, with several students now in graduate school studying sexual and gender identity development as a result of my mentorship.

NYU Department of Child and Adolescent Psychiatry

-Instructor: Cultural Competency in Child and Adolescent Psychiatry

-Director: LGBTQ Mental Health Elective

World Professional Association of Transgender Health

-Official Trainer: Global Education Initiative – one of two child psychiatrists charged with training providers in care of transgender youth and adults.

Peer Reviewed Publications

1. Janssen, A., Erickson-Schroth, L., “A New Generation of Gender: Learning Patience from our Gender Non-Conforming Patients,” *Journal of the American Academy of Child and Adolescent Psychiatry*, Volume 52, Issue 10, pp. 995-997, October, 2013.
2. Janssen, A., et. al. “Theory of Mind and the Intolerance of Ambiguity: Two Case Studies of Transgender Individuals with High-Functioning Autism Spectrum
3. Janssen A, Huang H, and Duncan C., *Transgender Health*. February 2016, “Gender Variance Among Youth with Autism: A Retrospective Chart Review.” 1(1): 63-68. doi:10.1089/trgh.2015.0007.
4. Goedel WC, Reisner SL, Janssen AC, Poteat TC, Regan SD, Kreski NT, Confident G, Duncan DT. (2017). Acceptability and Feasibility of Using a Novel Geospatial Method to Measure Neighborhood Contexts and Mobility Among Transgender Women in New York City. *Transgender Health*. July 2017, 2(1): 96-106.
5. Janssen A., et. al., “Gender Variance Among Youth with ADHD: A Retrospective Chart Review,” in review
6. Janssen A., et. al., “Initial Clinical Guidelines for Co-Occurring Autism Spectrum Disorder and Gender Dysphoria or Incongruence in Adolescents,” *Journal of Child & Adolescent Psychology*, 105-115, January 2018.
7. Janssen A., et. al., “A Review of Evidence Based Treatments for Transgender Youth Diagnosed with Social Anxiety Disorder,” *Transgender Health*, 3:1, 27–33, DOI: 10.1089/ trgh.2017.0037.
8. Janssen A., et. al., “The Complexities of Treatment Planning for Transgender Youth with Co-Occurring Severe Mental Illness: A Literature Review and Case Study,” *Archives of Sexual Behavior*, 2019. # 3563492
9. Kimberly LL, Folkers KM, Friesen P, Sultan D, Quinn GP, Bateman-House A, Parent B, Konnoth C, Janssen A, Shah LD, Bluebond-Langner R, Salas-Humara C., “Ethical Issues in Gender-Affirming Care for Youth,” *Pediatrics*, 2018 Dec;142(6).
10. Strang JF, Janssen A, Tishelman A, Leibowitz SF, Kenworthy L, McGuire JK, Edwards-Leeper L, Mazefsky CA, Rofey D, Bascom J, Caplan R, Gomez-Lobo V, Berg D, Zaks Z, Wallace GL, Wimms H, Pine-Twaddell E, Shumer D, Register-Brown K, Sadikova E, Anthony LG., “Revisiting the Link: Evidence of the Rates of Autism in Studies of Gender Diverse Individuals,” *Journal of the American Academy of Child and Adolescent Psychiatry*, 2018 Nov;57(11):885-887.
11. Goedel William C, Regan Seann D, Chaix Basile, Radix Asa, Reisner Sari L, Janssen Aron C, Duncan Dustin T, “Using global positioning system methods to explore mobility patterns and exposure to high HIV prevalence neighbourhoods among transgender women in New York City,” *Geospatial Health*, 2019 Jan; 14(2): 351-356.
12. Madora, M., Janssen, A., Junewicz, A., “Seizure-like episodes, but is it really epilepsy?” *Current Psychiatry*. 2019 Aug; 18(8): 42-47.

13. Janssen, A., Busa, S., Wernick, J., "The Complexities of Treatment Planning for Transgender Youth with Co-Occurring Severe Mental Illness: A Literature Review and Case Study," *Archives of Sexual Behavior*. 2019 Oct; 48(7): 2003-2009.
14. Wernick Jeremy A, Busa Samantha, Matouk Kareen, Nicholson Joey, Janssen Aron, "A Systematic Review of the Psychological Benefits of Gender-Affirming Surgery," *Urol Clin North Am*. 2019 Nov; 46(4): 475-486.
15. Strang, J.F., Knauss, M., van der Miesen, A.I.R., McGuire, J., Kenworthy, L., Caplan, R., Freeman, A.J., Sadikova, E., Zacks, Z., Pervez, N., Balleur, A., Rowlands, D.W., Sibarium, E., McCool, M.A., Ehrbar, R.D., Wyss, S.E., Wimms, H., Tobing, J., Thomas, J., Austen, J., Pine, E., Willing, L., Griffin, A.D., Janssen, A., Gomez-Lobo, A., Brandt, A., Morgan, C., Meagher, H., Gohari, D., Kirby, L., Russell, L., Powers, M., & Anthony, L.G., (in press 2020). A clinical program for transgender and gender-diverse autistic/neurodiverse adolescents developed through community-based participatory design. *Journal of Clinical Child and Adolescent Psychology*. DOI 10.1080/15374416.2020.1731817
16. Coyne, C. A., Poquiz, J. L., Janssen, A., & Chen, D. Evidence-based psychological practice for transgender and non-binary youth: Defining the need, framework for treatment adaptation, and future directions. *Evidence-based Practice in Child and Adolescent Mental Health*.
17. Janssen, A., Voss, R.. Policies sanctioning discrimination against transgender patients flout scientific evidence and threaten health and safety. *Transgender Health*.
18. Dubin, S., Cook, T., Liss, A., Doty, G., Moore, K., Janssen, A. (In press 2020). Comparing Electronic Health Records Domains' Utility to Identify Transgender Patients. *Transgender Health*, DOI 10.1089/trgh.2020.0069

Published Abstracts

1. Thrun, M., Janssen A., et. al. "Frequency of Patronage and Choice of Sexual Partners may Impact Likelihood of HIV Transmission in Bathhouses," original research poster presented at the 2007 Conference on Retroviruses and Opportunistic Infections, February, 2007.
2. Janssen, A., "Advocating for the mental health of Lesbian, Gay, Bisexual and Transgender (LGBT) population: The Role of Psychiatric Organizations." Workshop for the American Psychiatric Association Institute of Psychiatric Services Annual Meeting, October 2012.
3. Janssen, A., "Gender Variance in Childhood and Adolescents: Training the Next Generation of Psychiatrists," 23rd Symposium of the World Professional Association for Transgender Health, Amsterdam, The Netherlands, February 2014.
4. Janssen, A., "When Gender and Psychiatric Acuity/Comorbidities Overlap: Addressing Complex Issues for Gender Dysphoric and Non-Conforming Youth," AACAP Annual Meeting, October 2014.
5. Janssen, A., "Patient Experiences as Drivers of Change: A unique model for reducing transgender health disparities as an academic medical center," Philadelphia Transgender Health Conference, June 2016.
6. Janssen, A., "How much is too much? Assessments & the Affirmative Approach to TGNC Youth," 24th Symposium of the World Professional Association for Transgender Health, Amsterdam, The Netherlands, June 2016.

7. Janssen, A., "Trauma, Complex Cases and the Role of Psychotherapy," 24th Symposium of the World Professional Association for Transgender Health, Amsterdam, The Netherlands, June 2016.
8. Janssen, A., "Gender Variance Among Youth with Autism: A Retrospective Chart Review," Research Poster, 24th Symposium of the World Professional Association for Transgender Health, Amsterdam, The Netherlands, June 2016.
9. Janssen, A., "Gender Fluidity and Gender Identity Development," Center for Disease Control – STD Prevention Conference, September 2016.
10. Janssen, A., "Transgender Identities Emerging During Adolescents' Struggles With Mental Health Problems," AACAP Annual Conference, October 2016.
11. Janssen, A., "How Much is Too Much? Assessments and the Affirmative Approach to Transgender and Gender Diverse Youth," US Professional Association for Transgender Health Inaugural Conference, Los Angeles, February 2017.
12. Janssen, A., "Trauma, Complex Cases and the Role of Psychotherapy," US Professional Association for Transgender Health Inaugural Conference, Los Angeles, February 2017.
13. Sutter ME, Bowman-Curci M, Nahata L, Tishelman AC, Janssen AC, Salas-Humara C, Quinn GP. Sexual and reproductive health among transgender and gender-expansive AYA: Implications for quality of life and cancer prevention. Oral presentation at the Oncofertility Consortium Conference, Chicago, IL. November 14, 2017.
14. Janssen, A., Sidhu, S., Gwynette, M., Turban, J., Myint, M., Petersen, D., "It's Complicated: Tackling Gender Dysphoria in Youth with Autism Spectrum Disorders from the Bible Belt to New York City," AACAP Annual Conference, October 2017.
15. May 2018: "A Primer in Working with Parents of Transgender Youth," APA Annual Meeting.
16. October 2018: "Gender Dysphoria Across Development" – Institute for AACAP Annual Conference.
17. November 2018: "Gender Variance Among Youth with Autism," World Professional Association for Transgender Health Biannual Conference.
18. March 2019: "Gender Trajectories in Child and Adolescent Development and Identity," Austin Riggs Grand Rounds.
19. Janssen, A., et. al., "Ethical Principles in Gender Affirming Care," AACAP Annual Conference, October 2019.
20. Janssen, A., "Gender Diversity and Gender Dysphoria in Youth," EPATH Conference, April 2019
21. Englander, E., Janssen A., et. al., "The Good, The Bad, and The Risky: Sexual Behaviors Online," AACAP Annual Conference, October 2020
22. Englander, E., Janssen, A., et. al., "Love in Quarantine," AACAP Annual Conference, October 2021
23. Janssen, A., Leibowitz, S., et. al., "The Evidence and Ethics for Transgender Youth Care: Updates on the International Standards of Care, 8th Edition," AACAP Annual Conference, October 2021
24. Turban, J., Janssen, A., et. al., "Transgender Youth: Understanding "Detransition," Nonlinear Gender Trajectories, and Dynamic Gender Identities," AACAP Annual Conference, October 2021

Books

1. Janssen, A., Leibowitz, S (editors), *Affirmative Mental Health Care for Transgender and Gender Diverse Youth: A Clinical Casebook*, Springer Publishing, 2018.

Book Chapters

1. Janssen, A., Shatkin, J., “Atypical and Adjunctive Agents,” *Pharmacotherapy for Child and Adolescent Psychiatric Disorders*, 3rd Edition, Marcel Dekker, Inc, New York, 2012.
2. Janssen, A; Liaw, K: “Not by Convention: Working with People on the Sexual & Gender Continuum,” book chapter in *The Massachusetts General Hospital Textbook on Cultural Sensitivity and Diversity in Mental Health*. Humana Press, New York, Editor R. Parekh, January 2014.
3. Janssen, A; Glaeser, E., Liaw, K: “Paving their own paths: What kids & teens can teach us about sexual and gender identity,” book chapter in *Cultural Sensitivity in Child and Adolescent Mental Health*, MGH Psychiatry Academy Press, Editor R. Parekh, 2016
4. Janssen A., “Gender Identity,” *Textbook of Mental and Behavioral Disorders in Adolescence*, February 2018.
5. Busa S., Wernick, J., & Janssen, A. (In Review) *Gender Dysphoria in Childhood*. *Encyclopedia of Child and Adolescent Development*. Wiley, 2018.
6. Janssen A., Busa S., “Gender Dysphoria in Childhood and Adolescence,” *Complex Disorders in Pediatric Psychiatry: A Clinician’s Guide*, Elsevier, Editors Driver D., Thomas, S., 2018.
7. Wernick J.A., Busa S.M., Janssen A., Liaw K.R.L. “Not by Convention: Working with People on the Sexual and Gender Continuum.” Book chapter in *The Massachusetts General Hospital Textbook on Diversity and Cultural Sensitivity in Mental Health*, editors Parekh R., Trinh NH. August, 2019.
8. Weis, R., Janssen, A., & Wernick, J. The implications of trauma for sexual and reproductive health in adolescence. In *Not Just a nightmare: Thinking beyond PTSD to help teens exposed to trauma*. 2019
9. Connors J., Irastorza, I., Janssen A., Kelly, B., “Child and Adolescent Medicine,” *The Equal Curriculum: The Student and Educator Guide to LGBTQ Health*, editors Lehman J., et al. November 2019.
10. Janssen, A., et. al., “Gender and Sexual Diversity in Childhood and Adolescence,” *Dulcan’s Textbook of Child and Adolescent Psychiatry*, 3rd edition, editor Dulcan, M., (in press)
11. Busa S., Wernick J, Janssen, A., “Gender Dysphoria,” *The Encyclopedia of Child and Adolescent Development*, DOI: 10.1002/9781119171492. Wiley, December 2020.

Invited Academic Seminars/Lectures

1. April 2006: “How to Talk to a Gay Medical Student” – presented at the National AAMC Meeting.
2. March 2011: “Kindling Inspiration: Two Model Curricula for Expanding the Role of Residents as Educators” – workshop presented at National AADPRT Meeting.
3. May 2011: Janssen, A., Shuster, A., “Sex Matters: Identity, Behavior and Development,” Grand Rounds Presentation, NYU Department of Child and Adolescent Psychiatry.

4. March 2012: Janssen, A., Lothringer, L., "Gender Variance in Children and Adolescents," Grand Rounds Presentation, NYU Department of Child and Adolescent Psychiatry.
5. June 2012: Janssen, A., "Gender Variance in Childhood and Adolescence," Grand Rounds Presentation, Woodhull Department of Psychiatry
6. October 2012: "Advocating for the mental health of Lesbian, Gay, Bisexual and Transgender (LGBT) population: The Role of Psychiatric Organizations." Workshop for the American Psychiatric Association Institute of Psychiatric Services Annual Meeting.
7. March 2013: "Gender Variance in Childhood and Adolescence," Sexual Health Across the Lifespan: Practical Applications, Denver, CO.
8. October 18th, 2013: "Gender Variance in Childhood and Adolescence," Grand Rounds Presentation, NYU Department of Endocrinology.
9. October, 2014: GLMA Annual Conference: "Theory of Mind and Intolerance of Ambiguity: Two Case Studies of Transgender Individuals with High-Functioning ASD," Invited Presentation
10. October 2014: New York Transgender Health Conference: "Mental Health Assessment in Gender Variant Children," Invited Presentation.
11. November, 2014: Gender Spectrum East: "Affirmative Clinical Work with Gender-Expansive Children and Youth: Complex Situations."
12. October 2015: "Gender Dysphoria and Complex Psychiatric Co-Morbidity," LGBT Health Conference, Invited Speaker
13. October 2015: "Transgender Health Disparities: Challenges and Opportunities," Grand Rounds, Illinois Masonic Department of Medicine
14. November 2015: "Autism and Gender Variance," Gender Conference East, Invited Speaker
15. February 2016: "Working with Gender Variant Youth," New York State Office of Mental Health State Wide Grand Rounds, Invited Speaker
16. March, 2016: "Working with Gender Variant Youth," National Council for Behavioral Health Annual Meeting, Invited Speaker
17. March 2016: "Gender Variance Among Youth with Autism: A Retrospective Chart Review and Case Presentation," Working Group on Gender, Columbia University, Invited Speaker.
18. September, 2016: "Best Practices in Transgender Mental Health: Addressing Complex Issues for Gender Dysphoric and Non-Conforming Youth," DeWitt Wallace Institute for the History of Psychiatry, Weill Cornell.
19. October, 2016: "LGBTQ Youth Psychiatric Care," Midwest LGBTQ Health Symposim
20. October, 2016: "Gender Fluidity and Gender Identity Development," NYU Health Disparities Conference.
21. February, 2017: "Best Practices in Transgender Mental Health," Maimonides Grand Rounds
22. March, 2017: "Transgender Health: Challenges and Opportunities," Invited speaker, Center for Disease Control STD Prevention Science Series.
23. September 2017: "Autism and Gender Dysphoria," Grand Rounds, NYU Department of Neurology.
24. November 2017: "Consent and Assent in Transgender Adolescents," Gender Conference East.

25. November 2017: “Transgender Mental Health: Challenges and Opportunities,” Grand Rounds, Lenox Hill Hospital.
26. April 2018: “Gender Trajectories in Childhood and Adolescent Development and Identity,” Sex, Sexuality and Gender Conference, Harvard Medical School.
27. September 2019: “Social and Psychological Challenges of Gender Diverse Youth,” Affirmative Mental Health Care for Gender Diverse Youth, University of Haifa.
28. October 2019: “Best Practices in Transgender Mental Health,” Grand Rounds, Rush Department of Psychiatry.
29. February 2020: “The Overlap of Autism and Gender Dysphoria,” Grand Rounds, Northwestern University Feinberg School of Medicine Department of Psychiatry
30. February 2020: “Gender Dysphoria and Autism,” Grand Rounds, University of Illinois at Chicago Department of Psychiatry
31. September 2021: “Gender Diversity and Autism,” Grand Rounds, Kaiser Permanente Department of Pediatrics
32. October 2021: Gender Dysphoria and Autism,” Grand Rounds, Case Western Reserve University Department of Psychiatry.

Selected Invited Community Seminars/Lectures

1. April 2012: “Gender and Sexuality in Childhood and Adolescence,” Commission on Race, Gender and Ethnicity, NYU Steinhardt Speakers Series.
2. February 2013: “Supporting Transgender Students in School,” NYC Independent School LGBT Educators Panel, New York, NY.
3. June 2013: “LGBT Health,” Presentation for Neuropsychology Department
4. August 2013: “Chronic Fatigue Syndrome: Etiology, Diagnosis and Management,” invited presentation.
5. September 2013: Panelist, “LGBTQ Inclusive Sex Education.”
6. April 2015: Transgender Children, BBC News, BBCTwo, invited expert
7. January 2016: Gender Dysphoria and Autism – Ackerman Podcast - <http://ackerman.podbean.com/e/the-ackerman-podcast-22-gender-dysphoria-autism-with-aron-janssen-md/>
8. February 2016: “Best Practices in Transgender Mental Health,” APA District Branch Meeting, Invited Speaker.
9. May 2016: “Best Practices in Transgender Mental Health,” Washington D.C., District Branch, APA, Invited Speaker
10. July 2016: “Transgender Youth,” Union Square West
11. November 2017: “Understanding Gender: Raising Open, Accepting and Diverse Children,” Heard in Rye, Conversations in Parenting.
12. January 2018: “The Emotional Life of Boys,” Saint David’s School Panel, Invited Speaker
13. June 2018: “Supporting Youth Engaged in Gender Affirming Care,” NYU Child Study Center Workshop.
14. October 2018: “Medicine in Transition: Advances in Transgender Mental Health,” NYCPS HIV Psychiatry and LGBT Committee Meeting.
15. October 2018: “Understanding Gender Fluidity in Kids,” NYU Slope Pediatrics.
16. October, 2021: Issues of Ethical Importance: Health Care for Pediatric LGBTQ+ Patients, American Medical Association, Invited Talk

Selected Mentoring of Graduate Students, Residents, Post-Doctoral Fellows

2013-2014	Rebecca Hopkinson, Adult Psychiatry Resident, Provided clinical supervision for one year and training in transgender mental health. Dr. Hopkinson works as at Attending Child Psychiatrist at Seattle Children's and works with transgender youth
2013-2014	Sara Weekly, Chief Child and Adolescent Psychiatry Resident. Provided clinical supervision. Dr. Weekly is now an attending physician at Bay Area Children's Association in Oakland, California.
2013-present	Elizabeth Glaeser, Undergraduate Student. Provided research and administrative supervision. Elizabeth is now a PhD candidate in Psychology at Columbia and the director of research at the Gender and Family Project
2014-2015	Laura Erickson Schroth, Adult Psychiatry Resident. Provided clinical supervision for one year and training in transgender mental health. Dr. Erickson Schroth is the editor of Trans Bodies, Trans Selves, and Attending Psychiatrist at the Hetrick Martin Institute
2015-2016	Brandon Ito, Child Psychiatry Fellow, Provided Clinical Supervision. Dr. Ito is now an Attending Child and Adolescent Psychiatrist at UCLA.
2015-2017	Howard Huang, Undergraduate Student. Provided research supervision. Howard is now a PhD candidate in psychology at Boston College, pursuing work in gender and sexuality with published peer-reviewed literature.
2016-2019	Samantha Busa, PsyD, Post-Doctoral Fellow. Provide clinical supervision in transgender health. Dr. Busa joined the NYU Gender and Sexuality Service as faculty in 2017.
2016-2019	Lara Brodsinzy, PhD, Attending Psychologist. Provide clinical supervision in transgender health. Dr. Brodsinzy is an Attending Psychologist on the NYU Pediatric Consultation Liaison Service.
2016-2019	Jeremy Wernick, MSW. Provide clinical and administrative supervision.
2017-2019	Serena Chang, Child Psychiatry Fellow; provide clinical and research supervision.

Major Research Interests

Gender and Sexual Identity Development
 Member, Research Consortium for Gender Identity Development
 Delirium: Assessment, Treatment and Management
 Suicide Prevention

Research Studies

<u>Study Title</u>	<u>IRB Study#</u>	<u>Dates</u>
Suicide Attempts Identified in a Children's Hospital Before and During COVID-19	2021-4428	2/26/21-present
Lurie Children's Sex & Gender Development Program Clinical Measure Collection	2019-2898	2019-present
Adolescent Gender Identity Research Study (principal investigator) - unfunded	s15-00431	4/15-5/19
Co-Occurrence of Autism Spectrum Disorders and Gender Variance: Retrospective Chart Review (principal investigator) - unfunded	s14-01930	10/14-5/19

Expert Consensus on Social Transitioning Among Prepubertal Children Presenting with Transgender Identity and/or Gender Variance: A Delphi Procedure Study (principal investigator) - unfunded	s13-00576	3/16-5/19
Co-Occurrence of ADHD/Gender Dysphoria (principal investigator) - unfunded	s16-00001	1/16-5/19
PICU Early Mobility- unfunded	s16-02261	12/16-5/19
Metformin for Overweight and Obese Children and Adolescents with Bipolar Spectrum Disorders Treated with Second-Generation Antipsychotics – Funded by PCORI	s16-01571	8/16-5/19

Other

Grant Funding:
Zero Suicide Initiative, PI Aron Janssen, M.D.
Awarded by Cardinal Health Foundation, 9/2020
Total amount: \$100,000

Direct income for the department generated by teaching Sex Matters: Identity, Behavior and
Development for the Child and Adolescent Mental Health Studies (CAMS) undergraduate program at
NYU:

<u>Time Frame</u>	<u>Income</u>
2011 - 2016	\$1,968,950

Selected Media Appearances:

Guest Expert on Gender Identity on Anderson, “When Your Husband Becomes Your Wife,” Air
Date February 8th, 2012
Guest Host, NYU About Our Kids on Sirius XM, 2011
NYU Doctor Radio: LGBT Health, September 2013
NYU Doctor Radio: LGBT Kids, November 2013
NYU Doctor Radio: LGBT Health, July 2014
NYU Doctor Radio: Gender Variance in Childhood, December 2014
BBC Two: Transgender Youth, April 2015
NYU Doctor Radio: Transgender Youth, June 2015
Fox-5 News: Trump’s proposed military ban and Transgender Youth, July, 2017
Healthline.com: Mental Health Experts Call President’s Tweets ‘Devastating’ for Trans Teens,
July, 2017
Huffington Post: What the Military Ban Says to Our Transgender Youth: August, 2017
Metro: How to talk to your transgender kid about Trump, August 2017
NYU Doctor Radio: Transgender Youth, August 2017

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

B.P.J. by her next friend and mother, HEATHER JACKSON,

Plaintiff,

v.

WEST VIRGINIA STATE BOARD OF EDUCATION, HARRISON COUNTY BOARD OF EDUCATION, WEST VIRGINIA SECONDARY SCHOOL ACTIVITIES COMMISSION, W. CLAYTON BURCH in his official capacity as State Superintendent, DORA STUTLER in her official capacity as Harrison County Superintendent, and THE STATE OF WEST VIRGINIA,

Defendants,

and

LAINY ARMISTEAD,

Defendant-Intervenor.

Civil Action No. 2:21-cv-00316

Hon. Joseph R. Goodwin

**EXPERT REPORT AND DECLARATION OF
JOSHUA D. SAFER, MD, FACP, FACE**

1. I have been retained by counsel for Plaintiffs as an expert in connection with the above-captioned litigation.

2. The purpose of this expert report and declaration is to offer my expert opinion on: (1) relevant medical and scientific background regarding gender identity and the attempted regulation of transgender women playing women's sports, including the Endocrine Society's Guidelines for providing gender-affirming care to transgender people; (2) the policies of athletic organizations regarding the participation of transgender women in women's sports, the difficulties that have arisen when athletic associations have attempted to define a person's sex,

and the relationship of these policies to the scholastic context; and (3) whether there is any medical justification for West Virginia's exclusion of transgender women and girls from school sports, including whether the available scientific evidence supports West Virginia's assertion that "classification of athletic teams according to" an "individual's reproductive biology and genetics at birth sex" "is necessary to promote equal athletic opportunities for the female sex."

3. I have knowledge of the matters stated in this expert report and declaration and have collected and cite to relevant literature concerning the issues that arise in this litigation in the body of this declaration and in the attached bibliography.

4. In preparing this expert report and declaration, I relied on my scientific education and training, my research experience, and my knowledge of the scientific literature in the pertinent fields. The materials I have relied upon in preparing this declaration are the same types of materials that experts in my field of study regularly rely upon when forming opinions on the subject. I may wish to supplement these opinions or the bases for them as a result of new scientific research or publications or in response to statements and issues that may arise in my area of expertise.

PROFESSIONAL BACKGROUND

5. I am a Staff Physician in the Endocrinology Division of the Department of Medicine at the Mount Sinai Hospital and Mount Sinai Beth Israel Medical Center in New York, NY. I serve as Executive Director of the Center for Transgender Medicine and Surgery at Mount Sinai. I also hold an academic appointment as Professor of Medicine in Mount Sinai's Icahn School of Medicine. A true and correct copy of my CV is attached hereto as Exhibit A.

6. I have been Board Certified in Endocrinology, Diabetes and Metabolism by the American Board of Internal Medicine since 1997.

7. I graduated from the University of Wisconsin in Madison with a Bachelor of Science degree in 1986. I earned my Doctor of Medicine degree from the University of Wisconsin in 1990. I completed intern and resident training at Mount Sinai School of Medicine, Beth Israel Medical Center in New York, New York from 1990 to 1993. From 1993 to 1994, I was a Clinical Fellow in Endocrinology at Harvard Medical School and Beth Israel Deaconess Medical Center in Boston, Massachusetts. I stayed at the same institution, serving as a Clinical and Research Fellow in Endocrinology under Fredric Wondisford, from 1994 to 1996.

8. Since 1997, I have evaluated and treated patients along with conducting research in endocrinology. Since 2004, my patient care and research has been focused on the medicine/science specific to transgender people. I have led several other programs either in transgender medicine or in general endocrinology. In particular, I served as the Medical Director of the Center for Transgender Medicine and Surgery, Boston Medical Center, Boston, MA (2016-2018); as the Director of Medical Education, Endocrinology Section, Boston University School of Medicine, Boston, MA (2007-2018); as the Program Director for Endocrinology Fellowship Training, Boston University Medical Center, Boston, MA (2007-2018); and as Director of the Thyroid Clinic, Boston Medical Center, Boston, MA (1999-2003).

9. I have authored or coauthored over 100 peer-reviewed papers including many critical reviews; textbook chapters; and case reports in endocrinology and transgender medicine.

10. Among my publications are the latest review of transgender medicine in the New England Journal of Medicine and the latest review of transgender medicine in the Annals of Internal Medicine. See Safer JD, Tangpricha V. Care of transgender persons. *N Engl J Med* 2019; 381:2451-2460; Safer JD, Tangpricha V. Care of the transgender patient. *Ann Intern Med* 2019; 171:ITC1-ITC16. I am also a co-author of the sections of UpToDate that relate to gender-

affirming hormone treatment for transgender people. UpToDate is an evidence-based, physician authored, on-line medical guide and is currently the most widely used such guide among medical providers.

11. I was the inaugural President of the United States Professional Association for Transgender Health (“USPATH”). I have served in several other leadership roles in professional societies related to endocrinology and transgender health. These societies include the Alliance of Academic Internal Medicine, the American College of Physicians Council of Subspecialty Societies, the American Board of Internal Medicine, the Association of Program Directors in Endocrinology and Metabolism, and the American Thyroid Association.

12. Since 2014, I have held various roles as a member of the World Professional Association for Transgender Health (“WPATH”), the leading international organization focused on transgender health care. WPATH has approximately 2,000 members throughout the world and is comprised of physicians, psychiatrists, psychologists, social workers, surgeons, and other health professionals who specialize in health care for transgender people. From 2016 to the present, I have served on the Writing Committee for Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People.

13. I have served in various roles as a member of the Endocrine Society since 2014. I served on a nine-expert Task Force to develop the Endocrine Treatment of Transgender Persons Clinical Practice Guideline from 2014 to 2017. The experts on the Task Force which included me, a methodologist, and a medical writer co-authored the “Endocrine Treatment of Gender-Dysphoria/Gender Incongruent Persons: An Endocrine Society Clinical Practice Guideline,” (“Endocrine Society Guidelines”), available at <https://academic.oup.com/jcem/article/102/11/3869/4157558>.

14. I have served as a Transgender Medicine Guidelines Drafting Group Member for the International Olympic Committee (“IOC”) since 2017.

15. Since 2019, I have also served as a drafting group member of the transgender medical guidelines of World Athletics, formerly known as the International Amateur Athletic Federation (“IAAF”).

16. I have not previously testified as an expert witness in either deposition or at trial. I am being compensated at an hourly rate of \$250 per hour for preparation of expert declarations and reports, and \$400 per hour for time spent preparing for or giving deposition or trial testimony. My compensation does not depend on the outcome of this litigation, the opinions I express, or the testimony I provide.

RELEVANT MEDICAL AND SCIENTIFIC BACKGROUND

17. “Gender identity” is the medical term for a person’s internal, innate sense of belonging to a particular sex. *See* Endocrine Society Guidelines, Tbl.1 *and* Safer JD, Tangpricha V. Care of transgender persons. *N Engl J Med* 2019; 381:2451–2460, Tbl.1.

18. Although the detailed mechanisms are unknown, there is a medical consensus that there is a significant biologic component underlying gender identity. Safer JD, Tangpricha V. Care of transgender persons. *N Engl J Med* 2019; 381:2451-2460; Safer JD, Tangpricha V. Care of the transgender patient. *Ann Intern Med* 2019; 171:ITC1-ITC16. A person’s gender identity is durable and cannot be changed by medical intervention.

19. The terms “gender identity,” “gender roles,” and “gender expression” refer to different things.

20. Gender roles are behaviors, attitudes, and personality traits that a society (in a given culture and historical period) designates as masculine or feminine and/or that society

associates with or considers typical of the social role of men or women. See Endocrine Society Guidelines Tbl.1. The convention that girls wear pink and have longer hair, or that boys wear blue and have shorter hair, are examples of socially constructed gender roles from a particular culture and historical period.

21. By contrast, “gender identity” does not refer to a set of socially contingent behaviors, attitudes, or personality traits that a society designates as masculine or feminine. It is an internal and largely biological phenomenon.

22. Gender expression is how a person communicates gender identity both internally and to others. See Safer JD, Tangpricha V. Care of transgender persons. *N Engl J Med* 2019; 381:2451–2460, Tbl.1. For example, a person with a female gender identity might express her identity through typically feminine outward expressions of gender roles like wearing longer hair or more typically feminine clothing.

23. The phrase “biological sex” is an imprecise term that can cause confusion. A person’s sex encompasses the sum of several different biological attributes, including sex chromosomes, certain genes, gonads, sex hormone levels, internal and external genitalia, other secondary sex characteristics, and gender identity. Those attributes are not always aligned in the same direction. See Endocrine Society Guidelines; Safer JD, Tangpricha V. Care of transgender persons. *N Engl J Med* 2019; 381:2451–2460.

24. Before puberty, boys and girls typically have the same levels of circulating testosterone. After puberty, the typical range of circulating testosterone for non-transgender women is similar to before puberty (<1.7 nmol/L), and the typical range of circulating testosterone for non-transgender men is 9.4-35 nmol/L. See Endocrine Society Guidelines (p 3888) and Safer JD, Tangpricha V. Care of transgender persons. *N Engl J Med* 2019.

25. Before puberty, age-grade competitive sports records show minimal or no differences in athletic performance between non-transgender boys and non-transgender girls before puberty. But after puberty, non-transgender boys and men as a group have better average performance outcomes in most athletic competitions when compared to non-transgender girls and women as a group. Based on current research comparing non-transgender boys and men with non-transgender girls and women before, during, and after puberty, the primary known biological driver of these average group differences is testosterone starting at puberty, and not reproductive biology or genetics. See Handelsman DJ, et al. Circulating testosterone as the hormonal basis of sex differences in athletic performance. *Endocrine Reviews* 2018; 39:803–829, (p 820) (summarizing evidence rejecting hypothesis that physiological characteristics are driven by Y chromosome).

26. Although there are ranges of testosterone that are considered typical for non-transgender men and women, many non-transgender women have testosterone levels outside the typical range.

a. Approximately 6% to 10% of women have a condition called polycystic ovary syndrome (PCOS), which can raise women’s testosterone levels up to 4.8 nmol/L.

b. Some elite female athletes have “46,XY DSDs,” a group of conditions where individuals have XY chromosomes but are born with typically female external genitalia and assigned a female sex at birth. Among individuals with 46,XY DSD some may have inactive testosterone receptors (a syndrome called “complete androgen insensitivity syndrome, CAIS”) which means they don’t respond to testosterone despite very high levels. Usually, these individuals have female gender identity and have external genitalia

that are typically female. They do not develop the physical characteristics associated with typical male puberty.

c. Other individuals with 46,XY DSD may have responsive testosterone receptors. These individuals may have female gender identity but at puberty they may start to develop higher levels of testosterone along with secondary sex characteristics that are typically masculine.

WORLD ATHLETICS POLICIES FOR WOMEN WITH HYPERANDROGENISM AND WOMEN WHO ARE TRANSGENDER

27. World Athletics is the international governing body for the sport of track-and-field athletics. Beginning in 2011, World Athletics (then known as IAAF) began requiring that women with elevated levels of circulating testosterone lower their levels of testosterone below a threshold amount in order to compete in elite international women's sports competitions. Under the 2011 regulations, women with hyperandrogenemia (defined as serum testosterone levels above the normal range) were allowed to compete only if they demonstrated that they had testosterone levels below 10 nmol/L or that they had CAIS, preventing their bodies from responding to testosterone.¹

28. In 2018 the IAAF issued revised regulations lowering the maximum testosterone threshold to 5 nmol/L.² The revised regulations were upheld by the Court of Arbitration for Sport ("CAS") in 2019.

¹ A copy of the 2011 regulation is available at [https://www.bmj.com/sites/default/files/response_attachments/2014/06/IAAF%20Regulations%20\(Final\)-AMG-30.04.2011.pdf](https://www.bmj.com/sites/default/files/response_attachments/2014/06/IAAF%20Regulations%20(Final)-AMG-30.04.2011.pdf)

² A copy of the 2018 regulations is available at <https://www.iaaf.org/download/download?filename=fd2923ad-992f-4e43-9a70-78789d390113.pdf&urlslug=IAAF%20Eligibility%20Regulations%20for%20the%20Female%20Classification%20%5BAthletes%20with%20Differences%20of%20Sex%20Development%5D%20in%20force%20as%20from%208%20May%202019>

29. In 2019, the IAAF adopted regulations allowing women who are transgender to participate in elite international women's sports competitions if their total testosterone level in serum is beneath a particular threshold for at least one year before competition. The IAAF set the threshold at 5 nmol/L, which was the same threshold set by the IAAF's 2018 regulations for non-transgender women with hyperandrogenism that had been upheld by the CAS when contested.³

30. The IAAF rules are consistent with the Endocrine Society Guidelines for the treatment of women who are transgender, which recommend that hormone therapy target circulating testosterone levels to a typical female range at or below 1.7 nmol/L (Endocrine Society Guidelines, p. 3887) and with the study of testosterone levels achieved in practice by medically treated women who are transgender (Liang JJ, et al. Testosterone levels achieved by medically treated transgender women in a United States endocrinology clinic cohort. *Endocrine Practice* 2018; 24:135-142).

INTERNATIONAL OLYMPIC COMMITTEE POLICIES FOR WOMEN WHO ARE TRANSGENDER

31. Formal eligibility rules for the participation of transgender women in the Olympics were published in 2003. The 2003 rules required that transgender women athletes could compete in women's events only if they had genital surgery, a gonadectomy (*i.e.*, removal of the testes), and legal documentation of female sex.⁴

³ A copy of the 2019 regulations is available at <https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwi8qbO nsNL0AhUBkIkEHWdpAiQQFnoECAUQAQ&url=https%3A%2F%2Fwww.worldathletics.org%2Fdownload%2Fdownload%3Ffilename%3Dace036ec-a21f-4a4a-9646-fb3c40fe80be.pdf%26urlslug%3DC3.5%2520-%2520Eligibility%2520Regulations%2520Transgender%2520Athletes&usg=AOvVaw1aPuD3gUoz5hcGKgmumVb5>

⁴ A copy of the 2003 policy is available at <https://olympics.com/ioc/news/ioc-approves-consensus-with-regard-to-athletes-who-have-changed-sex-1>

32. However, many women who are transgender are treated with medicines alone and don't have gonadectomy. As well, many jurisdictions do not have systems to document the sex of transgender people. In some jurisdictions, being transgender is illegal, and disclosure that someone is transgender can be unsafe.

33. Therefore, in 2015, the IOC adopted new guidance modeled after the IAAF's 2011 regulations for non-transgender women with hyperandrogenism. Under the 2015 IOC guidance, women who are transgender were required to demonstrate that their total testosterone level in serum was below 10 nmol/L for at least one year prior to competition. The 10 nmol/L threshold was the same threshold set by the IAAF's 2011 regulations.⁵

34. In 2021, the IOC adopted a new "Framework on Fairness, Inclusion, and Non-Discrimination on the Basis of Gender Identity and Sex Variations" (the "2021 framework"), which replaces the 2015 guidance.⁶

35. Unlike the IOC's 2003 and 2015 policies, the IOC's 2021 framework does not attempt to adopt a single set of eligibility standards for the participation of transgender athletes that would apply universally to every IOC sport. Instead, the 2021 framework provides a set of governing principles for sporting bodies to follow when adopting eligibility rules for their particular sport.

36. Under the 2021 framework, "[n]o athlete should be precluded from competing or excluded from competition on the exclusive ground of an unverified, alleged or perceived unfair

⁵ A copy of the 2015 policy is available at https://stillmed.olympic.org/Documents/Commissions_PDFfiles/Medical_commission/2015-11_ioc_consensus_meeting_on_sex_reassignment_and_hyperandrogenism-en.pdf

⁶ A copy of the 2021 framework is available at https://stillmed.olympics.com/media/Documents/News/2021/11/IOC-Framework-Fairness-Inclusion-Non-discrimination-2021.pdf?_ga=2.207516307.1210589288.1636993769-1638189514.1636993769

competitive advantage due to their sex variations, physical appearance and/or transgender status.” Principle 5.1. “Until evidence . . . determines otherwise, athletes should not be deemed to have an unfair or disproportionate competitive advantage due to their sex variations, physical appearance and/or transgender status.” Principles 5.2.

37. The 2021 framework further provides that “[a]ny restrictions arising from eligibility criteria should be based on robust and peer reviewed research that: (a) demonstrates a consistent, unfair, disproportionate competitive advantage in performance and/or an unpreventable risk to the physical safety of other athletes; (b) is largely based on data collected from a demographic group that is consistent in gender and athletic engagement with the group that the eligibility criteria aim to regulate; and (c) demonstrates that such disproportionate competitive advantage and/or unpreventable risk exists for the specific sport, discipline and event that the eligibility criteria aim to regulate.” Principle 6.1

NCAA POLICIES FOR WOMEN WHO ARE TRANSGENDER

38. Since 2011, the National College Athletics Association (“NCAA”) has allowed women who are transgender to participate on the same teams as other women after one year of testosterone suppression. Under the NCAA policy transgender student-athletes certified that they have been on hormone therapy for a period of one year. The NCAA policy did not require ongoing testosterone testing.

39. The NCAA recently announced that it has revised its policy to adopt a “sport-by-sport approach” that “aligns transgender student-athlete participation for college sports with recent policy changes.” See NCAA Media Center: Board of Governors updates transgender participation policy (Jan. 19, 2022), at <https://www.ncaa.org/news/2022/1/19/media-center-board-of-governors-updates-transgender-participation-policy.aspx>. “Like the Olympics, the

updated NCAA policy calls for transgender participation for each sport to be determined by the policy for the national governing body of that sport, subject to ongoing review and recommendation by the NCAA Committee on Competitive Safeguards and Medical Aspects of Sports to the Board of Governors.” *Id.* The new NCAA policy contemplates that for certain sports, the national governing body for the sport may require transgender athletes “to document sport-specific testosterone levels.” *Id.*

PARTICIPATION OF GIRLS AND WOMEN WHO ARE TRANSGENDER IN THE SCHOLASTIC CONTEXT

40. The policies developed by World Athletics and the IOC for transgender athletes were based on the particular context of elite international competition. Not all of the same considerations apply in scholastic contexts.

41. The World Athletics and prior IOC policies were more stringent than the prior NCAA policy because those organizations were concerned with creating policies that cannot be manipulated by governments that are not bound by the rule of law. For example, there have been many well-known examples of state-sponsored doping scandals. The Russian Olympic team is currently banned from international competition due to an organized doping effort. Also, there have been cases where governments have issued fraudulent birth certificates and identification documents. In 2000, Yang Yun was a medal winner in Gymnastics from the Chinese team. She later reported that she was 14-years-old at the time in violation of the rule that all athletes for her events had to be at least 16-years-old. In 2008, He Kexin was 14-years-old when participating in Gymnastics for the Chinese team in violation of the same rule that athletes be at least 16-years-old in those events. A new passport for Ms. He had hastily appeared 6 months prior to the Olympic Games that year with a new birth year so that Ms. He could qualify.

42. To confront the significant problem of state-sponsored cheating, World Athletics and the IOC have to develop eligibility criteria for transgender athletes that can be independently verified to prevent manipulation by non-transgender athletes, and that do not depend on the gender marker listed on identification documentation issued by an athlete's home country. Those concerns do not apply to scholastic athletic competitions in the United States. Scholastic athletic associations can rely on school records to show that an athlete is a girl who is transgender and has socially transitioned to live consistently with her gender identity as a girl.

43. The eligibility criteria for World Athletics and the IOC were also created as part of a system in which elite athletes in international competitions are already regulated and monitored in some circumstances like for doping. Within that context, testing female athletes' levels of testosterone is somewhat analogous to the types of restrictions and invasion of privacy that already exist. By contrast, in athletic competitions that are not as heavily regulated and monitored, it is hard to justify singling out girls who are transgender, girls with 46,XY DSDs, or girls who may just appear more typically masculine for special testosterone requirements that impose a significant additional burden.

44. The concerns that animated the World Athletics and prior IOC policies are even more attenuated for students in middle school and high school, where athletes' ages typically range from 11-18, with different athletes in different stages of pubertal development. Increased testosterone begins to affect athletic performance at the beginning of puberty, but those effects continue to increase each year of puberty until about age 18, with the full impact of puberty resulting from the cumulative effect of each year. As a result, a 14, 15, or 16-year old has experienced less cumulative impact from testosterone than a 17 or 18-year old.

45. Finally, unlike elite international competitions, schools and colleges often provide athletic competition as part of a broader educational mission. In that context, when scholastic athletics are a component of the educational process, institutions may adopt policies designed to emphasize inclusion and to provide the most athletic opportunities to the greatest number of people.

WEST VIRGINIA’S HB 3293

46. There is no medical justification for West Virginia’s categorical exclusion of girls who are transgender from participating in scholastic athletics on the same teams as other girls.

47. HB 3293 states that “[c]lassification of teams according to biological sex is necessary to promote equal athletic opportunities for the female sex.” The law defines “biological sex” as “an individual’s physical form as a male or female based solely on the individual’s reproductive biology and genetics at birth.”

48. West Virginia’s definition of “biological sex” does not reflect any medical understanding of that ambiguous term. As noted above, a person’s sex encompasses the sum of several different biological attributes, including sex chromosomes, certain genes, gonads, sex hormone levels, internal and external genitalia, other secondary sex characteristics, and gender identity. Those attributes are not always aligned in the same direction. *See* Endocrine Society Guidelines; Safer JD, Tangpricha V. Care of transgender persons. *N Engl J Med* 2019; 381:2451-2460. For example, if West Virginia defines “biological sex” solely based on “reproductive biology and genetics at birth” it is not clear how West Virginia would define the “biological sex” of children with “46,XY DSDs,” who have XY chromosomes but typically female external reproductive anatomy.

49. Even as applied to people without intersex characteristics or 46,XY DSDs, the statutory definition of “biological sex” is inconsistent with West Virginia’s stated goal of “promot[ing] equal athletic opportunities for the female sex.” By excluding girls who are transgender based on “biological sex,” and defining that term to mean “reproductive biology and genetics at birth,” West Virginia categorically prevents girls who are transgender from participating on girls’ teams regardless of whether they are pre-pubertal, receiving puberty blockers, or receiving gender-affirming hormone therapy. But based on current research, the primary known biological cause of average differences in athletic performance between non-transgender men as a group and non-transgender women as a group is circulating testosterone—not “reproductive biology and genetics at birth.” A person’s genetic makeup and internal and external reproductive anatomy are not useful indicators of athletic performance and have not been used in elite competition for decades.

50. With respect to average athletic performance, girls and women who are transgender and who do not go through endogenous puberty are somewhat similarly situated to women with XY chromosomes who have complete androgen insensitivity syndrome. It has long been recognized that women with CAIS have no athletic advantage simply by virtue of having XY chromosomes. *See also* Handelsman DJ, *et al.* Circulating testosterone as the hormonal basis of sex differences in athletic performance. *Endocrine Reviews* 2018; 39:803–29, p .820 (summarizing evidence rejecting hypothesis that physiological characteristics are driven by Y chromosome).

51. HB 3293 is also dramatically out of step with even the most stringent policies of elite international athletic competitions for girls and women who are transgender and who have gone through endogenous puberty. Unlike the policies of the IOC, World Athletics, or the

NCAA, HB 3293 excludes girls and women who are transgender from participating on girls' and women's sports teams even if they have suppressed their circulating levels of testosterone through gender-affirming hormone therapy.

52. Some critics of the prior IOC guidelines and World Athletics and NCAA policies have speculated that lowering the level of circulating testosterone does not fully mitigate the athletic advantage derived from endogenous puberty. But there is no basis to assert with any degree of confidence that this hypothesis is true. Based on the limited data available, it is equally or more plausible to hypothesize that women who are transgender could be at a net *disadvantage* in particular sports after receiving gender affirming hormone therapy, as compared to non-transgender women.

53. For example, transgender women who go through typically male puberty will tend to have larger bones than non-transgender women, even after receiving gender-affirming hormone therapy. But larger bones may be a disadvantage for transgender women who have typically female levels of circulating testosterone. Muscle mass will be decreased with the shift to female levels of circulating testosterone. Having larger bones without corresponding levels of testosterone and muscle mass would mean that a runner has a bigger body to propel with less power to propel it.

54. Similarly, in a sport where athletes compete in different weight classes (*e.g.* weight lifting), the fact that a transgender woman has bigger bones may be a disadvantage because her ratio of muscle-to-bone will be much lower than the ratio for other women in her weight class who have smaller bones.

55. There are only two studies examining the effects of gender-affirming hormone therapy on the athletic performance of transgender female athletes. The first is a small study of

eight long-distance runners who are transgender women. The study showed that after undergoing gender-affirming medical intervention, which included lowering their testosterone levels, the athletes' performance was reduced so that their performance when compared to non-transgender women was proportionally the same as their performance had been before treatment relative to non-transgender men. See Harper J. Race times for transgender athletes. *Journal of Sporting Cultures and Identities* 2015; 6:1–9.

56. A more recent study retrospectively reviewed the military fitness test results of 46 transgender women in the U.S. Air Force before and after receiving gender-affirming hormone therapy. These authors found that any advantage transgender women had over non-transgender women in performing push-ups and sit-ups was negated after 2 years. The study also found that before beginning gender affirming hormone therapy, transgender women completed the 1.5 mile run 21% faster on average than non-transgender women; and after 2 years of gender-affirming hormone therapy, transgender women completed the 1.5 mile run 12% faster on average than non-transgender women. See Roberts TA, Smalley J, Ahrendt D. Effect of gender affirming hormones on athletic performance in transwomen and transmen: implications for sporting organisations and legislators. *Br J Sports Med*. 2020.

57. Neither of these limited studies proves there are meaningful athletic advantages for transgender women after receiving gender-affirming hormone therapy, which could only be shown by longitudinal transgender athlete case-comparison studies that control for variations in hormonal exposure and involve numerous indices of performance. Moreover, the ability to perform push-ups and sit-ups or to run 1.5 miles does not necessarily translate into an athletic advantage in any particular athletic event. Because different sports require different types of physical performance, the studies suggest that the existence and extent of a performance

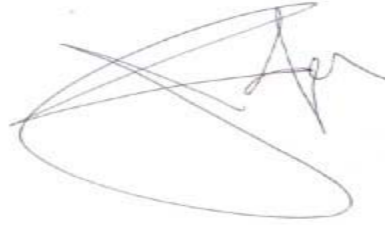
advantage may vary from sport to sport and should not be subject to a categorical across-the-board rule.

58. Even if evidence were eventually to show that on average transgender women have some level of advantage compared to average non-transgender women, those findings would have to be placed in context of all the other intra-sex genetic variations among athletes that can enhance athletic performance among different women or different men.

59. For example, in the academic literature, there are gene sequence variations that can be associated with athleticism referred to as “performance enhancing polymorphisms” or “PEPs.” A PEP is a variation in the DNA sequence that is associated with improved athletic performance. For example, variations in mitochondrial DNA have been associated with greater endurance capacity and greater mitochondrial density in muscles. Other PEPs are associated with blood flow or muscle structure. See Ostrander EA, et al. Genetics of athletic performance. *Annu Rev Genomics Hum Genet* 2009; 10:407–429.

60. As the IOC’s 2021 framework recognizes, there is no inherent reason why transgender women’s physiological characteristics related to athletic performance should be treated as any more of an “unfair” advantage than the advantages that already exist among different women athletes. The 2021 framework instructs that, even at the most elite level of competition, sporting organizations should base eligibility restrictions on whether there exists “a consistent, unfair, and disproportionate competitive advantage” when viewed within the broader context of all the other intra-sex variations that may give a comparative athletic advantage to a particular athlete.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

A handwritten signature in blue ink, appearing to read 'J. Safer', with a large, sweeping loop underneath.

Executed on January 21, 2022

Joshua D. Safer, MD, FACP, FACE

BIBLIOGRAPHY

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Harper J. Race times for transgender athletes. *Journal of Sporting Cultures and Identities* 2015; 6:1–9.

Hembree WC, et al. Endocrine treatment of gender-dysphoria/gender incongruent persons: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2017; 102: 3869–3903.

Ostrander EA, et al. Genetics of athletic performance. *Annu Rev Genomics Hum Genet* 2009; 10:407–429.

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Rogol AD, Pieper LP. The interconnected histories of endocrinology and eligibility in women's sports. *Horm Res Paediatr* 2018; 90:213–220.

Safer JD, Tangpricha V. Care of the transgender patient. *Ann Intern Med* 2019; 171:ITC1-ITC16.

Safer JD, Tangpricha V. Care of transgender persons. *N Engl J Med* 2019; 381:2451-2460.

EXHIBIT A

CURRICULUM VITAE

Joshua D. Safer, MD, FACP, FACE

January 6, 2022

Office Address: 275 7th Avenue, 15th Floor
New York, NY 10001

Tel: (212) 604-1790

E-mail: jsafer0115@gmail.com

Academic Training

1990 MD	University of Wisconsin School of Medicine, Madison, WI
1986 BS	University of Wisconsin, Madison, WI, Economics

Postdoctoral Training

1994 - 1996	Clinical and Research Fellow, Endocrinology, under Fredric Wondisford, Harvard Medical School - Beth Israel Deaconess Medical Center, Boston, MA
1993 - 1994	Clinical Fellow, Endocrinology, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, MA
1990 - 1993	Intern and Resident, Department of Medicine, The Mount Sinai School of Medicine, Beth Israel Medical Center, New York City, NY

Academic Appointments

2019 - present	Professor of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY
2006 - 2018	Associate Professor of Medicine and Molecular Medicine, Boston University School of Medicine
1999 - 2005	Assistant Professor of Medicine, Boston University School of Medicine
1996 - 1999	Instructor in Medicine, Harvard Medical School
1993 - 1996	Fellow in Medicine, Harvard Medical School

Hospital Appointments

2018 - present	Staff Physician, The Mount Sinai Hospital, New York City, NY
2018 - present	Staff Physician, Mount Sinai Beth Israel Medical Center, New York City, NY
1999 - 2018	Staff Physician, Boston University Medical Center, Boston, MA
2001 - 2006	Staff Physician, Veterans Administration Boston Health Care, Boston, MA
1996 - 1999	Staff Physician, Beth Israel Deaconess Medical Center, Boston, MA
1990 - 1993	House Staff, Beth Israel Medical Center, New York City, NY

Other Medical Staff Appointments

2004 - 2013	Staff Physician, Massachusetts Institute of Technology Medical, Cambridge, MA
1994 - 1999	Physician, Harvard Vanguard Medical Associates, Boston, MA
1987 - 1996	Captain, United States Army Reserve, Medical Corps

Joshua D. Safer, MD, FACP, FACE**Honors:**

2019	Fellow, American College of Endocrinology
2019	Preaw Hanseree Memorial Lecture, University of Wisconsin-Madison
2017	Lesbian, Gay, Bisexual and Transgender Health Award, Massachusetts Medical Society
2012	Outstanding Service Award, Association of Program Directors in Endocrinology and Metabolism
2007	Fellow, American College of Physicians
2004	Boston University School of Medicine Outstanding Student Mentor Award
2001	Abbott Thyroid Research Advisory Council Award
1996	Knoll Thyroid Research Clinical Fellowship Award, Endocrine Society
1995	Trainee Investigator Award for Excellence in Scientific Research, American Federation for Clinical Research (AFCR)
1994	Trainee Investigator Award for Excellence in Scientific Research, AFCR
1990	The University of Wisconsin Medical Alumni Association Award
1988-1990	Senior Class President, University of Wisconsin, School of Medicine

Licensure and Certification

1997	Board Certification in Endocrinology, Diabetes and Metabolism, American Board of Internal Medicine, recertified 2007, 2017
1994	Board Certification in Internal Medicine, American Board of Internal Medicine, recertified 2007
1993	Massachusetts License Registration #77459, inactive
1990	New York License Registration #187263-1

Departmental and University Committees***Icahn School of Medicine at Mount Sinai***

2020-present	Mount Sinai Disparities and Equity Research Taskforce Steering Committee

Boston Medical Center

2016-2018	Physician Satisfaction Task Force, Department of Medicine
2016-2018	Transgender Patient Task Force
2006-2017	Pharmacy and Therapeutics Committee, Health Net Plan

Boston University School of Medicine

2009-2018	Admissions Committee
2005	Review Committee, Department of Medicine Pilot Project Grants
2000	Residency and Fellowship Core Curriculum Committee,
2000-2018	Internship Selection Committee, Residency Program in Medicine

Joshua D. Safer, MD, FACP, FACE

Boston University Goldman School of Dental Medicine

2003-2018 Course Directors Committee, Goldman School of Dental Medicine

Teaching Experience and Responsibilities

Icahn School of Medicine at Mount Sinai

2019-present Lecturer in Endocrinology, Second-year Pathophysiology Course

Tufts University School of Medicine

2016-2018 Lecturer in Endocrinology, Second-year Pathophysiology Course

Boston University School of Medicine

2003-2018 Course Director, Disease and Therapy - Endocrinology Section

1999-2018 Regular lectures to medical students, residents, and fellows on thyroid disease, diabetes insipidus, and transgender medicine

Boston University Goldman School of Dental Medicine

2002-2018 Course Director, General Medicine and Dental Correlations

2002-2018 Course Director, Medical Concerns in the Dental Patient

Joshua D. Safer, MD, FACP, FACE**Major Administrative Responsibilities**

2018-present	Executive Director, Center for Transgender Medicine and Surgery, Mount Sinai Health System, New York City, NY
2016-2018	Medical Director, Center for Transgender Medicine and Surgery, Boston Medical Center, Boston, MA
2007-2018	Director, Medical Education, Endocrinology Section, Boston University School of Medicine, Boston, MA
2007-2018	Program Director, Endocrinology Fellowship Training, Boston University Medical Center, Boston, MA
1999-2003	Director, Thyroid Clinic, Boston Medical Center, Boston, MA

Other Professional Activities**Professional Societies: Memberships**

2016-present	United States Professional Association for Transgender Health (USPATH)
2014-present	World Professional Association for Transgender Health (WPATH)
2007-present	Association of Program Directors in Endocrinology and Metabolism (APDEM)
2007-present	Association of Specialty Professors (ASP), Alliance of Academic Internal Medicine (AAIM)
1999-present	American Association of Clinical Endocrinologists
1998-2018	American Thyroid Association
1995-present	Endocrine Society
1994-present	American College of Physicians
1994-1996	American Federation for Medical Research
1993-2018	Massachusetts Medical Society

Professional Societies: Offices Held and Committee Assignments**International*****World Athletics (formerly IAAF)***

2019-present	Drafting Group Member, Transgender Medical Guidelines

International Olympic Committee (IOC)

2017-present	Drafting Group Member, Transgender Medical Guidelines

World Professional Association for Transgender Health (WPATH)

2016-present	Writing Committee Member, Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People
2016-2018	Co-Chair, Scientific Committee, International Meeting, Buenos Aires - 2018
2015-2016	Chair, Scientific Committee, International Meeting, Amsterdam - 2016
2015-present	Task Force Member, Global Education Institute
2015-present	Media Liaison

Joshua D. Safer, MD, FACP, FACE

TransNet – International Consortium for Transgender Medicine and Health Research

2014-present Secretary and Co-Chair, Steering Committee

National

United States Professional Association for Transgender Health (USPATH)

2018-2019 President

Alliance of Academic Internal Medicine

2016-2019 Chair, Compliance Committee
 2016-2017 Committee member, Compensation
 2015-2016 President, Association of Specialty Professors (ASP)
 2014-2017 Council member
 2014-2019 Task Force member, Program Planning
 2014-2019 Work Group member, Survey Center
 2013-2015 Chair, Program Planning Committee, ASP
 2012-2017 Council member, ASP
 2012-2013 Chair, Membership Services Committee, ASP
 2010-2015 Chair, Program Directors Site Visit Training Seminar, ASP
 2007-2013 Committee member, Membership Services, ASP

American College of Physicians

2016-2018 Council of Subspecialty Societies member

Endocrine Society

2020-present Transgender Medicine, Special Interest Group member
 2017-present Advisory Board member, Transgender/Disorders of Sex Development
 2017-2020 Committee member, Clinical Endocrine Education
 2014-present Media Liaison for Transgender Medicine
 2014-2017 Task Force member, Endocrine Treatment of Transgender Persons Clinical Practice Guideline

American Board of Internal Medicine

2013-2018 Task Force member, Endocrinology Procedures
 2013 Task Force member, ASP/AAIM/ACGME/ABIM Joint Next Accreditation System Internal Medicine Subspecialty Milestones

Association of Program Directors in Endocrinology and Metabolism

2017-2018 Secretary-Treasurer
 2012-2018 Task Force member, Next Accreditation System Endocrinology Milestones
 2011-2012 Task Force member, Procedures Accreditation
 2010-2012 Council member
 2009-2016 Chair, Site Visit/Curriculum Web-Toolbox Committee

American Thyroid Association

2006-2009 Publications Committee member
 2004 Program Committee member

Joshua D. Safer, MD, FACP, FACE**Editorships and Editorial Boards**

2018-present	Associate Editor, <i>Transgender Health</i>
2017-present	Editorial Advisory Board, <i>Endocrine News</i>
2016-present	Transgender Section Co-Editor, <i>UpToDate</i>
2015-present	Editorial Board, <i>Transgender Health</i>
2015-present	Editorial Board, <i>International Journal of Transgender Health</i>
2013-2018	Associate Editor, <i>Journal of Clinical & Translational Endocrinology</i>
2007-present	Editorial Board, <i>Endocrine Practice</i>

External Medical Advising and Consulting**International**

2016-present	International transgender athlete guidelines, Medical and Scientific Commission, International Olympic Committee

National

2017	Transgender medical and surgical treatment, National Collegiate Athletic Association,
2017	Safety for transgender medical treatment, Food and Drug Administration, United States
2015-present	Transgender workforce and military readiness, Department of Defense, United States
2014	Transgender prison population health, Federal Bureau of Prisons, United States

Regional

2011-2018	Transgender prison population health, Massachusetts Department of Correction

Joshua D. Safer, MD, FACP, FACE

Past Other Support

2018-2022	Keith Haring Foundation, PI: Joshua D. Safer , Pilot Program to Develop Clinical Program in Transgender Medicine for Children and Adolescents
2015-2016	R13 HD084267, Multi-PI: Joshua D. Safer , TransNet: Developing a Research Agenda in Transgender Health and Medicine
2014-2015	Boston Foundation, Equality Fund, PI: Joshua D. Safer , Pilot Program to Educate Physicians in Transgender Medicine
2013-2014	Evans Foundation, PI: Joshua D. Safer , A Pilot Curriculum in Transgender Medicine
2001-2003	Thyroid Research Advisory Council, PI: Joshua D. Safer , Thyroid Hormone Action on Skin
2001-2002	Evans Foundation, PI: Joshua D. Safer , Thyroid Hormone Action on Skin
1996-2001	K08 DK02423, PI: Joshua D. Safer , Characterization of Central Resistance to Thyroid Hormone

Joshua D. Safer, MD, FACP, FACE

Conferences Organized

International Conferences

World Professional Association for Transgender Health

November, 2020 Bi-annual meeting, Planning Committee (remote)

November, 2018 Bi-annual meeting, Scientific Co-Chair, Buenos Aires, Argentina

June, 2016 Bi-annual meeting, Scientific Co-Chair, Amsterdam, Netherlands

November, 2015 Global Education Initiative, inaugural conference, Chicago, IL

TransNet – International Consortium for Transgender Health and Medicine Research

May, 2016 International meeting to set transgender medicine research priorities, Amsterdam, Netherlands

May, 2015 NIH conference to set transgender medicine research priorities, Bethesda, MD

June, 2014 Inaugural meeting, Chicago, IL

National Conferences

February, 2019 Live Surgery Course for Gender Affirmation Procedures, Mount Sinai Hospital and WPATH, New York City, NY

April, 2018 Live Surgery Course for Gender Affirmation Procedures, Mount Sinai Hospital and WPATH, New York City, NY

January, 2017 United States Professional Association for Transgender Health (USPATH) bi-annual meeting, Los Angeles, CA

November, 2015 NIH/Alliance for Academic Internal Medicine - Physician Researcher Workforce Taskforce Meeting, Washington, DC

October, 2015 National Internal Medicine Subspecialty Summit, Atlanta, GA

June, 2013 Special Symposium: “Transgender Medicine – What Every Physician Should Know” Annual Meeting of the Endocrine Society, San Francisco, CA

April, 2011 2011 ASP Accreditation Seminar "Meeting the ACGME and RRC-IM Standards for Successful Fellowship Programs" Arlington, VA

Alliance for Academic Internal Medicine

April, 2015 2015 ASP Accreditation Seminar “Moving Your Fellowship Program Forward” Spring Meeting, Houston, TX

April, 2014 2014 ASP Accreditation Seminar “NAS for Medical Subspecialties Is Almost Here” Spring Meeting, Nashville, TN

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Joshua D. Safer, MD, FACP, FACE

May, 2013	2013 ASP Accreditation Seminar “A Changing Landscape in Subspecialty Fellowship Education” Spring Meeting, Lake Buena Vista, FL
April, 2012	2012 ASP Accreditation Seminar “Meeting ACGME and RRC-IM Standards for Successful Fellowship Programs” Spring Meeting, Atlanta, GA

Invited Lectures and Presentations

International

January, 2020	“Transgender Medicine”, World Professional Association for Transgender Health Global Education Initiative, Hanoi, Vietnam
September, 2019	“Transgender Women” International Association of Athletics Federations (IAAF), Lausanne, Switzerland
November, 2018	“Transgender Medicine”, World Professional Association for Transgender Health Annual Meeting, Buenos Aires, Argentina
October, 2018	“Transgender Medicine”, Canadian Endocrine Diabetes Meeting, Halifax, NS, Canada
June, 2018	“21 st -Century Strategies: Transgender Hormone Care” CMIN Summit 2018, Porto, Portugal
February, 2017	“A 21 st -Century Framework to for Transgender Medical Care” Sheba Hospital, Tel Aviv, Israel
October, 2016	“A 21 st -Century Approach to Hormone Treatment of Transgender Individuals” EndoBridge, Antalya, Turkey
May, 2016	“Transgender Women” International Olympic Committee Headquarters, Lausanne, Switzerland
October, 2015	“Workshop on Guidelines for Transgender Health Care” Canadian Professional Association for Transgender Health, Halifax, NS
March, 2015	“Endocrinology - Hormone Induced Changes” Transgender Health Care in Europe, European Professional Association for Transgender Health, Ghent, Belgium
June, 2014	“What to Know to Feel Safe Providing Hormone Therapy for Transgender Patients” International Congress of Endocrinology, Chicago, IL
September, 2011	“Transgender Therapy – The Endocrine Society Guidelines” World Professional Association for Transgender Health, Atlanta, GA
February, 2007	“Treating skin disease by manipulating thyroid hormone action” Grand Rounds, Meier Hospital, Kfar Saba, Israel
March, 2004	“New Directions in Thyroid Hormone Action: Skin and Hair” Grand Rounds, Meier Hospital, Kfar Saba, Israel

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Joshua D. Safer, MD, FACP, FACE**National**

May, 2021 “Transgender Medicine”, University of Cincinnati Medicine Grand Rounds, Cincinnati, OH (scheduled)

September, 2020 “Transgender Medicine”, Peds Place Conference, University of Arkansas, AR (remote)

September, 2020 “Transgender Medicine”, University of California-Irvine Medicine Grand Rounds, Irvine, CA (remote)

June, 2020 “Transgender Medicine”, Inova Fairfax Medicine Grand Rounds, Fairfax, VA (remote)

December, 2019 “Transgender Medicine”, Vanderbilt University Surgery Grand Rounds, Nashville, TN

November, 2019 “Transgender Medicine”, Medical College of Wisconsin CME, Milwaukee, WI

September, 2019 “Transgender Medicine”, Beth Israel Deaconess Medicine Grand Rounds, Boston, MA

September, 2019 “Transgender Medicine”, United States Professional Association for Transgender Health Annual Meeting, Washington, DC

June, 2019 “Transgender Medicine”, Mount Sinai Hospital Internal Medicine CME, New York, NY

April, 2019 “A 21st-Century Strategy for Hormone Treatment of Transgender Individuals” National Transgender Health Summit, Oakland, CA

March, 2019 “Transgender Medicine” National Eating Disorders Meeting, New York, NY

January, 2019 “Transgender Medicine” Yale School of Medicine Obstetrics and Gynecology Grand Rounds, New Haven, CT

January, 2019 “Transgender Medicine” Yale School of Medicine Endocrinology Grand Rounds, New Haven, CT

January, 2019 “Transgender Medicine” Drexel School of Medicine Medicine Grand Rounds, Philadelphia, PA

September, 2018 “Current Guidelines and Strategy for Hormone Treatment of Transgender Individuals” Minnesota-Midwest Chapter - American Association of Clinical Endocrinologists Annual Meeting, Minneapolis, MN

July, 2018 “21st-Century Strategies for Transgender Hormone Care” Ohio River Valley Chapter - American Association of Clinical Endocrinologists Meeting, Indianapolis, IN

June, 2018 “21st-Century Strategies: Transgender Hormone Care” University of Connecticut School of Medicine, Hartford, CT

Joshua D. Safer, MD, FACP, FACE

- May, 2018 “A 21st-Century Strategy for Hormone Treatment of Transgender Individuals” American Association of Clinical Endocrinologists Annual Meeting, Boston, MA
- March, 2018 “21st-Century Strategies for Transgender Hormone Care” New Jersey Chapter - American Association of Clinical Endocrinologists Meeting, Morristown, NJ
- February, 2018 “A Strategy for the Medical Care of Transgender Individuals” Keynote Address for the International Society for Clinical Densitometry Annual Meeting, Boston, MA
- November, 2017 “A 21st-Century Strategy for Hormone Treatment of Transgender Individuals” National Transgender Health Summit, Oakland, CA
- September, 2017 “Transgender Therapy – The Endocrine Society Guidelines” Endocrine Society: Clinical Endocrinology Update, Chicago, IL
- May, 2017 “Transgender Medicine – a 21st Century Strategy for Patient Care” University of Arizona College of Medicine, Tucson, AR
- April, 2017 “Transgender Care Across the Age Continuum” Annual Meeting of the Endocrine Society, Orlando, FL
- March, 2017 “A 21st-Century Approach to Hormone Treatment of Transgender Individuals” Brown University School of Medicine, Providence, RI
- March, 2017 “What to Know: A 21st-Century Approach to Transgender Medical Care” United States Food and Drug Administration (FDA), Washington, DC
- February, 2017 “A 21st-Century Approach to Transgender Medical Care” United States Professional Association for Transgender Health, Los Angeles, CA
- February, 2017 “A 21st-Century Approach to Hormone Treatment of Transgender Individuals” Southern States American Association of Clinical Endocrinologists Annual Meeting, Memphis, TN
- December, 2016 “Transgender Medical Care in the United States Armed Forces” Global Education Initiative, World Professional Association for Transgender Health, Arlington, VA
- December, 2016 “Foundations in Hormone Treatment” Global Education Initiative, World Professional Association for Transgender Health, Arlington, VA
- November, 2016 “Developing a Transgender/Gender-Identity Curriculum for Medical Students” Association of American Medical Colleges National Meeting, Seattle, WA
- September, 2016 “A 21st-Century Approach to Hormone Treatment of Transgender Individuals” Endocrine Society: Clinical Endocrinology Update, Seattle, WA
- August, 2016 “A 21st-Century Approach to Hormone Treatment of Transgender Individuals” Oregon Health and Science University Ashland Endocrine Conference, Ashland, OR
- March, 2016 “State-of-the-Art: Use of Hormones in Transgender Individuals” Annual Meeting of the Endocrine Society, Boston, MA

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Joshua D. Safer, MD, FACP, FACE

October, 2015 “What Every Endocrinologist Should Know to Feel Safe Providing Hormone Therapy for Transgender Patients” University of Utah School of Medicine, Salt Lake City, UT

April, 2015 “What to Know –to Feel Safe Providing Hormone Therapy for Transgender Patients” Pritzker School of Medicine, University of Chicago, Chicago, IL

March, 2015 “What to Know –to Feel Safe with Hormone Therapy for Transgender Patients” Annual Transgender Health Symposium, Medical College of Wisconsin, Milwaukee, WI

May, 2014 “Transgendocrinology” Annual Meeting of the American Association of Clinical Endocrinologists, Las Vegas, NV

May, 2013 “Transgender Therapy – Hormone Action and Nuance” National Transgender Health Summit, Oakland, CA

April, 2013 “Transgender Therapy – What Every Provider Needs to Know” Empire Conference: Transgender Health and Wellness, Albany, NY

April, 2013 “Transgender Therapy – What Every Endocrinologist Needs to Know” University of Maryland School of Medicine, Baltimore, MD

November, 2012 “Transgender Therapy – What Every Endocrinologist Should Know” New York University School of Medicine, New York, NY

May, 2010 “Transgender Treatment: What Every Endocrinologist Needs to Know” Brown University School of Medicine, Providence, RI

November, 2009 “New Directions in Thyroid Hormone Action: Skin and Hair” Emory University School of Medicine, Atlanta, GA

November, 2009 “Primary Care Update in the Treatment of Thyroid Disorders” Emory University School of Medicine, Atlanta, GA

October, 2008 “Topical Iopanoic Acid Stimulates Epidermal Proliferation through Inhibition of the Type 3 Thyroid Hormone Deiodinase” Annual Meeting of the American Thyroid Association, Chicago, IL

February, 2005 “New Directions in Thyroid Hormone Action: Skin and Hair” Endocrinology Grand Rounds, University of Minnesota, Minneapolis, MN

February, 2005 “Thyroid Hormone Action on Skin and Hair: What We Thought We Knew” Dermatology Grand Rounds, University of Minnesota, Minneapolis, MN

December, 2004 “Transgender Therapy: The Role of the Endocrinologist” Endocrinology Grand Rounds, Brown Medical Center, Providence, RI

November, 2003 “New Directions in Thyroid Hormone Action: Skin and Hair” Endocrinology Grand Rounds, Dartmouth Medical Center, Hanover, NH

Joshua D. Safer, MD, FACP, FACE**Regional**

May, 2021 “Transgender Medicine”, New York GYN Society, New York, NY (scheduled)

July, 2020 “Transgender Medicine”, LGBT Health Conference CME, New York, NY

February, 2020 “Transgender Medicine”, Englewood Hospital Medicine Grand Rounds, Englewood, NJ

February, 2020 “Transgender Medicine”, Endocrinology Grand Rounds, Columbia College of Physicians and Surgeons, New York, NY

January, 2020 “Transgender Medicine”, CEI, Lake Placid, NY

November, 2019 “Transgender Medicine”, Weill Cornell Reproductive Endocrine Grand Rounds, New York, NY

November, 2019 “Transgender Medicine”, Acacia Network Grand Rounds, New York, NY

October, 2019 “Transgender Medicine”, American Association of Clinical Endocrinologists - New Jersey, annual meeting, Morristown, NJ

October, 2019 “Transgender Medicine”, Community Health Network annual conference, New York, NY

October, 2019 “Transgender Medicine”, Westchester Medical Center Medicine Grand Rounds, Valhalla, NY

September, 2019 “Transgender Medicine”, Weill Cornell Reproductive Endocrine CME, New York, NY

September, 2019 “Transgender Competency for Medical Providers”, Working Group on Gender, Columbia College of Physicians and Surgeons, New York, NY

April, 2019 “Transgender Medicine”, Weill Cornell Urology Grand Rounds, New York, NY

June, 2018 “21st-Century Strategies: Transgender Hormone Care” Medicine Grand Rounds, Staten Island University Hospital, Staten Island, NY

February, 2018 “Transgender Medicine – 21st Century Strategies for Patient Care” Medicine Rounds, Newton-Wellesley Hospital, Newton, MA

October, 2017 “Transgender Medicine – 21st Century Strategies for Patient Care” Medicine Rounds, Beth Israel-Milton Hospital, Milton, MA

September, 2017 “Transgender Medicine – 21st Century Strategies for Patient Care” Obstetrics-Gynecology Grand Rounds, Brigham and Women’s Hospital, Boston, MA

June, 2017 “State-of-the-Art: Hormone Therapy for Transgender Patients” Reproductive Endocrinology Rounds, Massachusetts General Hospital, Boston, MA

May, 2017 “A 21st-Century Strategy for Medical Treatment of Transgender Individuals” Boston Medical Center and Boston University School of Medicine, Boston, MA

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Joshua D. Safer, MD, FACP, FACE

March, 2017 “A 21st-Century Strategy for Medical Treatment of Transgender Individuals” Tufts Medicine Grand Rounds, Boston, MA

January, 2017 “What to Know: A 21st-Century Approach to Transgender Medical Care” Internal Medicine Rounds, Brigham and Women’s Hospital, Boston, MA

March, 2016 “State-of-the-Art: Hormone Therapy for Transgender Patients” Obstetrics-Gynecology Rounds, Brigham and Women’s Hospital, Boston, MA

November, 2015 “What Every Endocrinologist Should Know to Feel Safe Providing Hormone Therapy for Transgender Patients” Endocrinology Rounds, Tufts Medical Center, Boston, MA

May, 2015 “What Every Endocrinologist Should Know to Feel Safe Providing Hormone Therapy for Transgender Patients” Endocrinology Rounds, Massachusetts General Hospital, Boston, MA

December, 2014 “What to Know to Feel Safe Providing Hormone Therapy for Transgender Patients” Endocrinology Rounds, Beth Israel Deaconess Medical Center, Boston, MA

November, 2013 “Transgender Therapy – What Every Physician Should Know” Medicine Grand Rounds, Boston Veterans Administration Hospital, Boston, MA

May, 2005 “Transgender Therapy: The Role of the Endocrinologist”, Endocrinology Rounds, Tufts-New England Medical Center, Boston, MA

January, 2004 “New Directions in Thyroid Hormone Action: Skin and Hair”, Endocrinology Rounds, Brigham and Women’s Hospital, Boston, MA

October, 1999 “The Many Faces of Hypothyroidism”, Medicine Grand Rounds, Bedford Veterans Administration Hospital, Bedford, MA

Institutional, Icahn School of Medicine at Mount Sinai, New York, NY

October, 2019 “Transgender Medicine”, East Harlem HOP rounds, New York, NY

October, 2019 “Transgender Medicine”, Mount Sinai HIV rounds, New York, NY

August, 2019 “Transgender Medicine”, Mount Sinai Endocrinology Fellows Conference, New York, NY

February, 2019 “Transgender Medicine”, Mount Sinai Endocrinology Grand Rounds, New York, NY

February, 2019 “Transgender Medicine”, Mount Sinai Ob-Gyn Grand Rounds, New York, NY

April, 2018 “21st-Century Strategies for Transgender Hormone Care”, HIV Grand Rounds

Institutional, Boston University School of Medicine, Boston, MA

March, 2017 “State of the Art Hormone Therapy for Transgender Patients”, Section of Infectious Disease

Joshua D. Safer, MD, FACP, FACE

- January, 2017 “What you need to know – to supervise care for our transgender patients at BMC”,
Section of Endocrinology
- February, 2016 “State of the Art Hormone Therapy for Transgender Patients”, Department of Medicine
- November, 2015 “What the Family Medicine Physician Should Know to Feel Safe Providing Hormone
Therapy for Transgender Patients”, Department of Family Medicine
- November, 2014 “What the Anesthesiologist Should Know to Feel Safe Providing Hormone Therapy for
Transgender Patients”, Department of Anesthesia
- January, 2014 “Update on the Current Guidelines for Transgender Hormone Therapy”, Section of
Endocrinology
- October, 2011 “Transgender Therapy – What Every Physician Should Know”, Department of Medicine
- February, 2011 “Current Guidelines for Transgender Hormone Therapy: What Every Endocrinologist Should
Know”, Section of Endocrinology
- November, 2005 “Thyroiditis and Other Insults to Thyroid Function” Core Curriculum in Adult Primary Care
Medicine
- November, 2005 “Interpretation of Thyroid Function Tests Made Easy” Core Curriculum in Adult Primary
Care Medicine
- January, 2005 “Transgender Therapy: The Role of the Endocrinologist” Endocrinology Grand Rounds
- December, 2004 "Update in Endocrinology: Thyroid" Medicine Grand Rounds
- January, 2004 “New Directions in Thyroid Hormone Action: Skin and Hair” Medicine Grand Rounds
- March, 2003 “Thyroid Hormone Action on Hair and Skin” Endocrinology Grand Rounds
- November, 1999 “Central Resistance to Thyroid Hormone – From Bedside to Bench” Endocrinology Grand
Rounds

Joshua D. Safer, MD, FACP, FACE

Curriculum development with external dissemination

- 2014-present Web site for Association of Program Directors of Endocrinology and Metabolism (APDEM), which serves as ***the primary resource for endocrinology fellowship program directors throughout the United States and Canada.***
- Sample curricula
 - Streaming lectures to support specific curricular needs to fill programmatic gaps at certain programs
 - New assessment forms that map skills to milestones that conform to Next Accreditation System (NAS) standards of the Accreditation Council for Graduate Medical Education (ACGME)

- 2013-present Dissemination of Transgender Medicine Curriculum with local modification to institutions in the United States and Canada

Curriculum adopted

Johns Hopkins School of Nursing (sample video:
<http://vimeo.com/jhunursing/review/97477269/abbcf6d33a>)
Ohio State University College of Medicine
University of British Columbia, Faculty of Medicine
University of Central Florida College of Medicine
Tufts University School of Medicine

Curriculum in development

Dartmouth School of Medicine
University of Vermont College of Medicine

Work in progress in preparation for sharing transgender curriculum

Albany Medical College
Emory School of Medicine
George Washington University Medical School
Hofstra School of Medicine
University of California – San Diego School of Medicine
University of Kentucky College of Medicine
University of Louisville School of Medicine
University of Michigan Medical School
University of Minnesota Medical School
University of Nebraska School of Medicine
University of Pennsylvania School of Medicine
Washington University School of Medicine

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2013-2015 Co-author of the *Medical Subspecialty Reporting Milestones used for evaluation of Internal Medicine subspecialty medicine fellowship programs throughout the United States* by the Accreditation Council for Graduate Medical Education (ACGME).

<https://www.acgme.org/acgmeweb/Portals/0/PDFs/Milestones/InternalMedicineSubspecialtyMilestones.pdf>

2011-2014 Web site content expert for APDEM, which served as *the primary resource for endocrinology fellowship Program Directors throughout the United States and Canada*. Materials included sample curricula, streaming lectures to support specific curricular needs to feel programmatic gaps at certain programs, and guidance dealing with ACGME site-visits

Other curriculum development

2019-present Massive Open On-line Course (MOOC) curricular content. Transgender Medicine for General Medical Providers, Icahn School of Medicine at Mount Sinai
(<https://www.coursera.org/courses?query=transgender%20medicine%20for%20general%20medical%20providers&>)

2016-2018 Curricular Content to teach transgender hormone therapy in the LGBT elective at Harvard Medical School

2016-2018 Curricular Content to teach transgender hormone therapy at Tufts University School of Medicine.

2011-2018 Fully revised curriculum for the Boston University Medical Center Fellowship Training Program in Endocrinology, Diabetes and Nutrition.

2010-2018 Curricula to teach transgender hormone therapy at Boston University School of Medicine.

2006-2014 Written examination in endocrinology to complement the multiple-choice examination for medical students — validation relative to success later in medical school is in progress.

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** currently most influential papers are noted with double asterisks

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118. Choong K, **Safer JD**. Graves disease and gynecomastia in two roommates. *Endocr Pract* 2011; 17(4):647-650. PMID 21613048
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Dissemination Through Lay Press and Social Media

Mass Audience Programming:

“Transgender Health AMA” Reddit. July 24, 2017. Expert responses to questions about transgender medicine. https://www.reddit.com/r/science/comments/6p7uhb/transgender_health_ama_series_im_joshua_safer/ over 150,000 views, over 4200 comments

“Gender Revolution with Katie Couric” National Geographic Channel. Couric, Katie. February 6, 2017. Extended interview with Katie Couric threaded into a 2-hour television special. Trailer: <https://www.youtube.com/watch?v=y93MsRaC6Zw> broadcast in 143 countries

“Is gender identity biologically hard-wired?” Judd, Jackie. PBS NewsHour. May 13, 2015. Extended interview for Jackie Judd <http://www.pbs.org/newshour/bb/biology-gender-identity-children/> estimated just over 1,000,000 viewers per Nielsen

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Innovation	Significance/impact
<i>Development and leadership of the Transgender Medicine Clinical Center, Mount Sinai Health System and Icahn School of Medicine at Mount Sinai</i>	• The Center for Transgender Medicine and Surgery at Mount Sinai is the first comprehensive center for transgender medical care in New York and the most comprehensive program in the United States • The Center is one of only several such centers in North America that are housed in academic teaching hospitals where care can be integrated • The Center is a model for such care delivery in North America.
<i>Establishment, development, and leadership of the Transgender Medicine Clinical Center at Boston Medical Center</i>	• The Center for Transgender Medicine and Surgery at BMC is the first comprehensive center for transgender medical care in New England • The Center is one of only several such centers in North America that are housed in academic teaching hospitals where care can be integrated • The Center is a model for such care delivery in North America.
<i>Development and dissemination of the seminal reviews that are most widely cited in the lay press that explain the concept that gender identity is a biological phenomenon (see bibliography section above, e.g. PMID: 25667367).</i>	• The concept that gender identity is a biological phenomenon has been a key component of the recent culture change in favor of mainstream medical care for transgender individuals (see media section above)
<i>Development and dissemination of new and influential curricular content to teach the biology of gender identity in conventional medical education (see curriculum section above)</i>	The teaching of evidence-based approaches to transgender medical care to: • Medical students (see bibliography section above, e.g. PMID 23425656 and PMID 27042742) • Physician trainees (see bibliography section above, e.g. PMID 26151424) • Practicing physicians (see invited lectures section above) serves as a crucial component to the gained credence given to care for transgender individuals in conventional medical settings.
<i>Development and dissemination of seminal reviews supporting the safety of transgender hormone treatment regimens (see invited lectures section above)</i>	• Once mainstream medical providers learn of the biology underlying gender identity, their biggest concern is the relative safety of the medical interventions relative to the benefit. • The development and dissemination of the seminal reviews and lectures supporting the safety of current treatment regimens serves as a further crucial component to the culture change among conventional medical providers in favor of routine medical care for transgender individuals

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

B.P.J. by her next friend and mother, HEATHER JACKSON,

Plaintiff,

v.

WEST VIRGINIA STATE BOARD OF EDUCATION, HARRISON COUNTY BOARD OF EDUCATION, WEST VIRGINIA SECONDARY SCHOOL ACTIVITIES COMMISSION, W. CLAYTON BURCH in his official capacity as State Superintendent, DORA STUTLER in her official capacity as Harrison County Superintendent, and THE STATE OF WEST VIRGINIA,

Defendants,

and

LAINY ARMISTEAD,

Defendant-Intervenor.

Civil Action No. 2:21-cv-00316

Hon. Joseph R. Goodwin

**REBUTTAL EXPERT REPORT AND DECLARATION OF
JOSHUA D. SAFER, MD, FACP, FACE**

1. I have been retained by counsel for Plaintiff as an expert in connection with the above-captioned litigation.

2. My background and credentials are set forth in my previous expert report and declaration dated January 21, 2022 (“Safer Rep.”). I incorporate all conclusions and facts set forth in my previously submitted report into this rebuttal report as if fully stated herein.

3. I reviewed the expert reports of Gregory A. Brown, Ph.D. and Chad. A. Carlson, M.D., submitted in this case on February 23, 2022 (“Brown Rep.” and “Carlson Rep.”). I provide

this rebuttal report to explain the overall problems with the conclusions they draw and provide data showing why such conclusions are in error. I reserve the right to supplement my opinions in response to new information if necessary as the case proceeds.

SUMMARY OF OPINIONS

4. In this rebuttal report, I address four topics raised in the expert reports of Dr. Brown and Dr. Carlson that are related to this lawsuit.¹

- a. H.B. 3293's definition of "biological sex" as "reproductive biology and genetics at birth" is inaccurate and misleading. Especially in the context of transgender people or people with intersex characteristics, "biological sex" includes all the biological components of sex, including hormones and the biological underpinnings of gender identity.
- b. Circulating testosterone is the primary known biological driver of average differences in athletic performance, not "reproductive biology and genetics at birth." Differences in athletic performance between cisgender boys and girls before puberty are minor and cannot reliably be attributed to biological factors instead of social ones.
- c. Concerns about athletic advantage do not provide a scientific basis for H.B. 3293's categorical ban of transgender girls and women from all girls' teams sponsored by

¹ It is my understanding that H.B. 3293 seeks to exclude girls and women who are transgender if they are a student at a secondary school or institution of higher education in West Virginia. As a result, several of the studies discussed and conclusions reached by Dr. Brown and Dr. Carlson in their reports are unrelated to H.B. 3293 (e.g., discussions regarding elite athletes, such as Olympians). Although there are several issues with Dr. Carlson's and Dr. Brown's statements regarding these inapposite studies and the conclusions they reach are nothing more than conjecture, given that these studies are not related to H.B. 3293, I do not exhaustively respond to each inaccurate or misleading statement here.

a secondary school or institution of higher education in West Virginia. There is no basis to expect that transgender girls who receive puberty delaying medication followed by gender affirming hormones would have an athletic advantage, and Dr. Brown's sweeping arguments about an athletic advantage for transgender women who suppress testosterone after puberty are based on supposition and conjecture, not evidence.

- d. Concerns about safety also do not provide a scientific basis for H.B. 3293's categorical ban of transgender girls and women from all girls' teams sponsored by a secondary school or institution of higher education in West Virginia. Dr. Carlson's speculative arguments about safety risks apply only to contact and collision sports, and actual safety concerns can be addressed through even-handed rules instead of discriminating based on transgender status.

H.B. 3293'S DEFINITION OF "BIOLOGICAL SEX" IS INACCURATE AND MISLEADING

5. Ignoring all the other biological components of sex, H.B. 3293 defines "biological sex" exclusively as "an individual's physical form as a male or female based solely on the individual's reproductive biology and genetics at birth." As I explained in my initial report, however, the phrase "biological sex" is an imprecise term that can cause confusion, especially in the context of transgender people and people with intersex characteristics. A person's sex encompasses the sum of several different biological attributes, including sex chromosomes, certain genes, gonads, sex hormone levels, internal and external genitalia, other secondary sex characteristics, and the biological underpinnings of gender identity. Those attributes are not always aligned in the same direction. See Hembree WC, et al. *Endocrine Treatment of Gender-Dysphoria/Gender Incongruent Persons: An Endocrine Society Clinical Practice Guideline*. J Clin

Endocrinol Metab 2017; 102:3869–3903 (“Endocrine Society Guidelines 2017”) at 3875; Safer JD, Tangpricha V. *Care of Transgender Persons*. N Engl J Med 2019; 381:2451-2460 (“N Engl J Med 2019”).

6. In response to my initial report, Dr. Brown states that sex is rooted in biology. (Brown Rep. ¶¶ 1-3). I agree. But the fact that sex is rooted in biology does not mean that sex is defined exclusively by genetics or reproductive biology at birth. As reflected in the same sources cited by Dr. Brown, dimorphous sexual characteristics in men and women are produced by a combination of genes, prenatal androgen exposure to sex hormones, epigenetics and other environmental factors. Bhargava, A. et al. *Considering Sex as a Biological Variable in Basic and Clinical Studies: An Endocrine Society Scientific Statement*. Endocr Rev. 2021; 42:219-258 (“Bhargava 2021”) at 221-228; N Engl J Med 2019; Safer JD, Tangpricha V. *Care of the Transgender Patient*. Ann Intern Med 2019; 171: ITC1-ITC16 (“Ann Intern Med 2019”).

7. In addition, although the precise biological causes of gender identity are unknown, gender identity itself has biological underpinnings, possibly as a result of variations in prenatal exposure to sex hormones, gene sequences, epigenetics, or a combination of factors. And when transgender people receive puberty-delaying treatment and gender-affirming hormones, they develop other biological and physiological sex characteristics that align with their gender identity and not with their sex recorded at birth. Endocrine Society Guidelines 2017 at 3874-75, 3888-89; Bhargava 2021 at 227; N Engl J Med 2019; Ann Intern Med 2019.

THE PRIMARY KNOWN BIOLOGICAL DRIVER OF AVERAGE DIFFERENCES IN ATHLETIC PERFORMANCE IS CIRCULATING TESTOSTERONE

8. As explained in my previous report, the primary known biological cause of average differences in athletic performance between non-transgender men as a group and non-transgender women as a group is circulating testosterone—not “reproductive biology and genetics at birth.”

The existing “evidence makes it highly likely that the sex difference in circulating testosterone of adults explains most, if not all, of the sex differences in sporting performance.” See Handelsman DJ, et al. *Circulating Testosterone as the Hormonal Basis of Sex Differences in Athletic Performance*. Endocrine Reviews 2018; 39:803-829 (“Handelsman 2018”) at 823 (summarizing evidence rejecting hypothesis that physiological characteristics are driven by Y chromosome).²

9. Neither Dr. Brown nor Dr. Carlson disputes that circulating testosterone is the largest biological driver of average differences in athletic performance (Brown Rep. ¶ 114; Carlson Rep. ¶ 16), but Dr. Brown contends that cisgender boys and transgender girls have at least some biological advantages in athletic performance over cisgender girls even before puberty. In support, Dr. Brown relies primarily on demographic data from physical fitness tests or athletics in which prepubertal cisgender boys have outperformed prepubertal cisgender girls. But there is no reliable basis for Dr. Brown to attribute those differences to biology instead of social factors such as greater societal encouragement of athleticism in boys, greater opportunities for boys to play sports, or different preferences of the boys and girls surveyed. See Handelsman DJ. *Sex Differences in Athletic Performance Emerge Coinciding with the Onset of Male Puberty*. Clin Endocrinol (Oxf). 2017;87(1):68–72 (“Handelsman 2017”).

10. Dr. Brown also points out that there are physiological differences between cisgender boys and cisgender girls before puberty, largely as a result of exposure to hormones in

² Dr. Brown cites to Handelsman in his report but continually misrepresents Handelsman’s findings, notably omitting key portions of the reference. For example, Dr. Brown writes, “[t]here is convincing evidence that the sex differences in muscle mass and strength are sufficient to account for the increased strength and aerobic performance of men compared with women and is in keeping with the differences in world records between the sexes.” (Brown Rep. ¶ 55, citing Handelsman 2018). But Dr. Brown omits the following sentence which explains that “[t]he basis for the sex difference in muscle mass and strength is *the sex difference in circulating testosterone*.” (Handelsman 2018 at 816) (emphasis added).

utero or during infancy. (Brown Rep. ¶ 71 (citing McManus, A. and N. Armstrong, *Physiology of Elite Young Female Athletes*. J Med & Sport Sci 2011; 56:23-46)). But the article cited by Dr. Brown never draws a causal connection between those physiological differences and any differences in athletic performance between cisgender prepubertal boys and girls. Throughout the article, McManus and Armstrong acknowledge that differences between cisgender prepubertal boys and girls in various measurements are minimal or nonexistent. *See Id.* at 24 (“Prior to 11 years of age differences in average speed are minimal”); at 27 (“small sex difference in fat mass and percent body fat are evident from mid-childhood”); at 29 (“bone characteristics differ little between boys and girls prior to puberty”); at 32 (“There is little evidence that prior to puberty pulmonary structure or function limits oxygen uptake”); at 34 (“[N]o sex differences in arterial compliance have been noted in pre- and early- pubertal children”).

11. There is also no basis to confidently predict that patterns about the athletic performance of prepubertal cisgender boys will be the same for prepubertal transgender girls. To the extent that differences in performance are influenced by social influences, biases, or preferences, the experience of transgender girls might be more similar to the experience of cisgender girls than to cisgender boys. And to the extent that differences in performance are shown to have some connection to epigenetics or exposure to sex hormones in utero or infancy, we do not know whether those biological factors are always equally true for transgender girls in light of scientific studies documenting potential biological underpinnings of gender identity.

12. For example, studies have shown that even before initiating hormone therapy transgender women tend to have lower bone density than cisgender men. Van Caenegem E, Taes Y, Wierckx K, Vandewalle S, Toye K, Kaufman JM, et al. *Low Bone Mass is Prevalent in Male-to-Female Transsexual Persons Before the Start of Cross-Sex Hormonal Therapy and*

Gonadectomy. Bone 2013;54(1):92–7. We do not know whether those differences are explained by social factors or biological ones. But regardless of the cause, it cannot be assumed that the physiological characteristic of cisgender boys and men will automatically apply to transgender girls and women even in the absence of gender affirming hormones.

**CONCERNS ABOUT ATHLETIC ADVANTAGE
DO NOT PROVIDE A SCIENTIFIC BASIS FOR H.B. 3293**

13. In my previous report, I explained why “[t]here is no medical justification for West Virginia’s categorical exclusion of girls who are transgender from participating in scholastic athletics on the same teams as other girls.” (Safer Rep. ¶ 46). By excluding girls who are transgender based on “biological sex,” and defining that term to mean “reproductive biology and genetics at birth,” West Virginia categorically prevents girls who are transgender from participating on all girls’ teams sponsored by a secondary school or institution of higher education in West Virginia regardless of the particular sport at issue and regardless of whether they are pre-pubertal, receiving puberty blockers, or receiving gender-affirming hormone therapy. That sweeping and categorical ban is dramatically out of step with even the most stringent policies of elite international athletic competitions for girls and women who are transgender.

14. To support this sweeping ban, Dr. Brown makes a variety of claims that are either irrelevant or are based on speculation and inferences that are not supported by the data that we currently have.

15. As an initial matter, Dr. Brown provides no scientific support for excluding girls and women who are transgender and who had puberty blockers before endogenous puberty. To the contrary, even some of the most exclusionary policies cited by Dr. Brown allow transgender girls and women to participate if they did not experience endogenous puberty. See World Rugby Transgender Women’s Guidelines 2020 (“Transgender women who transitioned pre-puberty and

have not experienced the biological effects of testosterone during puberty and adolescence can play women's rugby").³

16. Dr. Brown contends that "there is no published scientific evidence that the administration of puberty blockers to males before puberty eliminates the pre-existing athletic advantage that prepubertal [transgender girls] have over prepubertal [cisgender] females." (Brown Rep. at 56). But as I explain above, there is no evidence that prepubertal transgender girls have any such pre-existing biological athletic advantages. *See supra* ¶¶ 9-12.

17. Dr. Brown's assertions also rest on a misunderstanding of the treatment of gender dysphoria. Indeed, Dr. Brown admits that his speculation about puberty blockers is outside his area of expertise. (Brown Rep. ¶ 110). Under current standards of care, transgender adolescents are eligible to receive puberty blockers when they reach Tanner 2—not Tanner 3—which is early enough to prevent endogenous puberty from taking place. *See* Endocrine Society Guidelines 2017 at 3869-3903. Following administration of puberty blockers, transgender girls and women will have also received gender-affirming care to allow them to go through puberty consistent with their female gender identity. As a result of a typically female puberty, these transgender girls and women will develop many of the same physiological and anatomical characteristics of cisgender girls and women, including bone size (Brown Rep. ¶¶ 46-48), skeletal structure (*id.* at ¶ 49), and "distinctive aspects of the female pelvis geometry [that] cut against athletic performance" (*id.* at ¶ 50). Thus, a transgender girl or women who received puberty blockers followed by gender-affirming hormones does not have the same physiology as a prepubertal cisgender boy.⁴

³ *See* <https://www.world.rugby/thegame/player-welfare/guidelines/transgender/women>

⁴ Dr. Brown cites to a study measuring body composition among transgender people who received puberty delaying medication followed by gender affirming hormones. (Brown Rep. ¶¶ 112-13 (citing Klaver M, et al. *Early Hormonal Treatment Affects Body Composition and Body Shape in*

18. Dr. Brown also cannot point to data justifying H.B. 3293's exclusion of transgender girls and women who experience endogenous puberty and then lower their levels of circulating testosterone. As I explained in my original report, concerns about athletic competition among college students and adults are more attenuated for students in middle school and high school, where athletes' ages typically range from 11-18, with different athletes in different stages of pubertal development. Increased testosterone begins to affect athletic performance at the beginning of puberty, but those effects continue to increase each year of puberty until about age 18, with the full impact of puberty resulting from the cumulative effect of each year. As a result, a 14, 15, or 16-year old has experienced less cumulative impact from testosterone than a 17 or 18-year old.

19. But even with respect to college students, Dr. Brown's sweeping arguments are not supported by his data. There have been only two studies that examined the effects of gender-affirming hormone therapy on the athletic performance of transgender female athletes. (Safer Rep. ¶¶ 55-57). The first is a small study of eight adult long-distance runners showing that when women who are transgender have lowered circulating testosterone, their performance when compared to non-transgender women was proportionally the same as their performance had been before treatment relative to non-transgender men. Harper J. *Race Times for Transgender Athletes*. *Journal of Sporting Cultures and Identities* 2015; 6:1-9. The second is a retrospective study that reviewed military fitness test results, showing that two years of gender-affirming hormone therapy negated any advantage transgender women had over non-transgender women in performing push-ups and

Young Transgender Adolescents. *J Sex Med* 2018; 15: 251-260)). This study confirms that the transgender women after treatment had body composition patterns that more closely resembled cisgender women than cisgender men (or cisgender prepubertal boys). The minimal remaining differences reported in some measurements are not large enough to plausibly confer a material athletic advantage, and those differences are likely attributable to the fact that the subjects do not appear to have started receiving treatments until ages 12.8 to 13.5 at the earliest. By contrast, the start of Tanner 2 for transgender girls usually begins at about age 11.5.

sit-ups, but did not completely negate transgender women's faster times in racing 1.5 miles. Roberts TA, et al. *Effect of gender affirming hormones on athletic performance in transwomen and transmen: implications for sporting organizations and legislators*. Br J Sports Med. 2020; 0:1–7. doi:10.1136/bjsports-2020-102329.

20. Neither of these studies provides enough data to support Dr. Brown's sweeping claim that transgender women who have lowered circulating testosterone have an advantage over cisgender women in all athletic events. To support that inference, Dr. Brown cites to a variety of studies of transgender women measuring discrete physiological characteristics such as muscle size or grip strength. (Brown Rep. ¶¶ 153-56). Dr. Brown predicts that if puberty-influenced characteristics like bone and muscle size are not completely reversed by testosterone suppression, then those characteristics will continue to provide an advantage for transgender women. But because changes in testosterone affect different parts of the body in different ways, we do not have enough information to confidently predict whether the combined effect of the changes will be an advantage or a disadvantage.

21. The study about military fitness tests (Roberts 2020) illustrates the point. Roberts TA, et al. *Br J Sports Med*. 2020; 0:1–7. After two years of suppressing testosterone any advantage that the transgender women had in performing push-ups or sit-ups was eliminated. But because the transgender women in the study weighed more than the cisgender women even after suppressing testosterone, the transgender women had to use more muscle strength to perform the same number of push-ups. In other words, the transgender women may have had more muscle strength, but that greater strength did not translate into an athletic advantage in a push-up contest. Because different sports require different types of physical performance, the existence and extent

of any performance advantage based on grip strength or leg-muscle size may vary from sport to sport and cannot support a categorical across-the-board rule.

22. Dr. Brown also refers to widely publicized anecdotes about isolated cases of transgender girls and women winning state championships in high school sports or NCAA championships in college. But transgender athletes and women have been competing in NCAA and secondary school athletics for many years at this point, and they remain dramatically underrepresented amongst champions. The occasional championships that have been widely publicized do not come close to constituting the rates one would expect if they won at rates that are proportional to their overall percentage of the population (which is approximately 1%).

**CONCERNS ABOUT SAFETY DO NOT PROVIDE
A SCIENTIFIC BASIS FOR H.B. 3293**

23. Dr. Carlson argues in his report that allowing transgender girls and women to participate on women's teams "creates significant additional risk of injury for the [cisgender] female participants competing alongside these transgender athletes." (Carlson Rep. at 2).

24. Even on their own terms, none of Dr. Carlson's arguments support H.B. 3293's categorical ban of all girls who are transgender from all girls' sports teams. Dr. Carlson's safety arguments relate solely to contact and collision sports and to physical characteristics developed during puberty. By contrast, H.B. 3293 applies even to non-contact sports like cross-country, and it applies even to transgender girls and women who have never experienced endogenous puberty as a result of hormone blocking medication and gender-affirming hormones.⁵

⁵ The declaration Dr. Carlson submitted earlier in this case dealt exclusively with physiological characteristics acquired during puberty. In his more recent report, Dr. Carlson vaguely asserts that "the conclusions of this paper can apply to a certain extent before . . . puberty" (Carlson Rep. at 56) but he does not attempt to argue that the relatively small differences in performance or physiology observed before puberty come anywhere close to creating an actual safety risk.

25. To the extent that Dr. Carlson's arguments related to some applications of H.B. 3293, those arguments are based on stereotypes and suppositions, not actual evidence that transgender girls and women pose a safety threat. Although transgender girls and women have been playing in NCAA and secondary school sports for at least the past 10 years, Dr. Carlson does not identify any instance in which a cisgender girl or woman has actually been injured as a result of competing against a girl or woman who is transgender. Rather, he theorizes that a greater number of people are identifying as transgender and that sporting organizations should adopt restrictions preemptively in response to what he characterizes as "this rapid social change." (Carlson Rep. at 59).

26. Dr. Carlson repeats the same mistakes as Dr. Brown by drawing unsubstantiated inferences about transgender women based on data from cisgender men and from measurements of discrete characteristics. As discussed above, we do not currently have sufficient information to predict how all the physiological effects of testosterone suppression will interact in combination each other or whether they will produce the same kinetic energy as typically produced by cisgender men. For instance, having larger bones without corresponding levels of testosterone and muscle mass would mean that a runner has a bigger body to propel with less power to propel it.

27. Dr. Carlson does not offer a cogent explanation for why alleged safety concerns based on average differences in size and strength should be addressed with an across-the-board exclusion of transgender women as opposed to tailored, non-discriminatory policies. Like Dr. Brown's arguments about athletic advantage, Dr. Carlson's arguments about safety must be considered in the context of all the intra-sex variations in height, weight, and muscle mass that pose comparable safety risks. Athletic organizations can protect athlete safety for women without drawing categorical lines based on transgender status.

CONCLUSION

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on 3/10/2022



Joshua D. Safer, MD, FACP, FACE

**IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION**

B.P.J, by her next friend and mother, HEATHER JACKSON

Plaintiff,

v.

WEST VIRGINIA STATE BOARD OF EDUCATION, HARRISON COUNTY BOARD OF EDUCATION, WEST VIRGINIA SECONDARY SCHOOL ACTIVITIES COMMISSION, W. CLAYTON BURCH in his official capacity as State Superintendent, DORA STUTLER in her official capacity as Harrison County Superintendent, and THE STATE OF WEST VIRGINIA

Defendants,

and

LAINY ARMISTEAD,

Defendant-Intervenor.

Case No. 2:21-cv-00316

Hon. Joseph R. Goodwin

**DEFENDANT-INTERVENOR
LAINY ARMISTEAD'S
RESPONSES AND OBJECTIONS TO
PLAINTIFF'S SECOND SET OF
REQUESTS FOR ADMISSION**

Pursuant to Rules 33 and 34 of the Federal Rules of Civil Procedure and the applicable Local Rules of the District West Virginia and this Court, Defendant-Intervenor Lainy Armistead provides the following answers to Plaintiff's Second Set of Requests for Admission to Defendant-Intervenor.

GENERAL OBJECTIONS

1. Ms. Armistead objects to the following Definitions presented in Plaintiff's First Set of Requests for Admission to Defendant-Intervenor:

CISGENDER means a person whose gender identity aligns with the sex they were assigned at birth.

Objection: Ms. Armistead objects to the definition of the term “cisgender.” There is no definitive, legally recognized definition of “cisgender,” Plaintiff’s definition relies on the term “gender identity” which, as noted below, is not defined, and finally, Ms. Armistead denies that sex is “assigned at birth.”

GENDER IDENTITY is synonymous with the meaning used in Plaintiff’s

First Amended Complaint, paragraphs 19-23.

Objection: Ms. Armistead objects to the meaning of the term “gender identity” as provided in Plaintiff’s First Amended Complaint paragraphs 19-23. First, gender identity was not defined in Plaintiff’s First Amended Complaint. Second, there is no definitive, legally recognized definition of “gender identity.” Moreover, Ms. Armistead denies that “there is a medical consensus that there is a significant biologic component underlying gender identity” (First Am. Compl. ¶ 20) and further denies that a person’s gender identity is “durable and deeply rooted” and “cannot be changed by social or medical intervention” (*Id.* ¶ 21).

TRANSGENDER is synonymous with the meaning used in Plaintiff’s First

Amended Complaint, paragraph 23.

Objection: Ms. Armistead objects to the definition of “transgender” as provided in Plaintiff’s First Amended Complaint paragraph 23: “A transgender person is someone who has a gender identity that does not align with their sex assigned at birth.” There is no definitive, legally recognized definition of “transgender,” Plaintiff’s definition relies on the term “gender identity” which, as noted above, is not defined, and finally, Ms. Armistead denies that sex is “assigned at birth.”

TRANSGENDER GIRL means a PERSON who has a female GENDER IDENTITY, and had a male sex assigned at birth.

Objection: Ms. Armistead objects to the definition of “transgender girl.” There is no definitive, legally recognized definition of “transgender girl,” Plaintiff’s definition relies on the term “gender identity” which, as noted above, is not defined, and finally, Ms. Armistead denies that sex is “assigned at birth.”

YOU, YOUR, or YOURS means Lainey Armistead as includes your agents, representatives, affiliates, attorneys, and consultants.

Objection: Ms. Armistead objects to the definition of “you, your, or yours” to the extent it purports to require Ms. Armistead to answer on behalf of any other person or based on knowledge not in her possession. Ms. Armistead has no duty to and will not identify documents or information that are not in her possession, custody, or control (as Plaintiff’s counsel similarly noted in Plaintiff’s Supplemental and Amended Responses and Objections to Defendant the State of West Virginia’s First Set of Interrogatories and Requests for Production, pg. 2). The responses to these Requests for Admission are made by Lainey Armistead only.

Moreover, Ms. Armistead objects to the extent this definition presumes to seek the identification of documents or communications protected by the attorney-client or the work product privilege—including those communications which include the mental impressions, conclusions, or opinions of counsel—which are not discoverable under the Federal Rules of Civil Procedure. All of Ms. Armistead’s communications with her counsel of record and their agents have been in the course and scope of representing her in this litigation, and Ms. Armistead objects to any request to identify documents or communications between or among Ms. Armistead, her agents, her counsel of record, and/or their agents from June 30, 2021, to present. Ms. Armistead notes that that Plaintiff’s counsel clarified in a letter to counsel for the State that Plaintiff “is not seeking the Attorney General’s litigation files, but rather is seeking non-

privileged responsive documents.” *See, e.g.*, Letter from Kathleen Hartnett to Curtis Capehart et al., 1 (Dec. 30, 2021). Ms. Armistead assumes the same is true for her counsel of record.

2. Ms. Armistead objects to the following Instruction presented in Plaintiff’s Second Set of Requests for Admission to Defendant-Intervenor:

**The response to each request shall include such information as is within
YOUR custody, possession, or control, or that of YOUR attorneys,
investigators, agents, employees, experts retained by YOU or YOUR
attorneys, or other representatives.**

Objection: Ms. Armistead objects to this Instruction to the extent it purports to require Ms. Armistead to answer on behalf of any other person or based on knowledge not in her possession. Ms. Armistead has no duty to and will not identify documents or information that are not in her possession, custody, or control (as Plaintiff’s counsel similarly noted in Plaintiff’s Supplemental and Amended Responses and Objections to Defendant the State of West Virginia’s First Set of Interrogatories and Requests for Production, pg. 2), nor will she admit or deny Requests for admissions on anyone’s behalf but her own or based on anyone’s knowledge but her own. The responses to these Requests for Admission are made by Lainey Armistead only.

Moreover, Ms. Armistead objects to the extent this definition presumes to seek the identification of documents or communications protected by the attorney-client or the work product privilege—including those communications which include the mental impressions, conclusions, or opinions of counsel—which are not discoverable under the Federal Rules of Civil Procedure. All of Ms. Armistead’s communications with her counsel of record and their agents have been in the course and scope of representing her in this litigation, and Ms. Armistead

objects to any request to identify documents or communications between or among Ms. Armistead, her agents, her counsel of record, and/or their agents from June 30, 2021, to present. Ms. Armistead notes that that Plaintiff's counsel clarified in a letter to counsel for the State that Plaintiff "is not seeking the Attorney General's litigation files, but rather is seeking non-privileged responsive documents." *See, e.g.*, Letter from Kathleen Hartnett to Curtis Capehart et al., 1 (Dec. 30, 2021). Ms. Armistead assumes the same is true for her counsel of record.

Ms. Armistead objects to the extent this Instruction seeks information in the custody or control of experts retained by counsel, which has already been disclosed in accordance with the scheduling order provided in this case.

3. Finally, Ms. Armistead objects to any other instruction or definition that imposes a burden beyond the scope of the Federal Rules of Civil Procedure, local rules, or other law.

REQUESTS FOR ADMISSION

REQUEST NO. 5:

Admit that Plaintiff B.P.J. has been diagnosed with gender dysphoria.

ANSWER: Ms. Armistead objects to this Request because there is no definitive, legally accepted definition of "gender dysphoria" and discovery on this issue is ongoing. Moreover, she objects to this Request because this topic is the subject of expert discovery and facts about the subjective state of the mind of the opposing party are an improper basis for a Request for Admission.

Subject to these objections, Ms. Armistead states that she has no independent knowledge of B.P.J.'s gender identity, nor any means of conducting examinations or tests to determine B.P.J.'s subjective state of mind or mental distress. Ms. Armistead has made a reasonable inquiry into the information known or readily attainable by her and admits that Plaintiff and B.P.J.'s medical providers have testified that B.P.J. has been diagnosed with gender dysphoria as B.P.J.

defines that term (which, again, is objectionable as set forth above). But Ms. Armistead has no personal or independent knowledge of B.P.J.'s inner sense of self and therefore denies this Request.

REQUEST NO. 6:

Admit that in 2021 Plaintiff B.P.J. was a member of Bridgeport Middle School's girls' cross-country team.

ANSWER: Subject to Ms. Armistead's general objections, Ms. Armistead states that she has no independent knowledge of B.P.J.'s participation on Bridgeport Middle Schools' girls' cross-country team in 2021, but she made a reasonable inquiry into the information readily attainable by her and admits that Plaintiff B.P.J. has testified that B.P.J. was a member of Bridgeport Middle School's girls' cross-country team, and that Defendant Harrison County has produced documentation of the same. Ms. Armistead therefore admits this Request.

REQUEST NO. 7:

Admit that Plaintiff B.P.J. placed 51 out of 66 competitors in the girls' middle school cross country Mountain Hollar MS Invitational meet in 2021.

ANSWER: Subject to Ms. Armistead's general objections, Ms. Armistead states that she has no independent knowledge of B.P.J.'s placements in 2021 cross-country meets, but she made a reasonable inquiry into the information readily attainable by her and admits that according to Athletic.Net, the results of the Mountain Hollar MS Invitational MS Women's 3,200 Meters Junior Varsity 2021 meet show that Plaintiff B.P.J. placed 51 out of 66 competitors. However, Ms. Armistead does not know the competitors' ages, the requirements for entry, or the rules of the race.

REQUEST NO. 8:

Admit that Plaintiff B.P.J. placed 123 out of 150 competitors in the girls' middle school cross country Doddridge Invitational meet in 2021.

ANSWER: Subject to Ms. Armistead's general objections, Ms. Armistead states that she has no independent knowledge of B.P.J.'s placements in 2021 cross-country meets, but she made a reasonable inquiry into the information readily attainable by her and admits that according to Athletic.Net, the results of the Doddridge Invitational MS, Women's 3,000 Meters Middle School 2021 meet show that Plaintiff B.P.J. placed 123 out of 150 competitors. However, Ms. Armistead does not know the competitors' ages, the requirements for entry, or the rules of the race.

REQUEST NO. 9:

Admit that you are not aware of any complaints associated with Plaintiff B.P.J.'s membership on Bridgeport Middle School's girls' cross-country team.

ANSWER: Ms. Armistead objects to the term "complaints associated with" as overbroad, vague, and ambiguous because "complaints" could include the inner thoughts, off-handed comments, private conversations of anyone, or official complaints submitted through Bridgeport Middle School or another entity. "Complaints associated with" could also refer to any subject "associated" with B.P.J.'s membership on the team, including Plaintiff's language, conduct, rule-compliance, etc. Finally, it is unclear whether the complaint needs to be specifically about B.P.J.'s participation on the team, or in girls' sports generally.

Subject to these objections, Ms. Armistead states that she has no independent knowledge of any complaints concerning B.P.J.'s membership on Bridgeport Middle School's girls' cross-country team, nor can she obtain any through a reasonable inquiry into the information readily

obtainable by her. Ms. Armistead is not in direct contact with any student, family member of any student, or employee of Bridgeport Middle School, so she has no reason to be aware of any complaints associated with Plaintiff's membership. But Ms. Armistead is aware of general critiques and complaints by members of the public about B.P.J.'s participation on girls' teams impacting fairness and equality in women's sports. These statements can be found in the Twitter replies at these links: <https://mobile.twitter.com/ACLU/status/1397622893832556549>; <https://mobile.twitter.com/WSAZnews/status/1397704112448364545>. She therefore denies this Request.

REQUEST NO. 10:

Admit that no middle school girl was harmed as a result of B.P.J.'s participation on Bridgeport Middle School's girls' cross-country team in 2021.

ANSWER: Ms. Armistead objects to this Request because "harm" is ambiguous, overbroad, and vague, and Plaintiffs do not specify whether "harm" is physical, emotional, mental, or otherwise for purposes of this Request. Ms. Armistead also objects to the term "middle school girl" because it is ambiguous, overbroad, and vague as to whether Plaintiff refers to middle school girls at Bridgeport Middle School, middle school girls at Bridgeport Middle School on the girls' cross-country team, middle school girls at any or all public secondary education schools in West Virginia, or every middle school girl in the United States.

Subject to these objections, Ms. Armistead denies this Request. Middle school girls who were members of the Bridgeport Middle School girls' cross-country team and middle school girls who were members of the girls' cross-country teams at other public secondary schools in West Virginia who competed against Bridgeport Middle School in girls' cross-country were harmed when (1) they were forced to compete with/against B.P.J., a biological male; (2) they

were subjected to an unfair advantage because B.P.J., as a biological male, has inherent athletic advantages over biological females, including advantages in strength and speed against comparably fit, trained, and aged females; and (3) Plaintiff B.P.J. placed higher and ran faster than at least 42 middle school girls in the Mountain Hollar and Doddridge Invitationals in 2021, and regularly finished higher at meets than girls on BMS team, sometimes resulting in their scores not being counted toward the team total. Moreover, other girls may have been deterred from participating in women's sports and suffered the stigma and emotional harm of watching a male compete against and win against biological females. Finally, B.P.J.'s participation in a race pursuant to the Court's order interpreting Title IX and the Equal Protection Clause to ban the government from uniformly separating sports competitions by biological sex hurts every female athlete competing at a secondary school in West Virginia.

REQUEST NO. 11:

Admit that no middle school girl was injured as a result of Plaintiff B.P.J.'s participation on Bridgeport Middle School's girls' cross-country team in 2021.

ANSWER: Ms. Armistead objects to this Request because "injured" is ambiguous, overbroad, and vague and Plaintiffs do not specify whether "injured" refers to physical, emotional, mental, or another form of injury for purposes of this Request. Ms. Armistead also objects to the term "middle school girl" because it is ambiguous, overbroad, and vague as to whether Plaintiff refers to middle school girls at Bridgeport Middle School, middle school girls at Bridgeport Middle School on the girls' cross-country team, middle school girls at public secondary education schools in West Virginia, or every middle school girl in the United States.

Subject to these objections, Ms. Armistead denies this Request. Middle school girls who were members of the Bridgeport Middle School girls' cross-country team and middle school

girls who were members of the girls' cross-country teams at other public secondary schools in West Virginia who competed against Bridgeport Middle School were injured when (1) they were forced to compete with/against B.P.J., a biological male; (2) they were subjected to an unfair advantage because B.P.J., as a biological male, has inherent athletic advantages over biological females, including advantages in strength and speed against comparably fit, trained, and aged females; and (3) Plaintiff B.P.J. placed higher and ran faster than at least 42 middle school biological girls in the Mountain Hollar and Doddridge Invitationals in 2021, and regularly finished higher at meets than girls on the BMS team, sometimes resulting in their scores not being counted toward the team total.

REQUEST NO. 12:

Admit that no Bridgeport Middle School girl student was prohibited from joining Bridgeport Middle School's girls' cross-country team in 2021.

ANSWER: Ms. Armistead objects to this Request because it is ambiguous, vague, and overbroad. Defendants' production and testimony demonstrate that Bridgeport Middle school girl students could have been prohibited from joining the Bridgeport Middle School's girl's cross-country team in 2021 for a myriad of reasons relating to, but not limited to, eligibility, grades, and residency. Moreover, the Request does not specify who prohibited the participation—parents, guardians, coaches, school administrators—or whether the prohibition was legal or factual.

Subject to this objection, Ms. Armistead states that she has no independent knowledge of Bridgeport Middle School's girls' cross country team's selection process or criteria for membership in 2021, or Bridgeport Middle School's reasoning or decision-making for membership requirements on the girls' cross-country team in 2021, or the reasons why students

did or did not join the team, even after making a reasonable inquiry into the information readily attainable by her. Ms. Armistead admits only that B.P.J. has testified that every person who tried out for the Bridgeport Middle School's girls' cross-country team in 2021 made the team. She denies the rest of this Request.

REQUEST NO. 13:

Admit that Bridgeport Middle School's girls' cross-country team did not turn anyone away from participating due to lack of space on the roster in 2021.

ANSWER: Ms. Armistead objects to this Request because it is ambiguous and vague. It is not clear who constitutes the "team" referenced in this Request—the Bridgeport Middle School cross-country coaches, school officials, or student athletes.

Subject to Ms. Armistead's general objections, Ms. Armistead states that she has no independent knowledge of Bridgeport Middle School's girls' cross country team's selection in 2021, even after making a reasonable inquiry into the information readily attainable by her. Ms. Armistead admits only that B.P.J. has testified that every person who tried out for the Bridgeport Middle School's girls' cross-country team in 2021 made the team. She denies the rest of this Request.

REQUEST NO. 14:

Admit that Plaintiff B.P.J. does not have an unfair athletic advantage over other girls participating on the Bridgeport Middle School girls' cross-country team.

ANSWER: Ms. Armistead objects to this Request because "unfair athletic advantage" is overbroad, vague, and ambiguous as it is unclear what kinds of unfair athletic advantages that Plaintiff might be referring to. It is also unclear whether "other girls" refers to each and every girl on Bridgeport Middle School's cross-country team, a similarly aged girl, or those girls in the

same grade as B.P.J. Moreover, she objects to this Request because this topic is the subject of expert discovery.

Subject to these objections, Ms. Armistead states that she has no independent knowledge of B.P.J.'s day-to-day performances in cross-country but has made a reasonable inquiry into the information readily attainable by her. Ms. Armistead denies this Request because B.P.J., as a biological male, has inherent athletic advantages over comparably fit, trained, and aged biological females, including in strength and speed. Ms. Armistead also notes that, according to documents produced by Defendant Harrison County Board of Education, Plaintiff B.P.J. placed higher than other members of the Bridgeport Middle School girls' cross-country team, and regularly finished higher at meets than girls on the BMS girls' cross-country team, sometimes resulting in those girls' scores not being counted toward the team total.

REQUEST NO. 15:

Admit that Plaintiff B.P.J. does not have an unfair athletic advantage over girls competing against the Bridgeport Middle School girls' cross-country team.

ANSWER: Ms. Armistead objects to this Request because "unfair athletic advantage" is overbroad, vague, and ambiguous as it is unclear what kinds of unfair athletic advantages that Plaintiffs might be referring to. Moreover, she objects to this Request because this topic is the subject of expert discovery and facts about the subjective state of the mind of the opposing party are an improper basis for a Request for Admission.

Subject to these objections, Ms. Armistead states that she has no independent knowledge of B.P.J.'s day-to-day performances in cross-country but has made a reasonable inquiry into the information readily attainable by her. Ms. Armistead denies this Request because B.P.J., as a biological male, has inherent athletic advantages over comparably fit, trained, and aged

biological females, including in strength and speed. Ms. Armistead also notes that, according to documents produced by Defendant Harrison County Board of Education, Plaintiff B.P.J. placed higher than other members of the Bridgeport Middle School girls' cross-country team, and regularly finished higher at meets than girls on the BMS girls' cross-country team, sometimes resulting in those girls' scores not being counted toward the team total.

REQUEST NO. 16:

Admit that cross-country is a sport that requires "competitive skill" as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

ANSWER: Ms. Armistead admits that cross-country is a sport that requires "competitive skill" as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

REQUEST NO. 17:

Admit that cross-country is a sport that requires "competitive skill" as that phrase is used in 34 C.F.R. § 106.41(b).

ANSWER: Ms. Armistead admits that cross-country is a sport that requires "competitive skill" as that phrase is used in 34 C.F.R. § 106.41(b).

REQUEST NO. 18:

Admit that cross-country is not a "contact sport" as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

ANSWER: Ms. Armistead admits that cross-country is not a "contact sport" as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

REQUEST NO. 19:

Admit that cross-country is not a "contact sport" as that phrase is used in 34 C.F.R. § 106.41(b).

ANSWER: Ms. Armistead admits that cross-country is not a “contact sport” as that phrase is used in 34 C.F.R. § 106.41(b).

REQUEST NO. 20:

Admit that, but for the injunction issued in this case (Dkt. 67), Plaintiff B.P.J. would not have been permitted to be a member of Bridgeport Middle School’s girls’ cross-country team in 2021 because of H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

ANSWER: Ms. Armistead objects to the extent this Request asks her to provide a legal conclusion about H.B. 3293. Ms. Armistead further objects to the extent this Request asks her to speculate how the Bridgeport Middle School’s girls’ cross-country team coach or Bridgeport Middle School administrators and athletics authorities, or other state officials, would interpret or apply H.B. 3293 to Plaintiff B.P.J.

Subject to these objections, Ms. Armistead admits that based on her personal reading and understanding of H.B. 3293, and the fact the Plaintiff has admitted that B.P.J. is biologically male, the law would not permit Plaintiff B.P.J. to be a member of Bridgeport Middle School’s girls’ cross-country team in 2021. But Ms. Armistead lacks personal knowledge of how the coaches, school administrators, or athletic authorities at Bridgeport Middle School, or other state officials, would interpret or apply H.B. 3293 to B.P.J. absent the preliminary injunction issued in this case, and thus denies this Request.

REQUEST NO. 21:

Admit that, but for the injunction issued in this case (Dkt. 67), Plaintiff B.P.J. would not be permitted to be a member of any girls’ athletic team offered at Bridgeport Middle School because of H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

ANSWER: Ms. Armistead objects to the extent this Request asks her to provide a legal conclusion about H.B. 3293. Ms. Armistead further objects to the extent this Request asks her to speculate how the Bridgeport Middle School's girls' athletic teams' coaches, school administrators, or athletics authorities would interpret or apply H.B. 3293 to Plaintiff B.P.J. absent the preliminary injunction issued in this case.

Subject to these objections, Ms. Armistead admits that based on her personal reading and understanding of H.B. 3293, and the fact the Plaintiff has admitted that B.P.J. is biologically male, the law would not permit Plaintiff B.P.J. to be a member of any Bridgeport Middle School's girls' athletic teams in 2021 because of H.B. 3293. But Ms. Armistead lacks personal knowledge of how the coaches, school administrators, or athletic authorities at Bridgeport Middle School would interpret or apply H.B. 3293 to B.P.J. absent the preliminary injunction issued in this case, and thus denies this Request.

REQUEST NO. 22:

Admit that H.B. 3293 prohibits Plaintiff B.P.J. from participating on girls' athletic teams at all public secondary schools located in West Virginia.

ANSWER: Ms. Armistead objects to the extent this Request asks her to provide a legal conclusion about H.B. 3293. Ms. Armistead further objects to the extent this Request asks her to speculate how coaches, school administrators, or athletic authorities at all public secondary schools located in West Virginia would interpret or apply H.B. 3293 to Plaintiff B.P.J. regarding participation on girls' sports teams, absent the preliminary injunction issued in this case.

Subject to these objections, Ms. Armistead admits that based on her personal understanding of H.B. 3293, the law would not permit Plaintiff B.P.J. to compete on an athletic team designated for girls at a public secondary school in West Virginia. But Ms. Armistead lacks

personal knowledge and independent knowledge of how the coaches or school administrators at any/all public secondary schools in West Virginia, or other state officials, would interpret or apply H.B. 3293 to B.P.J. absent the preliminary injunction issued in this case, and thus denies this Request.

REQUEST NO. 23:

Admit that the State Board of Education and the State Superintendent must comply with H.B. 3293 unless enjoined from doing so by a court.

ANSWER: Ms. Armistead objects to this Request because “must comply with” is vague and does not indicate what type of legal obligation or necessity is imposed. Ms. Armistead will interpret this Request to mean the State Board and Superintendent have a legal obligation to follow H.B. 3293. Ms. Armistead further objects to the extent this Request asks her to provide a legal conclusion about H.B. 3293. Ms. Armistead also objects to the extent this Request asks her to speculate how the State Board of Education and the State Superintendent would comply with H.B. 3293 absent the preliminary injunction issued in this case.

Subject to these objections, Ms. Armistead admits that state officials generally have a legal duty to comply with state laws that apply to them, including HB 3293, but she lacks personal knowledge of all the specific legal duties and obligations on State Board of Education and the State Superintendent and how these particular entities interpret the laws and regulations imposing these duties, and thus denies this Request.

REQUEST NO. 24:

Admit that H.B. 3293 prohibits the State Board of Education and the State Superintendent from adopting or enforcing a policy that would allow B.P.J. to participate on girls’ athletic teams at Bridgeport Middle School.

ANSWER: Ms. Armistead objects to the extent this Request asks her to provide a legal conclusion about H.B. 3293. Ms. Armistead further objects to the extent this Request asks her to speculate how the State Board of Education and the State Superintendent would adopt or enforce a policy that would allow B.P.J. to participate on girls' athletic teams at Bridgeport Middle School in accordance with H.B. 3293.

Subject to these objections, Ms. Armistead admits that H.B. 3293 prohibits males, including B.P.J., from competing on girls' teams at secondary schools in West Virginia, but lacks personal knowledge of how the law is enforced or the specific legal duties imposed on the State Board of Education and the State Superintendent and therefore denies this Request.

REQUEST NO. 25:

Admit that the Harrison County Board of Education and the Harrison County School Superintendent must comply with H.B. 3293 unless enjoined from doing so by a court.

ANSWER: Ms. Armistead objects to this Request because "must comply with" is vague and does not indicate what type of legal obligation is or necessity is imposed. Ms. Armistead will interpret this Request to mean the Harrison County Board of Education and School Superintendent have a legal obligation to follow H.B. 3293. Ms. Armistead objects to the extent this Request asks her to provide a legal conclusion about H.B. 3293. Ms. Armistead further objects to the extent this Request asks her to speculate how the Harrison County Board of Education and the Harrison County School Superintendent would comply with H.B. 3293 absent the preliminary injunction issued in this case.

Subject to these objections, Ms. Armistead admits that county officials generally have a legal duty to comply with state laws that apply to them, including HB 3293, but she lacks personal knowledge of all the specific legal duties and obligations on Harrison County Board of

Education and School Superintendent and how these particular entities interpret the laws and regulations imposing these duties, and thus denies this Request.

REQUEST NO. 26:

Admit that H.B. 3293 prohibits the Harrison County Board of Education and the Harrison County Superintendent from adopting or enforcing a policy that would allow B.P.J. to participate on girls' athletic teams at Bridgeport Middle School.

ANSWER: Ms. Armistead objects to the extent this Request asks her to provide a legal conclusion about H.B. 3293. Ms. Armistead further objects to the extent this Request asks her to speculate how the Harrison County Board of Education and the Harrison County Superintendent would adopt or enforce a policy that would allow B.P.J. to participate on girls' athletic teams at Bridgeport Middle School in accordance with H.B. 3293.

Subject to these objections, Ms. Armistead admits that H.B. 3293 prohibits males, including B.P.J., from competing on girls' teams at secondary schools in West Virginia, but lacks personal knowledge of how the law is enforced or the specific legal duties imposed on the Harrison County Board of Education and School Superintendent and therefore denies this Request.

REQUEST NO. 27:

Admit that the West Virginia Secondary School Athletic Commission must comply with H.B. 3293 unless enjoined from doing so by a court.

ANSWER: Ms. Armistead objects to the extent this Request asks her to provide a legal conclusion about H.B. 3293. Ms. Armistead further objects to the extent this Request asks her to speculate how the West Virginia Secondary School Athletic Commission would comply with H.B. 3293 absent the preliminary injunction issued in this case.

Subject to these objections, Ms. Armistead Ms. Armistead admits that H.B. 3293 prohibits males, including B.P.J., from competing on girls' teams at secondary schools in West Virginia, but lacks personal knowledge of how the law is enforced or the specific legal duties imposed on the West Virginia Secondary School Athletic Commission and therefore denies this Request.

REQUEST NO. 28:

Admit that H.B. 3293 prohibits the West Virginia Secondary School Athletic Commission from adopting or enforcing a policy that would allow B.P.J. to participate on girls' athletic teams at Bridgeport Middle School.

ANSWER: Ms. Armistead objects to the extent this Request asks her to provide a legal conclusion about H.B. 3293. Ms. Armistead further objects to the extent this Request asks her to speculate how the West Virginia Secondary School Athletic Commission would adopt or enforce a policy that would allow B.P.J. to participate on girls' athletic teams at Bridgeport Middle School in accordance with H.B. 3293.

Subject to these objections, Ms. Armistead admits that H.B. 3293 prohibits males, including B.P.J., from competing on girls' teams at secondary schools in West Virginia, but lacks personal knowledge of how the law is enforced or the specific legal duties imposed on the West Virginia Secondary School Athletic Commission and therefore denies this Request.

REQUEST NO. 29:

Admit that there are no athletic teams designated as "coed or mixed," as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), offered at Bridgeport Middle School.

ANSWER: Ms. Armistead lacks personal and independent knowledge of whether Bridgeport Middle School offers any coed or mixed athletic teams. Even after conducting a reasonable

investigation, Ms. Armistead cannot find sufficient information to determine whether there are any athletic teams designated as coed or mixed at Bridgeport Middle School and notes there is conflicting evidence in the record on this point, and thus denies this Request.

REQUEST NO. 30:

Admit that there are no athletic teams designated as “coed or mixed,” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), that compete interscholastically offered at any public secondary school located in West Virginia.

ANSWER: Ms. Armistead objects to this Request because it is unduly burdensome to research and determine whether every public secondary school located in West Virginia offers coed or mixed athletic teams. Ms. Armistead points to West Virginia Secondary School Activities Commission’s Responses to Plaintiff’s First Set of Interrogatories, Response to Interrogatory No. 11, showing there are at least 277 public secondary schools who are members of the West Virginia Secondary School Activities Commission, notwithstanding any additional non-member public schools in West Virginia.

Subject to these objections, Ms. Armistead lacks personal and independent knowledge of whether any public secondary school in West Virginia offers any coed or mixed athletic teams. Even after conducting a reasonable investigation, Ms. Armistead cannot find sufficient information to determine whether there are any athletic teams designated as coed or mixed that compete interscholastically at any public secondary schools located in West Virginia, and thus denies this Request.

REQUEST NO. 31:

Admit that there are no cross-country teams designated as “coed or mixed,” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), that

compete interscholastically offered by any member school of the West Virginia Secondary School Activities Commission.

ANSWER: Ms. Armistead objects to this Request because it is unduly burdensome and overbroad to research and determine whether every member public secondary school of the West Virginia Secondary School Activities Commission offers coed or mixed athletic teams. Ms. Armistead points to West Virginia Secondary School Activities Commission's Responses to Plaintiff's First Set of Interrogatories, Response to Interrogatory No. 11, showing there are at least 277 public secondary schools who are members of the West Virginia Secondary School Activities Commission.

Subject to these objections, Ms. Armistead lacks personal and independent knowledge of whether any West Virginia Secondary public secondary school in West Virginia offers any coed or mixed cross-country teams. Even after conducting a reasonable investigation, Ms. Armistead cannot find sufficient information to determine whether there are any cross-country teams designated as coed or mixed at any West Virginia Secondary School Activities Commission member public secondary schools located in West Virginia that compete interscholastically, and thus denies this Request.

REQUEST NO. 32:

Admit that there are no athletic leagues designated as "coed or mixed," as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), that comprise teams from more than one school supervised by the West Virginia Secondary School Activities Commission.

ANSWER: Ms. Armistead objects to this Request because it is unduly burdensome to research and determine whether every public secondary school located in West Virginia offers coed or mixed athletic teams. Ms. Armistead points to WVSSAC's Responses to Plaintiff's First Set of

Interrogatories, Response to Interrogatory No. 11, showing there are at least 277 public secondary schools who are members of WVSSAC, notwithstanding any additional non-member public schools in West Virginia.

Subject to these objections, Ms. Armistead lacks personal and independent knowledge of whether there are any athletic leagues comprised of West Virginia Secondary public secondary schools' athletic teams that are supervised by the West Virginia Secondary School Activities Commission. Even after conducting a reasonable investigation, Ms. Armistead cannot find sufficient information to determine whether there are any athletic leagues comprised of West Virginia Secondary public secondary schools' athletic teams that are supervised by the West Virginia Secondary School Activities Commission, and thus denies this Request.

REQUEST NO. 33:

Admit that there are no athletic teams designated as "coed or mixed," as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), "that compete interscholastically offered by any public secondary school under the supervision of the West Virginia State Board of Education.

ANSWER: Ms. Armistead objects to this Request because it is unduly burdensome to research and determine whether every public secondary school located in West Virginia offers coed or mixed athletic teams. Ms. Armistead points to WVSSAC's Responses to Plaintiff's First Set of Interrogatories, Response to Interrogatory No. 11, showing there are at least 277 public secondary schools who are members of WVSSAC, notwithstanding any additional non-member public schools in West Virginia.

Subject to these objections, Ms. Armistead lacks personal and independent knowledge of whether any West Virginia Secondary public secondary school in West Virginia offers any coed or mixed athletic teams that compete interscholastically under the supervision of the West

Virginia State Board of Education. Even after conducting a reasonable investigation, Ms. Armistead cannot find sufficient information to determine whether any West Virginia Secondary public secondary school in West Virginia offers any coed or mixed athletic teams that compete interscholastically under the supervision of the West Virginia State Board of Education, and thus denies this Request.

REQUEST NO. 34:

Admit that H.B. 3293 does not prohibit a cisgender girl student at Bridgeport Middle School from joining a girls' athletic team offered at Bridgeport Middle School.

ANSWER: Ms. Armistead objects to the meaning of the term "cisgender". There is no definitive, legally recognized definition of "cisgender", Plaintiff's definition relies on the term "gender identity" which, as noted above, is not defined, and finally, Ms. Armistead denies that sex is "assigned at birth." Ms. Armistead further objects to the extent this Request asks her to provide a legal conclusion about H.B. 3293 and objects to the extent this Request asks her to speculate how Bridgeport Middle School would enforce H.B. 3293 regarding its girls' athletic teams.

Subject to these objections, Ms. Armistead admits only that, based on her personal understanding and reading of H.B. 3293, the law does not prohibit biological girls of appropriate age, academic standing, and eligibility, from trying out for or joining a girls' athletic team offered at Bridgeport Middle School.

REQUEST NO. 35:

Admit that H.B. 3293 does not prohibit a cisgender girl student at any public secondary school in West Virginia from joining a girls' athletic team offered by her public secondary school.

ANSWER: Ms. Armistead objects to the meaning of the term “cisgender”. There is no definitive, legally recognized definition of “cisgender”, Plaintiff’s definition relies on the term “gender identity” which, as noted above, is not defined, and finally, Ms. Armistead denies that sex is “assigned at birth.” Ms. Armistead further objects to the extent this Request asks her to provide a legal conclusion about H.B. 3293 and objects to the extent this Request asks her to speculate how any and all public secondary school in West Virginia would enforce H.B. 3293 regarding its girls’ athletic teams.

Subject to these objections, Ms. Armistead only admits that based on her personal understanding and reading of H.B. 3293, the law does not prohibit biological girls of appropriate age, academic standing, and eligibility from trying out for or otherwise joining a girls’ athletic team offered at any public secondary school in West Virginia.

REQUEST NO. 36:

Admit that H.B. 3293 prohibits a Bridgeport Middle School transgender girl student from joining a girls’ athletic team offered at Bridgeport Middle School.

ANSWER: Ms. Armistead objects to the definition of “transgender” as provided in Plaintiff’s First Amended Complaint paragraph 23: “A transgender person is someone who has a gender identity that does not align with their sex assigned at birth.” There is no definitive, legally recognized definition of “transgender”, Plaintiff’s definition relies on the term “gender identity” which, as noted above, is not defined, and finally, Ms. Armistead denies that sex is “assigned at birth.” Ms. Armistead further objects to the extent this Request asks her to provide a legal conclusion about H.B. 3293 and objects to the extent this Request asks her to speculate how Bridgeport Middle School would enforce H.B. 3293 regarding the inner sense of self of biological males seeking to join its girls’ athletic teams.

Subject to these objections, Ms. Armistead admits that H.B. 3293 prohibits biological males, regardless of how they identify, from competing on a team designated for women or girls at Bridgeport Middle School. But Ms. Armistead lacks personal knowledge of how the coaches, school administrators or athletic authorities at Bridgeport Middle School, or other state officials, intend to or would interpret or apply H.B. 3293.

REQUEST NO. 37:

Admit that H.B. 3293 prohibits any transgender girl secondary school student located in West Virginia from joining a girls' athletic team offered by her public secondary school.

ANSWER: Ms. Armistead objects to the definition of “transgender” as provided in Plaintiff’s First Amended Complaint paragraph 23: “A transgender person is someone who has a gender identity that does not align with their sex assigned at birth.” There is no definitive, legally recognized definition of “transgender”, Plaintiff’s definition relies on the term “gender identity” which, as noted above, is not defined, and finally, Ms. Armistead denies that sex is “assigned at birth.” Ms. Armistead further objects to the extent this Request asks her to provide a legal conclusion about H.B. 3293 and objects to the extent this Request asks her to speculate how any public secondary school in West Virginia, or other state officials, would enforce H.B. 3293 regarding the inner sense of self of biological males seeking to join girls’ athletic teams.

Subject to these objections, Ms. Armistead admits that H.B. 3293 prohibits biological males, regardless of how they identify, from competing on an athletic team designated for women or girls at a public secondary school in West Virginia. But Ms. Armistead lacks personal knowledge of how the coaches, school administrators, or athletic authorities at every public secondary school in West Virginia, or state officials, intend to or would interpret or apply H.B. 3293 to biological males.

REQUEST NO. 38:

Admit that prior to the enactment of H.B. 3293, cisgender boy students at Bridgeport Middle School were prohibited from joining girls' athletic teams offered at Bridgeport Middle School.

ANSWER: Ms. Armistead objects to the phrase “prohibited from joining” because it is unclear whether the Request asks for whether the law forbade this or whether any male athletes wanted to join and were barred from doing so. Additionally, the term “cisgender” is vague as it has no definitive, legally recognized definition, Plaintiff’s definition relies on the term “gender identity” which, as noted above, is not defined, and finally, Ms. Armistead denies that sex is “assigned at birth.” Ms. Armistead further objects to the extent this Request asks her to provide a legal conclusion about H.B. 3293 and objects to the extent this Request asks her to speculate whether biological male students at Bridgeport Middle School were prohibited from joining girls’ athletic teams offered at Bridgeport Middle School. Finally, this Request has no time limit and is therefore vastly overbroad. It is impossible for Ms. Armistead to know all the rules and regulations at all times prior to the passage of H.B. 3293, how officials interpreted and applied those rules, and all the reasons why and if males attempted to join a girls’ team and were in fact prohibited from doing so.

Subject to these objections, Ms. Armistead admits that Title IX has, for nearly 50 years in our country, prohibited males from competing in federally funded girls’ sports where competitive skill or physical contact is involved, but she has no personal knowledge about how West Virginia officials have interpreted or intend to interpret Title IX. But more recently, some courts, administrative agencies, athletic bodies, and government officials have adopted a different understanding of Title IX, adopted a different understanding of what it means to be male and female, and therefore created confusion about who can compete in girls’ sports and on what conditions they could do so. Finally, Ms. Armistead has no personal or independent

knowledge as to how officials interpreted state and federal law prior to passing H.B. 3293, and therefore denies the same.

REQUEST NO. 39:

Admit that prior to the enactment of H.B. 3293, a cisgender boy student at any public secondary school in West Virginia was prohibited from joining girls' athletic teams offered at his public secondary school.

ANSWER: Ms. Armistead objects to the phrase "prohibited from joining" because it is unclear whether the Request asks for whether the law forbade this or whether any male athletes attempted to join and were barred from doing so. Ms. Armistead also objects to the meaning of the term "cisgender". There is no definitive, legally recognized definition of "cisgender", Plaintiff's definition relies on the term "gender identity" which is not defined, and finally, Ms. Armistead denies that sex is "assigned at birth." Ms. Armistead further objects to the extent this Request asks her to provide a legal conclusion about H.B. 3293 and objects to the extent this Request asks her to speculate whether biological male students were prohibited from joining girls' athletic teams offered at any public secondary school in West Virginia. Finally, this Request has no time limit and is therefore vastly overbroad. It is impossible for Ms. Armistead to know all the rules and regulations at all times prior to the passage of H.B. 3293, how officials interpreted and applied those rules, and all the reasons why and if males attempted to join a girls' team and were in fact prohibited from doing so.

Subject to these objections, Ms. Armistead admits that Title IX has, for nearly 50 years in our country, prohibited males from competing in federally funded girls' sports where competitive skill or physical contact is involved, but she has no personal knowledge about how West Virginia officials have interpreted or intend to interpret Title IX. But more recently, some courts, administrative agencies, athletic bodies, and government officials have adopted a

different understanding of Title IX, adopted a different understanding of what it means to be male and female, and therefore created confusion about who can compete in girls' sports and on what conditions they could do so. Finally, Ms. Armistead has no personal or independent knowledge as to how officials interpreted state and federal law prior to passing H.B. 3293, and therefore denies the same.

REQUEST NO. 40:

Admit that prior to the enactment of H.B. 3293, you are not aware of any transgender student athlete participating on an athletic team offered by Bridgeport Middle School.

ANSWER: Ms. Armistead objects to the definition of "transgender" as provided in Plaintiff's First Amended Complaint paragraph 23: "A transgender person is someone who has a gender identity that does not align with their sex assigned at birth." There is no definitive, legally recognized definition of "transgender", Plaintiff's definition relies on the term "gender identity" which, as noted above, is not defined, and finally, Ms. Armistead denies that sex is "assigned at birth."

Subject to these objections, Ms. Armistead admits that prior to the enactment of H.B. 3293, she had no personal or independent knowledge of the internal sense of self of members of the athletic teams at Bridgeport Middle School and whether that internal sense has changed, nor would she have any reason to know or possess that information. After a reasonable inquiry into the knowledge and information available to her, she states that she is aware of testimony from the WVSSAC indicating that at least one other male who identified as female tried to compete in girls' sports, but she does not know where the student attended school. This could have been at Bridgeport Middle School, so Ms. Armistead denies this Request.

REQUEST NO. 41:

Admit that prior to the enactment of H.B. 3293, you are not aware of any transgender student athlete participating on an athletic team offered by a public secondary school in West Virginia.

ANSWER: Ms. Armistead objects to the definition of “transgender” as provided in Plaintiff’s First Amended Complaint paragraph 23: “A transgender person is someone who has a gender identity that does not align with their sex assigned at birth.” There is no definitive, legally recognized definition of “transgender”, Plaintiff’s definition relies on the term “gender identity” which, as noted above, is not defined, and finally, Ms. Armistead denies that sex is “assigned at birth.”

Subject to these objections, Ms. Armistead admits that prior to the enactment of H.B. 3293, she had no personal or independent knowledge of the internal sense of self of members of the athletic teams at a public secondary school in West Virginia, nor would she have any reason to know or possess that information. After a reasonable inquiry into the knowledge and information available to her, Ms. Armistead states that she is aware of testimony from the WVSSAC indicating that at least one other male who identified as female tried to compete in girls’ sports at a secondary school in West Virginia, but she does not know where the student attended school.

REQUEST NO. 42:

Admit that other than Plaintiff B.P.J., you are not aware of a transgender student athlete participating on an athletic team offered by Bridgeport Middle School.

ANSWER: Ms. Armistead objects to the definition of “transgender” as provided in Plaintiff’s First Amended Complaint paragraph 23: “A transgender person is someone who has a gender identity that does not align with their sex assigned at birth.” There is no definitive, legally recognized definition of “transgender”, Plaintiff’s definition relies on the term “gender identity”

which, as noted above, is not defined, and finally, Ms. Armistead denies that sex is “assigned at birth.”

Subject to these objections, Ms. Armistead admits that other than Plaintiff B.P.J., she is currently not aware of and has no personal or independent knowledge of the current internal sense of self of members of the athletic teams at Bridgeport Middle School, nor does she have any reason to know or possess that information.

REQUEST NO. 43:

Admit that other than Plaintiff B.P.J., you are not aware of a transgender student athlete participating on an athletic team offered by a public secondary school in West Virginia.

ANSWER: Ms. Armistead objects to the definition of “transgender” as provided in Plaintiff’s First Amended Complaint paragraph 23: “A transgender person is someone who has a gender identity that does not align with their sex assigned at birth.” There is no definitive, legally recognized definition of “transgender”, Plaintiff’s definition relies on the term “gender identity” which, as noted above, is not defined, and finally, Ms. Armistead denies that sex is “assigned at birth.”

Subject to these objections, Ms. Armistead admits that she is currently not aware of, and she has no personal or independent knowledge of the internal sense of self of members of the athletic team offered by a public secondary school in West Virginia, nor would she have any reason to know or possess that information.

REQUEST NO. 44:

Admit that students derive social benefits from participation on athletic teams offered by public secondary schools in West Virginia.

ANSWER: Ms. Armistead objects to the term “social benefits” as overbroad, vague, and ambiguous because it is not clear how, why, or what kind of social benefits different individuals

experience and Ms. Armistead has no personal or independent knowledge of the social benefits that students other than herself may or may not derive from participating on athletic teams. Moreover, she objects to this Request because this topic is the subject of expert discovery and facts about the subjective state of the mind of the opposing party are an improper basis for a Request for Admission.

Subject to these objections, Ms. Armistead admits that she has personally derived social benefits as a student from playing soccer when the competition was safe and fair such as mental and physical toughness, perseverance, good sportsmanship, the value of hard work and discipline, the importance of teamwork, and leadership. Ms. Armistead further admits that she has observed other fellow athletes similarly benefiting from participation on athletic teams and believes that students generally benefit from participation when the competition is safe and fair. But Ms. Armistead never participated in sports in secondary schools in West Virginia and therefore cannot speak to the personal experience of every student.

REQUEST NO. 45:

Admit that students derive psychological benefits from participation on athletic teams offered by public secondary schools in West Virginia.

ANSWER: Ms. Armistead objects to the term “psychological benefits” as overbroad, vague, and ambiguous because it is not clear how, why, or what kind of psychological benefits different students may or may not experience from participating on athletic teams offered by public secondary schools in West Virginia. And Ms. Armistead has no personal or independent knowledge of the psychological benefits that students other than herself may or may not derive from participating on athletic teams. Moreover, she objects to this Request because this topic is the subject of expert discovery and facts about the subjective state of the mind of the opposing party are an improper basis for a Request for Admission.

Subject to these objections, Ms. Armistead admits that she has personally derived psychological benefits from playing soccer when the competition was safe and fair such as mental and physical toughness, perseverance, good sportsmanship, the value of hard work and discipline, the importance of teamwork, and leadership. Ms. Armistead further admits that she has observed fellow athletes similarly benefitting from participation on athletic teams when the competition is safe and fair. But Ms. Armistead never participated in sports in secondary schools in West Virginia and therefore cannot speak to the personal experience of every student.

REQUEST NO. 46:

Admit that interscholastic athletic competition benefits middle school students.

ANSWER: Ms. Armistead objects to the term “benefits” as overbroad, vague, and ambiguous because it is not clear how, why, or what kind of benefits different students may or may not experience from interscholastic athletic competition. And Ms. Armistead has no personal or independent knowledge of the all the benefits that middle school students may or may not derive from interscholastic athletic competition. Ms. Armistead also objects to the term “middle school students” as overbroad, vague, and ambiguous. It is not clear whether Plaintiff refers to middle school students in West Virginia, the United States of America, or the entire world. Moreover, she objects to this Request because this topic is the subject of expert discovery and facts about the subjective state of the mind of the opposing party are an improper basis for a Request for Admission.

Subject to these objections, Ms. Armistead lacks personal and independent knowledge of how and if interscholastic competition benefits each and every middle school student, but she admits that interscholastic competition—when fair and safe—generally benefits students and she has personally benefitted from such fair and safe competition.

REQUEST NO. 47:

Admit that middle school students who participate in interscholastic athletics receive benefits regardless whether they win or lose.

ANSWER: Ms. Armistead objects to the term “benefits” as overbroad, vague, and ambiguous because it is not clear how, why, or what kind of benefits different students may or may not receive from participating in interscholastic athletics regardless whether they win or lose, or whether the benefit is monetary, emotional, or psychological. And Ms. Armistead has no personal or independent knowledge of all the benefits that middle school students may or may not receive from participating in interscholastic athletics regardless whether they win or lose. Ms. Armistead also objects to the term “middle school students” as overbroad, vague, and ambiguous because it is not clear whether Plaintiff refers to middle school students in West Virginia, the United States of America, or the entire world. Moreover, she objects to this Request because this topic is the subject of expert discovery and facts about the subjective state of the mind of the opposing party are an improper basis for a Request for Admission.

Subject to these objections, Ms. Armistead admits that she personally benefited when she competed in safe and fair sports in middle school regardless of whether she won or lost. And based on her personal experience, she believes that competing in safe and fair sports generally benefits middle schoolers, but she cannot speak to the personal experience of every middle school interscholastic athlete.

REQUEST NO. 48:

Admit that student athletes who participate in interscholastic athletics receive benefits regardless whether they win or lose.

ANSWER: Ms. Armistead objects to the term “benefits” as overbroad, vague, and ambiguous because it is not clear how, why, or what kind of benefits different student athletes may or may not receive from participating in interscholastic athletics regardless whether they win or lose, or

whether the benefit is monetary, emotional, or psychological. And Ms. Armistead has no personal or independent knowledge of all the benefits that student athletes may or may not receive from participating in interscholastic athletics regardless whether they win or lose. Ms. Armistead also objects to the term “student athletes” as overbroad, vague, and ambiguous because it is not clear whether Plaintiff refers to all student athletes in West Virginia, the United States of America, or the entire world, or the age range/grade level of student athletes. “Student athletes” could include any student of any age who plays sports or considers themselves an athlete. Moreover, she objects to this Request because this topic is the subject of expert discovery and facts about the subjective state of the mind of the opposing party are an improper basis for a Request for Admission.

Subject to these objections, Ms. Armistead Ms. Armistead admits that she personally benefited when she competed in safe and fair sports as an interscholastic athlete regardless of whether she won or lost. And based on her personal experience, she believes that competing in safe and fair sports generally benefits interscholastic athletes, but she cannot speak to the personal experience of every interscholastic athlete.

Respectfully submitted this 10th day of March, 2022.

/s/ Christiana Holcomb

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**IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION**

**B.P.J., by her next friend and mother,
HEATHER JACKSON,
Plaintiff,**

v.

**Civil Action No. 2:21-cv-00316
Honorable Joseph R. Goodwin, Judge**

**WEST VIRGINIA STATE BOARD OF EDUCATION,
HARRISON COUNTY BOARD OF EDUCATION,
WEST VIRGINIA SECONDARY SCHOOL
ACTIVITIES COMMISSION, W. CLAYTON BURCH
in his official capacity as State Superintendent, and
DORA STUTLER in her official capacity as
Harrison County Superintendent,
Defendants.**

CERTIFICATE OF SERVICE

I hereby certify that I, Roberta F. Green, have this day, the 9th day of March, 2022, filed a true and exact copy of the Certificate of Service for **“WVSSAC’S RESPONSES TO SECOND SET OF REQUESTS FOR ADMISSION”** with the Clerk of Court using the CM/ECF System, and have served by electronic transmission the pleading upon the following counsel of record:

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**IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION**

**B.P.J., by her next friend and mother,
HEATHER JACKSON,
Plaintiff,**

v.

**Civil Action No. 2:21-cv-00316
Honorable Joseph R. Goodwin, Judge**

**WEST VIRGINIA STATE BOARD OF EDUCATION,
HARRISON COUNTY BOARD OF EDUCATION,
WEST VIRGINIA SECONDARY SCHOOL
ACTIVITIES COMMISSION, W. CLAYTON BURCH
in his official capacity as State Superintendent,
DORA STUTLER in her official capacity as
Harrison County Superintendent, and
THE STATE OF WEST VIRGINIA,
Defendants,**

and

**LAINY ARMISTEAD,
Intervenor Defendant.**

**WVSSAC'S RESPONSES TO SECOND SET
OF REQUESTS FOR ADMISSION**

Now comes West Virginia Secondary School Activities Commission (WVSSAC), by counsel, and responds to Plaintiff's Second Set of Requests for Admission, as follows. Defendant West Virginia Secondary School Activities Commission has not completed discovery in this civil action and has not completed its preparation for trial. For these reasons, the Defendant's responses are based upon only such information and documents as are presently available and known to WVSSAC. Further discovery and independent investigation may lead to other responsive information and/or documents. The following responses are given in good faith but without prejudice to the Defendant's right to produce evidence of subsequently discovered facts or documents.

The Defendant avails itself of all rights under the Federal Rules of Civil Procedure and such other applicable rules and law, and objects to the instructions contained in Plaintiff's discovery requests to the extent such instructions attempt to impose burdens on the Defendant that are outside the scope of the Rules or the law generally. The Defendant is not bound to follow any instructions which may be contrary to the Rules and other law. Further, WVSSAC objects to Plaintiff's Definitions as subjective, without appellation to an authoritative or objective source, and outside this Defendant's knowledge, such that Defendant has insufficient information, knowledge or belief to admit or deny any assertions based upon them. *See Lynn v. Monarch Recovery Mgmt.*, 28 F.R.D. 350, 368 (2012).

With these objections in place, WVSSAC responds as follows.

REQUESTS FOR ADMISSION

REQUEST NO. 5: Admit that Plaintiff B.P.J. has been diagnosed with gender dysphoria.

RESPONSE:

WVSSAC admits that Plaintiff has produced medical records that reflect a diagnosis of 'gender dysphoria' and admits that Plaintiff and her prior treater Dr. Montano both testified to that diagnosis under oath. However, beyond that, WVSSAC has no independent knowledge of this assertion that would allow it to admit or deny this statement, and therefore denies same.

REQUEST NO. 6: Admit that in 2021 Plaintiff B.P.J. was a member of Bridgeport Middle School's girls' cross-country team.

RESPONSE:

Admitted on information and belief. WVSSAC is aware that Bridgeport Middle School has posted a roster that includes B.P.J. Beyond that, Plaintiff and Plaintiff's witnesses testified to B.P.J.'s participation on that team. While WVSSAC has no independent knowledge of the participation, it has notice of the roster, which is an official document in its course of business. In reliance thereon, WVSSAC admits this assertion on information and belief.

REQUEST NO. 7: Admit that Plaintiff B.P.J. placed 51 out of 66 competitors in the girls' middle school cross country Mountain Hollar MS Invitational meet in 2021.

RESPONSE:

WVSSAC has no independent knowledge of this assertion that would allow it to admit or deny same. Therefore, based upon that lack of knowledge, WVSSAC denies the assertion.

REQUEST NO. 8: Admit that Plaintiff B.P.J. placed 123 out of 150 competitors in the girls' middle school cross country Doddridge Invitational meet in 2021.

RESPONSE:

WVSSAC has no independent knowledge of this assertion that would allow it to admit or deny same. Therefore, based upon that lack of knowledge, WVSSAC denies the assertion.

REQUEST NO. 9: Admit that you have not received any complaints associated with Plaintiff B.P.J.'s membership on Bridgeport Middle School's girls' cross-country team.

RESPONSE:

On information and belief, admitted.

REQUEST NO. 10: Admit that no middle school girl was harmed as a result of B.P.J.'s participation on Bridgeport Middle School's girls' cross-country team in 2021.

RESPONSE:

Objection; unclear, undefined term 'harmed.' Beyond that, WVSSAC has no independent knowledge of this assertion that would allow it to admit or deny same. Therefore, based upon that lack of knowledge, WVSSAC denies the assertion.

REQUEST NO. 11: Admit that no middle school girl was injured as a result of Plaintiff B.P.J.'s participation on Bridgeport Middle School's girls' cross-country team in 2021.

RESPONSE:

Objection; unclear, undefined term 'injured.' WVSSAC has no independent knowledge of this assertion that would allow it to admit or deny same. Therefore, based upon that lack of knowledge, WVSSAC denies the assertion.

REQUEST NO. 12: Admit that no Bridgeport Middle School girl student was prohibited from joining Bridgeport Middle School's girls' cross-country team in 2021.

RESPONSE:

WVSSAC has no independent knowledge of this assertion that would allow it to admit or deny same. Therefore, based upon that lack of knowledge, WVSSAC denies the assertion.

REQUEST NO. 13: Admit that Bridgeport Middle School's girls' cross-country team did not turn anyone away from participating due to lack of space on the roster in 2021.

RESPONSE:

WVSSAC has no independent knowledge of this assertion that would allow it to admit or deny same. Therefore, based upon that lack of knowledge, WVSSAC denies the assertion.

REQUEST NO. 14: Admit that Plaintiff B.P.J. does not have an unfair athletic advantage over other girls participating on the Bridgeport Middle School girls' cross-country team.

RESPONSE:

WVSSAC has no independent knowledge of this assertion that would allow it to admit or deny same. Therefore, based upon that lack of knowledge, WVSSAC denies the assertion.

REQUEST NO. 15: Admit that Plaintiff B.P.J. does not have an unfair athletic advantage over girls competing against the Bridgeport Middle School girls' cross-country team.

RESPONSE:

WVSSAC has no independent knowledge of this assertion that would allow it to admit or deny same. Therefore, based upon that lack of knowledge, WVSSAC denies the assertion.

REQUEST NO. 16: Admit that cross country is a sport that requires “competitive skill” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE:

WVSSAC has insufficient knowledge of this assertion in this context, in particular, of the term ‘competitive skill’ relative to middle school cross country, so as to allow it to admit or deny same. Therefore, based upon that lack of knowledge, WVSSAC denies the assertion.

REQUEST NO. 17: Admit that cross country is a sport that requires “competitive skill” as that phrase is used in 34 C.F.R. § 106.41(b).

RESPONSE:

On information and belief, admitted that in some instances cross country can be seen as requiring competitive skill, although (also on information and belief) persons may participate in some instances with varying skill levels with or without ‘competitive’ skill involved.

REQUEST NO. 18: Admit that cross country is not a “contact sport” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)). 7

RESPONSE:

Admitted.

REQUEST NO. 19: Admit that cross country is not a “contact sport” as that phrase is used in 34 C.F.R. § 106.41(b).

RESPONSE:

Admitted.

REQUEST NO. 20: Admit that, but for the injunction issued in this case (Dkt. 67), Plaintiff B.P.J. would not have been permitted to be a member of Bridgeport Middle School’s girls’ cross-country team in 2021 because of H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE:

Objection; calls for a legal conclusion; incomplete hypothetical. For these reasons and based upon the fact that WVSSAC has insufficient first-hand information on these issues and the underlying variables, WVSSAC denies same.

REQUEST NO. 21: Admit that, but for the injunction issued in this case (Dkt. 67), Plaintiff B.P.J. would not be permitted to be a member of any girls' athletic team offered at Bridgeport Middle School because of H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE:

Objection; calls for a legal conclusion; incomplete hypothetical. For these reasons and based upon the fact that WVSSAC has insufficient first-hand information on these issues and the underlying variables, WVSSAC denies same.

REQUEST NO. 22: Admit that H.B. 3293 prohibits Plaintiff B.P.J. from participating on girls' athletic teams at all public secondary schools located in West Virginia.

RESPONSE:

Objection; calls for a legal conclusion; incomplete hypothetical. For these reasons and based upon the fact that WVSSAC has insufficient first-hand information on these issues and the underlying variables, WVSSAC denies same. However, WVSSAC admits that H.B. 3293 as codified at West Virginia Code Section 18-2-25d provides that "Athletic teams or sports designated for females, women, or girls shall not be open to students of the male sex where selection for such teams is based upon competitive skill or the activity involved is a contact sport."

REQUEST NO. 23: Admit that the State Board of Education and the State Superintendent must comply with H.B. 3293 unless enjoined from doing so by a court.

RESPONSE:

Objection; calls for a legal conclusion; incomplete hypothetical. For these reasons and based upon the fact that WVSSAC has insufficient first-hand information on these issues and the underlying variables, WVSSAC denies same while admitting the general principle that all individuals, entities must comply with any and all State laws that apply to them.

REQUEST NO. 24: Admit that H.B. 3293 prohibits the State Board of Education and the State Superintendent from adopting or enforcing a policy that would allow B.P.J. to participate on girls' athletic teams at Bridgeport Middle School.

RESPONSE:

Objection; calls for a legal conclusion; incomplete hypothetical. For these reasons and based upon the fact that WVSSAC has insufficient first-hand information on these issues and the underlying variables, WVSSAC denies same while admitting the general principle that all individuals, entities must comply with any and all State laws that apply to them.

REQUEST NO. 25: Admit that the Harrison County Board of Education and the Harrison County School Superintendent must comply with H.B. 3293 unless enjoined from doing so by a court.

RESPONSE:

Objection; calls for a legal conclusion; incomplete hypothetical. For these reasons and based upon the fact that WVSSAC has insufficient first-hand information on these issues and the underlying variables, WVSSAC denies same while admitting the general principle that all individuals, entities must comply with any and all State laws that apply to them.

REQUEST NO. 26: Admit that H.B. 3293 prohibits the Harrison County Board of Education and the Harrison County Superintendent from adopting or enforcing a policy that would allow B.P.J. to participate on girls' athletic teams at Bridgeport Middle School.

RESPONSE:

Objection; calls for a legal conclusion; incomplete hypothetical. For these reasons and based upon the fact that WVSSAC has insufficient first-hand information on these issues and the underlying variables, WVSSAC denies same while admitting the general principle that all individuals, entities must comply with any and all State laws that apply to them.

REQUEST NO. 27: Admit that the West Virginia Secondary School Athletic Commission must comply with H.B. 3293 unless enjoined from doing so by a court.

RESPONSE:

Admitted and denied. WVSSAC denies that H.B. 3293 includes express provisions, prescriptions, duties or other relative to WVSSAC. However, WVSSAC admits that it must follow all laws that include a duty for it.

REQUEST NO. 28: Admit that H.B. 3293 prohibits the West Virginia Secondary School Athletic Commission from adopting or enforcing a policy that would allow B.P.J. to participate on girls' athletic teams at Bridgeport Middle School.

RESPONSE:

Objection; calls for a legal conclusion; incomplete hypothetical. Further, WVSSAC denies that H.B. 3293 includes express provisions, prescriptions, duties or other relative to WVSSAC, including, by example only, adopting or enforcing related policies. For these reasons and based upon the fact that WVSSAC has insufficient first-hand information on these issues and the underlying variables as relates to this student, WVSSAC admits only that it cannot adopt or enforce any policy that conflicts with state law.

REQUEST NO. 29: Admit that there are no athletic teams designated as "coed or mixed," as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), offered at Bridgeport Middle School.

RESPONSE:

Denied. On information and belief as to the use of the pbrase in HB 3293, football, cheer, wrestling, baseball.

REQUEST NO. 30: Admit that there are no athletic teams designated as "coed or mixed," as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), that compete interscholastically offered at any public secondary school located in West Virginia.

RESPONSE:

Denied. On information and belief as to the use of the phrase in HB 3293, football, cheer, wrestling, baseball.

REQUEST NO. 31: Admit that there are no cross-country teams designated as “coed or mixed,” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), that compete interscholastically offered by any member school of the West Virginia Secondary School Activities Commission.

RESPONSE:

Admitted.

REQUEST NO. 32: Admit that there are no athletic leagues designated as “coed or mixed,” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), that comprise teams from more than one school supervised by the West Virginia Secondary School Activities Commission.

RESPONSE:

Objection; form of the question (which WVSSAC does not understand). In a good faith effort to respond and reserving all rights to amend, revise, retract or other upon clarification, WVSSAC asserts that the coed or mixed sports of football, cheer, wrestling, baseball allow for competition between schools.

REQUEST NO. 33: Admit that there are no athletic teams designated as “coed or mixed,” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), that compete interscholastically offered by any public secondary school under the supervision of the West Virginia State Board of Education.

RESPONSE:

Denied. On information and belief as to the use of the phrase in HB 3293, football, cheer, wrestling, baseball.

REQUEST NO. 34: Admit that H.B. 3293 does not prohibit a cisgender girl student at Bridgeport Middle School from joining a girls’ athletic team offered at Bridgeport Middle School.

RESPONSE:

Objection; calls for a legal conclusion. Without waiving that objection, on information and belief, admitted.

REQUEST NO. 35: Admit that H.B. 3293 does not prohibit a cisgender girl student at any public secondary school in West Virginia from joining a girls' athletic team offered by her public secondary school.

RESPONSE:

Objection; calls for a legal conclusion. Beyond that, on information and belief, admitted.

REQUEST NO. 36: Admit that H.B. 3293 prohibits a Bridgeport Middle School transgender girl student from joining a girls' athletic team offered at Bridgeport Middle School.

RESPONSE:

Objection; calls for a legal conclusion. Beyond that, on information and belief, admitted.

REQUEST NO. 37: Admit that H.B. 3293 prohibits any transgender girl secondary school student located in West Virginia from joining a girls' athletic team offered by her public secondary school.

RESPONSE:

Objection; calls for a legal conclusion. Beyond that, on information and belief, admitted.

REQUEST NO. 38: Admit that prior to the enactment of H.B. 3293, cisgender boy students at Bridgeport Middle School were prohibited from joining girls' athletic teams offered at Bridgeport Middle School.

RESPONSE:

Admitted, both before and after H.B. 3293.

REQUEST NO. 39: Admit that prior to the enactment of H.B. 3293, a cisgender boy student at any public secondary school in West Virginia was prohibited from joining girls' athletic teams offered at his public secondary school.

RESPONSE:

Admitted, both before and after H.B. 3293.

REQUEST NO. 40: Admit that prior to the enactment of H.B. 3293, you are not aware of any transgender student athlete participating on an athletic team offered by Bridgeport Middle School.

RESPONSE:

Admitted and denied. While WVSSAC admits that it is not aware of any transgender student athlete who participated on an athletic team offered by Bridgeport Middle School prior to the enactment of H.B. 3293, WVSSAC denies that it would have any reason to know of same, as the only information WVSSAC has about students is what is recorded on the rosters, i.e., boys, girls.

REQUEST NO. 41: Admit that prior to the enactment of H.B. 3293, you are not aware of any transgender student athlete participating on an athletic team offered by a public secondary school in West Virginia.

RESPONSE:

Admitted and denied. While WVSSAC admits that it is not aware of any transgender student athlete who participated on an athletic team offered by a public secondary school prior to the enactment of H.B. 3293, WVSSAC denies that it would have any reason to know of same, as the only information WVSSAC has about students is what is recorded on the rosters, i.e., boys, girls.

REQUEST NO. 42: Admit that other than Plaintiff B.P.J., you are not aware of a transgender student athlete participating on an athletic team offered by Bridgeport Middle School.

RESPONSE:

Admitted and denied. While WVSSAC admits that it is not aware of any other transgender student athlete participating on an athletic team offered by Bridgeport Middle School, WVSSAC denies that it would have any reason to know of same, as the only information WVSSAC has about students is what is recorded on the rosters, i.e., boys, girls.

REQUEST NO. 43: Admit that other than Plaintiff B.P.J., you are not aware of a transgender student athlete participating on an athletic team offered by a public secondary school in West Virginia.

RESPONSE:

Admitted and denied. While WVSSAC admits that it is not aware of any other transgender student athlete participating on an athletic team offered by a public secondary school in West Virginia, WVSSAC denies that it would have any reason to know of same, as the only information WVSSAC has about students is what is recorded on the rosters, i.e., boys, girls.

REQUEST NO. 44: Admit that students derive social benefits from participation on athletic teams offered by public secondary schools in West Virginia.

RESPONSE:

Objection; form of the question – undefined term ('social benefits'). Beyond that, however, on information and belief only, WVSSAC admits that, in general, participation in athletics and activities provides an opportunity for leadership, personal health, camaraderie and cooperation.

REQUEST NO. 45: Admit that students derive psychological benefits from participation on athletic teams offered by public secondary schools in West Virginia.

RESPONSE:

Objection; form of the question – undefined term ('psychological benefits') and beyond the specialization of WVSSAC. However, on information and belief only, WVSSAC admits that, in general, participation in athletics and activities provides an opportunity for leadership, personal health, camaraderie and cooperation.

REQUEST NO. 46: Admit that interscholastic athletic competition benefits middle school students.

RESPONSE:

Objection; form of the question – overly broad, vague ('benefits'). However, on information and belief only, WVSSAC admits that, in general, participation in interscholastic athletic competition 'benefits' middle school students by providing provides an opportunity for leadership, personal health, camaraderie and cooperation.

REQUEST NO. 47: Admit that middle school students who participate in interscholastic athletics receive benefits regardless whether they win or lose.

RESPONSE:

Objection; form of the question – overly broad, vague (‘benefits’). However, on information and belief only, WVSSAC admits that, in general, participation in interscholastic athletics ‘benefits’ middle school students, win or lose, by providing provides an opportunity for leadership, personal health, camaraderie and cooperation.

REQUEST NO. 48: Admit that after H.B. 3293 was signed into law you decided that, for athletic eligibility purposes, a student athlete’s gender would be determined by referring to the gender identified in West Virginia Education Information System (“WVEIS”).

RESPONSE:

Denied. The extent to which WVSSAC relied upon WVEIS was not changed by H.B. 3293. However, of note, WVSSAC has no access to and therefore no direct reliance upon WVEIS.

REQUEST NO. 49: Admit that Plaintiff B.P.J.’s gender is identified in WVEIS as “male.”

RESPONSE:

WVSSAC has no independent knowledge of this assertion that would allow it to admit or deny same. Therefore, based upon that lack of knowledge, WVSSAC denies the assertion.

REQUEST NO. 50: Admit that, as long as H.B. 3293 is in effect, you will not permit a student designated as “male” in WVEIS to participate on Bridgeport Middle School’s girls’ cross-country team unless ordered to permit that student to participate by a court.

RESPONSE:

WVSSAC denies that H.B. 3293 includes express provisions, prescriptions, duties or other relative to WVSSAC, including, by example only, adopting or enforcing related policies. For these reasons and based upon the fact that WVSSAC has insufficient first-hand information on these issues and the underlying variables in WVEIS as relates to the referenced student, WVSSAC admits that it cannot adopt or enforce any policy that conflicts with state law.

REQUEST NO. 51: Admit that, under your Rules and Regulations, the WVSSAC is composed of secondary schools which have certified in writing to the State Superintendent of Schools of West Virginia that they have elected to delegate the control, supervision, and regulation of their interscholastic athletic and band activities to you. See WVSSAC0000134.

RESPONSE:

Admitted, although WVSSAC's area of control is limited by the same Rules and Regulations, and state law.

REQUEST NO. 52: Admit that, under your Rules and Regulations, the WVSSAC shall supervise and control interscholastic athletics and band activities among member schools. See WVSSAC0000133.

RESPONSE:

Admitted, although WVSSAC's area of control is limited by the same Rules and Regulations, and state law.

REQUEST NO. 53: Admit that Bridgeport Middle School has delegated control, supervision, and regulation of its interscholastic athletics to you.

RESPONSE:

Admitted, although WVSSAC's area of control is limited by the same Rules and Regulations, and state law.

REQUEST NO. 54: Admit that you cannot promulgate any rule that conflicts with H.B. 3293 unless a court enjoins enforcement of H.B. 3293.

RESPONSE:

Objection; calls for a legal conclusion. Beyond that, admitted and denied. WVSSAC denies that H.B. 3293 includes express provisions, prescriptions, duties or other relative to WVSSAC, including, by example only, promulgating rules. On information and belief, any rule relative to H.B. 3293 would be adopted by the State Board and placed in the rule book directly, similarly to the 2.0 Rule. However, WVSSAC admits that it must follow state law.

REQUEST NO. 55: Admit that you cannot promulgate any rule that conflicts with rules promulgated by the State Board of Education to implement H.B. 3293 unless a court enjoins enforcement of H.B. 3293.

RESPONSE:

Admitted and denied. WVSSAC denies that H.B. 3293 includes express provisions, prescriptions, duties or other relative to WVSSAC, including, by example only, promulgating rules. On information and belief, any rule relative to H.B. 3293 would be adopted by the State Board and placed in the rule book directly, similarly to the 2.0 Rule. However, WVSSAC admits that it must follow state law.

REQUEST NO. 56: Admit that you promulgate rules governing student eligibility to participate in interscholastic athletics at secondary schools in West Virginia.

RESPONSE:

Admitted and denied. WVSSAC admits that it promulgates most rules governing student eligibility in interscholastic athletics at secondary schools. However, State Board rules, such as the 2.0 rule and, on information and belief, any rule promulgated pursuant to H.B. 3293, are promulgated by the State Board and placed as promulgated into the rule book.

REQUEST NO. 57: Admit that your Executive Director is designated as the person who shall receive complaints and make investigations concerning violations of your rules regarding student eligibility.

RESPONSE:

Admitted and denied. Admitted that the Executive Director is one of the persons designated to receive complaints and make investigations. Denied that it is only the Executive Director who receives complaints and makes investigations, as the three Assistant Executive Directors also participate in these processes.

REQUEST NO. 58: Admit that your Executive Director is designated as the person who shall render decisions and impose penalties in athletic eligibility disputes related to interscholastic athletics at secondary schools in West Virginia.

RESPONSE:

Admitted.

REQUEST NO. 59: Admit that your Board of Directors can overturn eligibility determinations made by your Executive Director.

RESPONSE:

Admitted.

REQUEST NO. 60: Admit that in exercising his duties to receive complaints and make investigations concerning violations of your rules regarding student eligibility, your Executive Director must comply with H.B. 3293 unless enjoined from doing so by a court.

RESPONSE:

Admitted and denied. WVSSAC denies that H.B. 3293 includes express provisions, prescriptions, duties or other relative to WVSSAC, including, by example only, provisions with which WVSSAC would or must comply. However, WVSSAC admits on information and belief that it could be called upon by a State Board rule to determine eligibility that could draw on the tenets of H.B. 3293.

REQUEST NO. 61: Admit that in exercising his duties to render decisions and impose penalties in athletic eligibility disputes, your Executive Director must comply with H.B. 3293 unless enjoined from doing so by a court.

RESPONSE:

Admitted and denied. WVSSAC denies that H.B. 3293 includes express provisions, prescriptions, duties or other relative to WVSSAC, including, by example only, provisions with which WVSSAC would or must comply. However, WVSSAC admits on information and belief that it could be called upon by a State Board rule to determine eligibility that could draw on the tenets of H.B. 3293.

REQUEST NO. 62: Admit that when reviewing eligibility determinations made by your Executive Director, your Board of Directors must comply with H.B. 3293 unless enjoined from doing so by a court.

RESPONSE:

Admitted and denied. WVSSAC denies that H.B. 3293 includes express provisions, prescriptions, duties or other relative to WVSSAC's Executive Director or Board of Directors, including, by example only, provisions with which WVSSAC by and/or through either its Executive Director or Board would or must comply. However, WVSSAC admits on information and belief that its Executive Director and/or its Board of Directors could be called upon by a State Board rule to determine eligibility and/or review an eligibility determination that could draw on the tenets of H.B. 3293.

**WEST VIRGINIA SECONDARY SCHOOL
ACTIVITIES COMMISSION,
By Counsel.**

/S/ Roberta F. Green

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**IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION**

B.P.J., by her next friend and mother, HEATHER JACKSON,

Plaintiff,

v.

**Civil Action No. 2:21-cv-00316
Honorable Joseph R. Goodwin**

WEST VIRGINIA STATE BOARD OF EDUCATION, HARRISON COUNTY BOARD OF EDUCATION, WEST VIRGINIA SECONDARY SCHOOL ACTIVITIES COMMISSION, W. CLAYTON BURCH in his official capacity as State Superintendent, DORA STUTLER, in her official capacity as Harrison County Superintendent, and THE STATE OF WEST VIRGINIA,

Defendants,

and

LAINIEY ARMISTEAD,

Defendant-Intervenor.

**DEFENDANT WEST VIRGINIA STATE BOARD OF EDUCATION'S RESPONSES
TO PLAINTIFF'S SECOND SET OF REQUESTS FOR ADMISSION**

NOW COMES Defendant West Virginia State Board of Education (hereinafter "WVBOE"), by and through counsel, Kelly C. Morgan, Kristen V. Hammond, Michael W. Taylor, and the law firm of Bailey & Wyant, P.L.L.C., and, pursuant to Rule 33 of the *Federal Rules of Civil Procedure*, hereby responds and objects to "*Plaintiff's Second Set of Requests for Admissions to Defendant West Virginia State Board of Education*" as follows:

GENERAL OBJECTIONS AND PRELIMINARY STATEMENT

A. WVBOE objects to the definitions as stated in Plaintiff's Second Set of Requests for

Admission, including specifically the following definitions:

“STATE BOARD means the West Virginia State Board of Education, as well as its officers, directors, employees, partners, corporate parent, subsidiaries, affiliates, attorneys, accountants, consultants, representatives, and agents.”

“STATE SUPERINTENDENT means W. Clayton Burch in his official capacity as Superintendent of the STATE BOARD, as includes each of the officers, directors, employees, partners, corporate parent, subsidiaries, affiliates, attorneys, accountants, consultants, representatives, and agents that report to him in his official capacity. It also means any PERSON who assumes any of Mr. Burch’s official positions or responsibilities in part, whether temporarily or permanently.”

These definitions are overly broad and outside the permissible scope of discovery under the *Federal Rules of Civil Procedure* as these definitions improperly broaden the identity of parties in this case.

These responses are made by WVBOE only.

B. These responses are based upon information and documentation presently available to WVBOE and which it believes to be complete and accurate. Said responses are made without prejudice to WVBOE’s right to rely upon subsequently discovered facts or evidence.

C. No incidental or implied admission of fact by WVBOE is made as to the responses provided herein. The fact that WVBOE has responded to the discovery requests of Plaintiff, may not properly be taken as an admission that WVBOE accepts or admits the existence of any facts set forth or assumed by such response or that such response constitutes admissible evidence.

D. Responses to Plaintiff’s discovery requests may be supplemented by WVBOE upon further investigation and acquisition of information or documentation which it does not possess or have knowledge of at this time. However, any such further supplementation shall be made only in accordance with *Federal Rules of Civil Procedure*.

E. WVBOE objects to each and every request insofar as it seeks information which is protected by the attorney-client privilege, or which falls within the scope of the work-product doctrine. WVBOE also objects to Plaintiff’s discovery requests to the extent that the information

and/or documentation sought has or could have been obtained from other sources that were more convenient, less burdensome, or less expensive.

F. WVBOE objects to any definitions and instructions set forth in Plaintiff's discovery requests to the extent that such definitions and instructions are inconsistent and confusing, and to the extent that they attempt to impose requirements which are more burdensome or in addition to those set forth in Rule 26 of the *Federal Rules of Civil Procedure*.

G. WVBOE objects to Plaintiff's discovery requests to the extent that they seek to discover confidential information or documentation. WVBOE will produce such information and/or documentation, if essential to the litigation, only upon the entry of an appropriate Protective Order and upon permission of any third parties with whom WVBOE may have obligations concerning confidential information.

H. WVBOE objects to Plaintiff's discovery requests based on insufficient information, knowledge, or belief to admit or deny any assertions set forth in such requests.

I. WVBOE states that the word usage and sentence structure may be that of the attorney assisting in the preparation of the following responses and, thus, does not necessarily purport to be the precise language of the executing party.

J. WVBOE is answering and responding to these discovery requests in conformity with the requirements set forth in *Federal Rules of Civil Procedure* and not necessarily in compliance with the instructions and definitions set forth in "*Plaintiff's Second Set of Requests for Admission to Defendant West Virginia State Board of Education*."

K. WVBOE objects to the discovery requests to the extent that the information and/or documents sought are not in its possession.

REQUESTS FOR ADMISSION

REQUEST NO. 5:

Admit that Plaintiff B.P.J. has been diagnosed with gender dysphoria.

RESPONSE: WVBOE has made a reasonable inquiry and admits that Plaintiff B.P.J. has produced documentation that attests Plaintiff B.P.J. has been diagnosed with gender dysphoria and that Plaintiff B.P.J.'s witnesses have testified to the same. However, WVBOE lacks sufficient independent knowledge to admit or deny the assertions set forth in this Request.

REQUEST NO. 6:

Admit that in 2021 Plaintiff B.P.J. was a member of Bridgeport Middle School's girls' cross-country team.

RESPONSE: WVBOE has made a reasonable inquiry and admits that Plaintiff B.P.J. has produced documentation that attests Plaintiff B.P.J. was a member of Bridgeport Middle School's girls' cross-country team in 2021 and that Plaintiff B.P.J.'s witnesses have testified to the same. However, WVBOE lacks sufficient independent knowledge to admit or deny the assertions in this Request.

REQUEST NO. 7:

Admit that Plaintiff B.P.J. placed 51 out of 66 competitors in the girls' middle school cross country Mountain Hollar MS Invitational meet in 2021.

RESPONSE: WVBOE has made a reasonable inquiry and lacks sufficient knowledge or information to admit or deny the assertions in this Request.

REQUEST NO. 8:

Admit that Plaintiff B.P.J. placed 123 out of 150 competitors in the girls' middle school cross country Doddridge Invitational meet in 2021.

RESPONSE: WVBOE has made a reasonable inquiry and lacks sufficient knowledge or information to admit or deny the assertions in this Request.

REQUEST NO. 9:

Admit that you have not received any complaints associated with Plaintiff B.P.J.'s membership on Bridgeport Middle School's girls' cross country team.

RESPONSE: WVBOE admits this Request.

REQUEST NO. 10:

Admit that no middle school girl was harmed as a result of B.P.J.'s participation on Bridgeport Middle School's girls' cross country team in 2021.

RESPONSE: WVBOE has made a reasonable inquiry and lacks sufficient knowledge or information to admit or deny the assertions in this Request.

REQUEST NO. 11:

Admit that no middle school girl was injured as a result of Plaintiff B.P.J.'s participation on Bridgeport Middle School's girls' cross country team in 2021.

RESPONSE: WVBOE has made a reasonable inquiry and lacks sufficient knowledge or

information to admit or deny the assertions in this Request.

REQUEST NO. 12:

Admit that no Bridgeport Middle School girl student was prohibited from joining Bridgeport Middle School's girls' cross-country team in 2021.

RESPONSE: WVBOE has made a reasonable inquiry and admits that Plaintiff B.P.J. and Defendant Dora Stutler have testified that all Bridgeport Middle School girl students who tried out for Bridgeport Middle School's girls' cross-country team in 2021 made the team. However, WVBOE lacks sufficient independent knowledge to admit or deny the assertions in this Request.

REQUEST NO. 13:

Admit that Bridgeport Middle School's girls' cross-country team did not turn anyone away from participating due to lack of space on the roster in 2021.

RESPONSE: WVBOE has made a reasonable inquiry and admits that Plaintiff B.P.J. and Defendant Dora Stutler have testified that all Bridgeport Middle School girl students who tried out for Bridgeport Middle School's girls' cross-country team in 2021 made the team. However, WVBOE lacks sufficient independent knowledge to admit or deny the assertions in this Request.

REQUEST NO. 14:

Admit that Plaintiff B.P.J. does not have an unfair athletic advantage over other girls participating on the Bridgeport Middle School girls' cross-country team.

RESPONSE: Objection. The phrase “unfair athletic advantage” is vague, undefined, and subject to multiple interpretation. Without waiving this objection, WVBOE has made a reasonable inquiry and lacks sufficient knowledge or information to admit or deny the assertions in this Request.

REQUEST NO. 15:

Admit that Plaintiff B.P.J. does not have an unfair athletic advantage over girls competing against the Bridgeport Middle School girls’ cross-country team.

RESPONSE: Objection. The phrase “unfair athletic advantage” is vague, undefined, and subject to multiple interpretation. Without waiving this objection, WVBOE has made a reasonable inquiry and lacks sufficient knowledge or information to admit or deny the assertions in this Request.

REQUEST NO. 16:

Admit that cross country is a sport that requires “competitive skill” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: WVBOE denies as “competitive skill” is not defined in H.B. 3293 or *West Virginia Code* § 18-2-25d and said provision has not yet been defined by a Court having jurisdiction over WVBOE or through regulations.

REQUEST NO. 17:

Admit that cross country is a sport that requires “competitive skill” as that phrase is used in 34 C.F.R. § 106.41(b).

RESPONSE: WVBOE denies as “competitive skill” is not defined in 34 C.F.R. § 106.41(b) and said provision has not yet been defined by a Court having jurisdiction over WVBOE or through regulations.

REQUEST NO. 18:

Admit that cross country is not a “contact sport” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: WVBOE denies as “contact sport” is not defined in H.B. 3293 or *West Virginia Code* § 18-2-25d and said provision has not yet been defined by a Court having jurisdiction over WVBOE or through regulations.

REQUEST NO. 19:

Admit that cross country is not a “contact sport” as that phrase is used in 34 C.F.R. § 106.41(b).

RESPONSE: WVBOE denies as “contact sport” is not fully defined in 34 C.F.R. § 106.41(b) and WVBOE is not aware of any exhaustive definition by a Court having jurisdiction over it or through regulations.

REQUEST NO. 20:

Admit that, but for the injunction issued in this case (Dkt. 67), Plaintiff B.P.J. would not have been permitted to be a member of Bridgeport Middle School’s girls’ cross-country team in 2021 because of H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: WVBOE admits that the plain language of H.B. 3293 (codified at *West Virginia*

Code § 18-2-25d(c)(2)) would not have been permitted Plaintiff B.P.J. to be a member of Bridgeport Middle School's girls' cross-country team after July 8, 2021 and that the injunction issued in this case permitted Plaintiff B.P.J. to be a member of the same.

REQUEST NO. 21:

Admit that, but for the injunction issued in this case (Dkt. 67), Plaintiff B.P.J. would not be permitted to be a member of any girls' athletic team offered at Bridgeport Middle School because of H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: WVBOE admits that the plain language of H.B. 3293 (codified at *West Virginia Code* § 18-2-25d(c)(2)) would not have been permitted Plaintiff B.P.J. to be a member of any girls' athletic team offered at Bridgeport Middle School after July 8, 2021 and that the injunction issued in this case would have permitted Plaintiff B.P.J. to be a member of the same.

REQUEST NO. 22:

Admit that H.B. 3293 prohibits Plaintiff B.P.J. from participating on girls' athletic teams at all public secondary schools located in West Virginia.

RESPONSE: WVBOE admits that the plain language of H.B. 3293 (codified at *West Virginia Code* § 18-2-25d) prohibits Plaintiff B.P.J. from participating on girls' athletic teams at all public secondary schools located in West Virginia.

REQUEST NO. 23:

Admit that the State Board of Education and the State Superintendent must comply with

H.B. 3293 unless enjoined from doing so by a court.

RESPONSE: WVBOE admits as all persons and entities must comply with the law, unless enjoined from doing so by a court.

REQUEST NO. 24:

Admit that H.B. 3293 prohibits the State Board of Education and the State Superintendent from adopting or enforcing a policy that would allow B.P.J. to participate on girls' athletic teams at Bridgeport Middle School.

RESPONSE: WVBOE admits that all persons and entities must comply with the law but denies the remaining request as it misstates the law. H.B. 3293 only requires WVBOE to promulgate rules to "implement" *West Virginia Code* § 18-2-25d, not to enforce it.

REQUEST NO. 25:

Admit that the Harrison County Board of Education and the Harrison County School Superintendent must comply with H.B. 3293 unless enjoined from doing so by a court.

RESPONSE: WVBOE admits that all persons and entities must comply with the law, unless enjoined from doing so by a court.

REQUEST NO. 26:

Admit that H.B. 3293 prohibits the Harrison County Board of Education and the Harrison County Superintendent from adopting or enforcing a policy that would allow B.P.J. to participate on girls' athletic teams at Bridgeport Middle School.

RESPONSE: WVBOE admits as all persons and entities must comply with the law, unless

enjoined from doing so by a court.

REQUEST NO. 27:

Admit that the West Virginia Secondary School Athletic Commission must comply with H.B. 3293 unless enjoined from doing so by a court.

RESPONSE: WVBOE admits as all persons and entities must comply with the law, unless enjoined from doing so by a court.

REQUEST NO. 28:

Admit that H.B. 3293 prohibits the West Virginia Secondary School Athletic Commission from adopting or enforcing a policy that would allow B.P.J. to participate on girls' athletic teams at Bridgeport Middle School.

RESPONSE: WVBOE admits as all persons and entities must comply with the law, unless enjoined from doing so by a court.

REQUEST NO. 29:

Admit that there are no athletic teams designated as "coed or mixed," as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), offered at Bridgeport Middle School.

RESPONSE: WVBOE has made a reasonable inquiry and lacks sufficient knowledge or information to admit or deny the assertions in this Request.

REQUEST NO. 30:

Admit that there are no athletic teams designated as “coed or mixed,” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), that compete interscholastically offered at any public secondary school located in West Virginia.

RESPONSE: WVBOE has made a reasonable inquiry and lacks sufficient knowledge or information to admit or deny the assertions in this Request.

REQUEST NO. 31:

Admit that there are no cross-country teams designated as “coed or mixed,” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), that compete interscholastically offered by any member school of the West Virginia Secondary School Activities Commission.

RESPONSE: WVBOE has made a reasonable inquiry and lacks sufficient knowledge or information to admit or deny the assertions in this Request.

REQUEST NO. 32:

Admit that there are no athletic leagues designated as “coed or mixed,” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), that comprise teams from more than one school supervised by the West Virginia Secondary School Activities Commission.

RESPONSE: WVBOE has made a reasonable inquiry and lacks sufficient knowledge or information to admit or deny the assertions in this Request.

REQUEST NO. 33:

Admit that there are no athletic teams designated as “coed or mixed,” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)),” that compete interscholastically offered by any public secondary school under the supervision of the West Virginia State Board of Education.

RESPONSE: WVBOE has made a reasonable inquiry and lacks sufficient knowledge or information to admit or deny the assertions in this Request.

REQUEST NO. 34:

Admit that H.B. 3293 does not prohibit a cisgender girl student at Bridgeport Middle School from joining a girls’ athletic team offered at Bridgeport Middle School.

RESPONSE: WVBOE admits that the plain language of H.B. 3293 (codified at *West Virginia Code* § 18-2-25d) does not prohibit a cisgender girl student at Bridgeport Middle School from joining a girls’ athletic team offered at Bridgeport Middle School.

REQUEST NO. 35:

Admit that H.B. 3293 does not prohibit a cisgender girl student at any public secondary school in West Virginia from joining a girls’ athletic team offered by her public secondary school.

RESPONSE: WVBOE admits that the plain language of H.B. 3293 (codified at *West Virginia Code* § 18-2-25d) does not prohibit a cisgender girl student at any public secondary school in West Virginia from joining a girls’ athletic team offered by her public secondary school.

REQUEST NO. 36:

Admit that H.B. 3293 prohibits a Bridgeport Middle School transgender girl student from

joining a girls' athletic team offered at Bridgeport Middle School.

RESPONSE: WVBOE admits that the plain language of H.B. 3293 (codified at *West Virginia Code* § 18-2-25d) prohibits a Bridgeport Middle School transgender girl student from joining a girls' athletic team offered at Bridgeport Middle School.

REQUEST NO. 37:

Admit that H.B. 3293 prohibits any transgender girl secondary school student located in West Virginia from joining a girls' athletic team offered by her public secondary school.

RESPONSE: WVBOE admits that the plain language of H.B. 3293 (codified at *West Virginia Code* § 18-2-25d) prohibits any transgender girl secondary school student located in West Virginia from joining a girls' athletic team offered by her public secondary school.

REQUEST NO. 38:

Admit that prior to the enactment of H.B. 3293, cisgender boy students at Bridgeport Middle School were prohibited from joining girls' athletic teams offered at Bridgeport Middle School.

RESPONSE: This Defendant admits to the extent that Section 3.8 of 127 C.S.R. 2 is applicable.

REQUEST NO. 39:

Admit that prior to the enactment of H.B. 3293, a cisgender boy student at any public secondary school in West Virginia was prohibited from joining girls' athletic teams offered at his public secondary school.

RESPONSE: This Defendant admits to the extent that Section 3.8 of 127 C.S.R. 2 is applicable.

REQUEST NO. 40:

Admit that prior to the enactment of H.B. 3293, you are not aware of any transgender student athlete participating on an athletic team offered by Bridgeport Middle School.

RESPONSE: WVBOE admits this Request.

REQUEST NO. 41:

Admit that prior to the enactment of H.B. 3293, you are not aware of any transgender student athlete participating on an athletic team offered by a public secondary school in West Virginia.

RESPONSE: WVBOE admits this Request.

REQUEST NO. 42:

Admit that other than Plaintiff B.P.J., you are not aware of a transgender student athlete participating on an athletic team offered by Bridgeport Middle School.

RESPONSE: WVBOE admits this Request.

REQUEST NO. 43:

Admit that other than Plaintiff B.P.J., you are not aware of a transgender student athlete participating on an athletic team offered by a public secondary school in West Virginia.

RESPONSE: WVBOE admits this Request.

REQUEST NO. 44:

Admit that students derive social benefits from participation on athletic teams offered by public secondary schools in West Virginia.

RESPONSE: Objection. The phrase “derive social benefits” is vague, undefined, and subject to multiple interpretations. Without waiving this objection, WVBOE admits that there are certain benefits to students from participation on athletic teams offered by public secondary schools in West Virginia.

REQUEST NO. 45:

Admit that students derive psychological benefits from participation on athletic teams offered by public secondary schools in West Virginia.

RESPONSE: Objection. The phrase “derive psychological benefits” is vague, undefined, and subject to multiple interpretations. Without waiving this objection, WVBOE admits that there are certain benefits to students from participation on athletic teams offered by public secondary schools in West Virginia.

REQUEST NO. 46:

Admit that interscholastic athletic competition benefits middle school students.

RESPONSE: Objection. The phrase “benefits” is vague, undefined, and subject to multiple interpretations. Without waiving this objection, WVBOE admits that there are certain benefits to middle school students who participate in interscholastic sports.

REQUEST NO. 47:

Admit that middle school students who participate in interscholastic athletics receive benefits regardless whether they win or lose.

RESPONSE: Objection. The phrase “benefits” is vague, undefined, and subject to multiple

interpretations. Without waiving this objection, WVBOE admits that there are certain benefits to middle school students who participate in interscholastic sports.

REQUEST NO. 48:

Admit that Plaintiff B.P.J.'s gender is identified as "male" in the West Virginia Education Information System ("WVEIS").

RESPONSE: WVBOE admits this Request.

REQUEST NO. 49:

Admit that you have the ability to change Plaintiff B.P.J.'s gender in WVEIS to "female."

RESPONSE: WVBOE denies this Request as it does not have this ability.

REQUEST NO. 50:

Admit that you are required to supervise public secondary schools in West Virginia.

RESPONSE: WVBOE admits that it has general supervision and oversight over the free schools of the state of West Virginia, not including private schools.

REQUEST NO. 51:

Admit that you have control over the county boards of education in West Virginia.

RESPONSE: WVBOE admits that it can only exercise such "control" as it possesses by West Virginia Constitution or statute. WVBOE denies this request to the extent that W.Va. Code §18-2-25 speaks for itself.

REQUEST NO. 52:

Admit that you have control over Defendant Harrison County Board of Education.

RESPONSE: OBJECTION. WVBOE admits that it can only exercise such “control” as it possesses by West Virginia Constitution or statute. WVBOE denies this request to the extent that W.Va. Code §18-2-25 speaks for itself.

REQUEST NO. 53:

Admit that you have control over Defendant West Virginia Secondary School Activities Commission.

RESPONSE: OBJECTION. WVBOE admits that it can only exercise such “control” as it possesses by West Virginia Constitution or statute. WVBOE denies this request to the extent that W.Va. Code §18-2-25 speaks for itself.

REQUEST NO. 54:

Admit that you have delegated control over public secondary school athletics to the county boards of education.

RESPONSE: WVBOE admits that it can only exercise such “control” as it possesses by West Virginia Constitution or statute. WVBOE denies this request to the extent that W.Va. Code §18-2-25 speaks for itself.

REQUEST NO. 55:

Admit that you have delegated control over public secondary school athletics to Defendant West Virginia Secondary School Activities Commission.

RESPONSE: WVBOE admits that it can only exercise such “control” as it possesses by West Virginia Constitution or statute. WVBOE denies this request to the extent that W.Va. Code §18-2-25 speaks for itself.

REQUEST NO. 56:

Admit that you have delegated control over Bridgeport Middle School’s athletics to the Harrison County Board of Education.

RESPONSE: WVBOE denies this request to the extent that W.Va. Code §18-2-25 speaks for itself.

REQUEST NO. 57:

Admit that you have delegated control over Bridgeport Middle School’s athletics to Defendant West Virginia Secondary School Activities Commission.

RESPONSE: WVBOE denies this request to the extent that W.Va. Code §18-2-25 speaks for itself.

REQUEST NO. 58:

Admit that you must approve all rules issued by the West Virginia Secondary School Activities Commission.

RESPONSE: WVBOE admits this Request.

REQUEST NO. 59:

Admit that you receive federal financial assistance.

RESPONSE: WVBOE admits this Request.

REQUEST NO. 60:

Admit that you are required to promulgate rules implementing H.B. 3293 unless enjoined from doing so by a court.

RESPONSE: WVBOE admits this Request as it must comply with the law.

REQUEST NO. 61:

Admit that any rules you promulgate pursuant to H.B. 3293 cannot conflict with the plain language of H.B. 3293.

RESPONSE: WVBOE admits this Request as it must comply with the law.

REQUEST NO. 62:

Admit that under any rules you promulgate pursuant to H.B. 3293, students defined as “male” under H.B. 3293 would not be allowed to participate on girls’ athletic teams offered by public secondary schools in West Virginia.

RESPONSE: WVBOE admits this Request as it must comply with the law.

REQUEST NO. 63:

Admit that under and rules you promulgate pursuant to H.B. 3293 Plaintiff B.P.J. would not be allowed to participate on girls’ athletic teams offered by public secondary schools in West Virginia.

RESPONSE: WVBOE admits this Request as all persons and entities must comply with the

law.

REQUEST NO. 64:

Admit that the West Virginia Secondary School Activities Commission must comply with any rule you promulgate pursuant to H.B. 3293 unless enjoined from doing so by a court.

RESPONSE: WVBOE admits this Request as all persons and entities must comply with the law, unless enjoined from doing so by a court.

REQUEST NO. 65:

Admit that the Harrison County Board of Education and Harrison County School Superintendent must comply with any rule you promulgate pursuant to H.B. 3293 unless enjoined from doing so by a court.

RESPONSE: WVBOE admits this Request as all persons and entities must comply with the law, unless enjoined from doing so by a court.

REQUEST NO. 66:

Admit that you selected Heather Hutchens to be the person responsible for promulgating rules implementing H.B. 3293.

RESPONSE: This Defendant denies this request as stated; however, this Defendant admits that Heather Hutchens and/or other counsel on behalf of the West Virginia Department of Education are generally tasked with drafting rules.

REQUEST NO. 67:

Admit that you must comply with Title IX of the Education Amendments of 1972, 20 U.S.C. § 1681 *et seq.*

RESPONSE: WVBOE admits this Request as it must comply with the law.

REQUEST NO. 68:

Admit that you are required to enforce H.B. 3293 assuming the Court has not enjoined you from doing so.

RESPONSE: WVBOE denies this Request as *West Virginia Code* § 18-2-25d only requires it to promulgate rules, including emergency rules, pursuant to *West Virginia Code* § 29A-3B-1 *et seq.*, to implement the provisions of this section.

**WEST VIRGINIA STATE BOARD
OF EDUCATION,**

By Counsel,

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**IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION**

B.P.J., by her next friend and mother, HEATHER JACKSON,

Plaintiff,

v.

**Civil Action No. 2:21-cv-00316
Honorable Joseph R. Goodwin**

**WEST VIRGINIA STATE BOARD OF
EDUCATION, HARRISON COUNTY BOARD OF
EDUCATION, WEST VIRGINIA SECONDARY
SCHOOL ACTIVITIES COMMISSION, W.
CLAYTON BURCH in his official capacity as State
Superintendent, DORA STUTLER, in her official
capacity as Harrison County Superintendent, and
THE STATE OF WEST VIRGINIA,**

Defendants,

and

LAINEY ARMISTEAD,

Defendant-Intervenor.

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that a true and correct copy of foregoing “**Defendant West Virginia State Board of Education’s Responses to Plaintiff’s Second Set of Requests for Admission**” was served upon the following parties through the Court’s Electronic Case Filing (ECF) system and via electronic mail on this day, Thursday, March 10, 2022:

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**IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION**

B.P.J., by her next friend and mother, HEATHER JACKSON,

Plaintiff,

v.

**Civil Action No. 2:21-cv-00316
Honorable Joseph R. Goodwin**

WEST VIRGINIA STATE BOARD OF EDUCATION, HARRISON COUNTY BOARD OF EDUCATION, WEST VIRGINIA SECONDARY SCHOOL ACTIVITIES COMMISSION, W. CLAYTON BURCH in his official capacity as State Superintendent, DORA STUTLER, in her official capacity as Harrison County Superintendent, and THE STATE OF WEST VIRGINIA,

Defendants,

and

LAINIEY ARMISTEAD,

Defendant-Intervenor.

**DEFENDANT STATE SUPERINTENDENT W. CLAYTON BURCH'S RESPONSES
TO PLAINTIFF'S SECOND SET OF REQUESTS FOR ADMISSION**

NOW COMES Defendant Superintendent W. Clayton Burch (hereinafter "Defendant"), by and through his counsel, Kelly C. Morgan, Kristen V. Hammond, Michael W. Taylor, and the law firm of Bailey & Wyant, P.L.L.C., and, pursuant to Rule 33 of the *Federal Rules of Civil Procedure*, hereby responds and objects to "*Plaintiff's Second Set of Requests for Admissions to Defendant W. Clayton Burch*" as follows:

GENERAL OBJECTIONS AND PRELIMINARY STATEMENT

A. This Defendant objects to the definitions as stated in Plaintiff's Second Set of

Requests for Admission, including specifically the following definitions:

“STATE BOARD means the West Virginia State Board of Education, as well as its officers, directors, employees, partners, corporate parent, subsidiaries, affiliates, attorneys, accountants, consultants, representatives, and agents.”

“STATE SUPERINTENDENT means W. Clayton Burch in his official capacity as Superintendent of the STATE BOARD, as includes each of the officers, directors, employees, partners, corporate parent, subsidiaries, affiliates, attorneys, accountants, consultants, representatives, and agents that report to him in his official capacity. It also means any PERSON who assumes any of Mr. Burch’s official positions or responsibilities in part, whether temporarily or permanently.”

These definitions are overly broad and outside the permissible scope of discovery under the *Federal Rules of Civil Procedure* as these definitions improperly broaden the identity of parties in this case.

These responses are made by this Defendant only.

B. These responses are based upon information and documentation presently available to this Defendant and which he believes to be complete and accurate. Said responses are made without prejudice to this Defendant’s right to rely upon subsequently discovered facts or evidence.

C. No incidental or implied admission of fact by this Defendant is made as to the responses provided herein. The fact that this Defendant has responded to the discovery requests of Plaintiff, may not properly be taken as an admission that this Defendant accepts or admits the existence of any facts set forth or assumed by such response or that such response constitutes admissible evidence.

D. Responses to Plaintiff’s discovery requests may be supplemented by this Defendant upon further investigation and acquisition of information or documentation which he does not possess or have knowledge of at this time. However, any such further supplementation shall be made only in accordance with *Federal Rules of Civil Procedure*.

E. This Defendant objects to each and every request insofar as it seeks information which is protected by the attorney-client privilege, or which falls within the scope of the work-

product doctrine. This Defendant also objects to Plaintiff's discovery requests to the extent that the information and/or documentation sought has or could have been obtained from other sources that were more convenient, less burdensome, or less expensive.

F. This Defendant objects to any definitions and instructions set forth in Plaintiff's discovery requests to the extent that such definitions and instructions are inconsistent and confusing, and to the extent that they attempt to impose requirements which are more burdensome or in addition to those set forth in the *Federal Rules of Civil Procedure*.

G. This Defendant objects to Plaintiff's discovery requests to the extent that they seek to discover confidential information or documentation. This Defendant will produce such information and/or documentation, if essential to the litigation, only upon the entry of an appropriate Protective Order and upon permission of any third parties with whom Superintendent Burch may have obligations concerning confidential information.

H. This Defendant objects to Plaintiff's discovery requests based on insufficient information, knowledge, or belief to admit or deny any assertions set forth in such requests.

I. This Defendant states that the word usage and sentence structure may be that of the attorney assisting in the preparation of the following responses and, thus, does not necessarily purport to be the precise language of the executing party.

J. This Defendant is answering and responding to these discovery requests in conformity with the requirements set forth in *Federal Rules of Civil Procedure* and not necessarily in compliance with the instructions and definitions set forth in "*Plaintiff's Second Set of Requests for Admission to State Superintendent W. Clayton Burch.*"

K. This Defendant objects to the discovery requests to the extent that the information and/or documents sought are not in his possession.

REQUESTS FOR ADMISSION

REQUEST NO. 5:

Admit that Plaintiff B.P.J. has been diagnosed with gender dysphoria.

RESPONSE: This Defendant has made a reasonable inquiry and admits that Plaintiff B.P.J. has produced documentation that attests Plaintiff B.P.J. has been diagnosed with gender dysphoria and that Plaintiff B.P.J.'s witnesses have testified to the same. However, this Defendant lacks sufficient independent knowledge to admit or deny the assertions set forth in this Request.

REQUEST NO. 6:

Admit that in 2021 Plaintiff B.P.J. was a member of Bridgeport Middle School's girls' cross-country team.

RESPONSE: This Defendant has made a reasonable inquiry and admits that Plaintiff B.P.J. has produced documentation that attests Plaintiff B.P.J. was a member of Bridgeport Middle School's girls' cross-country team in 2021 and that Plaintiff B.P.J.'s witnesses and Defendant Dora Stutler have testified to the same. However, this Defendant lacks sufficient independent knowledge to admit or deny the assertions in this Request.

REQUEST NO. 7:

Admit that Plaintiff B.P.J. placed 51 out of 66 competitors in the girls' middle school cross country Mountain Hollar MS Invitational meet in 2021.

RESPONSE: RESPONSE: This Defendant has made a reasonable inquiry and lacks sufficient knowledge or information to admit or deny the assertions in this Request.

REQUEST NO. 8:

Admit that Plaintiff B.P.J. placed 123 out of 150 competitors in the girls' middle school cross country Doddridge Invitational meet in 2021.

RESPONSE: This Defendant has made a reasonable inquiry and lacks sufficient knowledge or information to admit or deny the assertions in this Request.

REQUEST NO. 9:

Admit that you have not received any complaints associated with Plaintiff B.P.J.'s membership on Bridgeport Middle School's girls' cross country team.

RESPONSE: This Defendant admits this Request.

REQUEST NO. 10:

Admit that no middle school girl was harmed as a result of B.P.J.'s participation on Bridgeport Middle School's girls' cross country team in 2021.

RESPONSE: This Defendant has made a reasonable inquiry and lacks sufficient knowledge or information to admit or deny the assertions in this Request.

REQUEST NO. 11:

Admit that no middle school girl was injured as a result of Plaintiff B.P.J.'s participation on Bridgeport Middle School's girls' cross country team in 2021.

RESPONSE: This Defendant has made a reasonable inquiry and lacks sufficient knowledge or information to admit or deny the assertions in this Request.

REQUEST NO. 12:

Admit that no Bridgeport Middle School girl student was prohibited from joining Bridgeport Middle School's girls' cross-country team in 2021.

RESPONSE: This Defendant has made a reasonable inquiry and admits that Plaintiff B.P.J. and Defendant Dora Stutler have testified that all Bridgeport Middle School girl students who tried out for Bridgeport Middle School's girls' cross-country team in 2021 made the team. However, this Defendant lacks sufficient independent knowledge to admit or deny the assertions in this Request.

REQUEST NO. 13:

Admit that Bridgeport Middle School's girls' cross-country team did not turn anyone away from participating due to lack of space on the roster in 2021.

RESPONSE: This Defendant has made a reasonable inquiry and admits that Plaintiff B.P.J. and Defendant Dora Stutler have testified that all Bridgeport Middle School girl students who tried out for Bridgeport Middle School's girls' cross-country team in 2021 made the team. However, this Defendant lacks sufficient independent knowledge to admit or deny the assertions in this Request.

REQUEST NO. 14:

Admit that Plaintiff B.P.J. does not have an unfair athletic advantage over other girls participating on the Bridgeport Middle School girls' cross-country team.

RESPONSE: Objection. The phrase "unfair athletic advantage" is vague, undefined, and subject to multiple interpretation. Without waiving this objection, this Defendant has made a

reasonable inquiry and lacks sufficient knowledge or information to admit or deny the assertions in this Request.

REQUEST NO. 15:

Admit that Plaintiff B.P.J. does not have an unfair athletic advantage over girls competing against the Bridgeport Middle School girls' cross-country team.

RESPONSE: Objection. The phrase “unfair athletic advantage” is vague, undefined, and subject to multiple interpretation. Without waiving this objection, this Defendant has made a reasonable inquiry and lacks sufficient knowledge or information to admit or deny the assertions in this Request.

REQUEST NO. 16:

Admit that cross country is a sport that requires “competitive skill” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: This Defendant denies as “competitive skill” is not defined in H.B. 3293 or *West Virginia Code* § 18-2-25d and said provision has not yet been defined by a Court having jurisdiction over this Defendant or through regulations.

REQUEST NO. 17:

Admit that cross country is a sport that requires “competitive skill” as that phrase is used in 34 C.F.R. § 106.41(b).

RESPONSE: This Defendant denies as “competitive skill” is not defined in 34 C.F.R. § 106.41(b) and said provision has not yet been defined by a Court having jurisdiction over this

Defendant or through regulations.

REQUEST NO. 18:

Admit that cross country is not a “contact sport” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: This Defendant denies as “contact sport” is not defined in H.B. 3293 or *West Virginia Code* § 18-2-25d and said provision has not yet been defined by a Court having jurisdiction over this Defendant or through regulations.

REQUEST NO. 19:

Admit that cross country is not a “contact sport” as that phrase is used in 34 C.F.R. § 106.41(b).

RESPONSE: This Defendant denies as “contact sport” is not fully defined in 34 C.F.R. § 106.41(b) and this Defendant is not aware of any exhaustive definition by a Court having jurisdiction over this Defendant or through regulations.

REQUEST NO. 20:

Admit that, but for the injunction issued in this case (Dkt. 67), Plaintiff B.P.J. would not have been permitted to be a member of Bridgeport Middle School’s girls’ cross-country team in 2021 because of H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: This Defendant admits that the plain language of H.B. 3293 (codified at *West Virginia Code* § 18-2-25d(c)(2)) would not have been permitted Plaintiff B.P.J. to be a member of Bridgeport Middle School’s girls’ cross-country team after July 8, 2021 and that the

injunction issued in this case permitted Plaintiff B.P.J. to be a member of the same.

REQUEST NO. 21:

Admit that, but for the injunction issued in this case (Dkt. 67), Plaintiff B.P.J. would not be permitted to be a member of any girls' athletic team offered at Bridgeport Middle School because of H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: This Defendant admits that the plain language of H.B. 3293 (codified at *West Virginia Code* § 18-2-25d(c)(2)) would not have been permitted Plaintiff B.P.J. to be a member of any girls' athletic team offered at Bridgeport Middle School after July 8, 2021 and that the injunction issued in this case would have permitted Plaintiff B.P.J. to be a member of the same.

REQUEST NO. 22:

Admit that H.B. 3293 prohibits Plaintiff B.P.J. from participating on girls' athletic teams at all public secondary schools located in West Virginia.

RESPONSE: This Defendant admits that the plain language of H.B. 3293 (codified at *West Virginia Code* § 18-2-25d) prohibits Plaintiff B.P.J. from participating on girls' athletic teams at all public secondary schools located in West Virginia.

REQUEST NO. 23:

Admit that the State Board of Education and the State Superintendent must comply with H.B. 3293 unless enjoined from doing so by a court.

RESPONSE: This Defendant admits as all persons and entities must comply with the law,

unless enjoined from doing so by a court.

REQUEST NO. 24:

Admit that H.B. 3293 prohibits the State Board of Education and the State Superintendent from adopting or enforcing a policy that would allow B.P.J. to participate on girls' athletic teams at Bridgeport Middle School.

RESPONSE: This Defendant admits that all persons and entities must comply with the law but denies the remaining request as it misstates the law. H.B. 3293 only requires WVBOE to promulgate rules to “implement” *West Virginia Code* § 18-2-25d, not to enforce it.

REQUEST NO. 25:

Admit that the Harrison County Board of Education and the Harrison County School Superintendent must comply with H.B. 3293 unless enjoined from doing so by a court.

RESPONSE: This Defendant admits that all persons and entities must comply with the law, unless enjoined from doing so by a court.

REQUEST NO. 26:

Admit that H.B. 3293 prohibits the Harrison County Board of Education and the Harrison County Superintendent from adopting or enforcing a policy that would allow B.P.J. to participate on girls' athletic teams at Bridgeport Middle School.

RESPONSE: This Defendant admits as all persons and entities must comply with the law, unless enjoined from doing so by a court.

REQUEST NO. 27:

Admit that the West Virginia Secondary School Athletic Commission must comply with H.B. 3293 unless enjoined from doing so by a court.

RESPONSE: This Defendant admits as all persons and entities must comply with the law, unless enjoined from doing so by a court.

REQUEST NO. 28:

Admit that H.B. 3293 prohibits the West Virginia Secondary School Athletic Commission from adopting or enforcing a policy that would allow B.P.J. to participate on girls' athletic teams at Bridgeport Middle School.

RESPONSE: This Defendant admits as all persons and entities must comply with the law, unless enjoined from doing so by a court.

REQUEST NO. 29:

Admit that there are no athletic teams designated as "coed or mixed," as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), offered at Bridgeport Middle School.

RESPONSE: This Defendant has made a reasonable inquiry and lacks sufficient knowledge or information to admit or deny the assertions in this Request.

REQUEST NO. 30:

Admit that there are no athletic teams designated as "coed or mixed," as that phrase is used

in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), that compete interscholastically offered at any public secondary school located in West Virginia.

RESPONSE: This Defendant has made a reasonable inquiry and lacks sufficient knowledge or information to admit or deny the assertions in this Request.

REQUEST NO. 31:

Admit that there are no cross-country teams designated as “coed or mixed,” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), that compete interscholastically offered by any member school of the West Virginia Secondary School Activities Commission.

RESPONSE: This Defendant has made a reasonable inquiry and lacks sufficient knowledge or information to admit or deny the assertions in this Request.

REQUEST NO. 32:

Admit that there are no athletic leagues designated as “coed or mixed,” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), that comprise teams from more than one school supervised by the West Virginia Secondary School Activities Commission.

RESPONSE: This Defendant has made a reasonable inquiry and lacks sufficient knowledge or information to admit or deny the assertions in this Request.

REQUEST NO. 33:

Admit that there are no athletic teams designated as “coed or mixed,” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), that compete

interscholastically offered by any public secondary school under the supervision of the West Virginia State Board of Education.

RESPONSE: This Defendant has made a reasonable inquiry and lacks sufficient knowledge or information to admit or deny the assertions in this Request.

REQUEST NO. 34:

Admit that H.B. 3293 does not prohibit a cisgender girl student at Bridgeport Middle School from joining a girls' athletic team offered at Bridgeport Middle School.

RESPONSE: This Defendant admits that the plain language of H.B. 3293 (codified at *West Virginia Code* § 18-2-25d) does not prohibit a cisgender girl student at Bridgeport Middle School from joining a girls' athletic team offered at Bridgeport Middle School.

REQUEST NO. 35:

Admit that H.B. 3293 does not prohibit a cisgender girl student at any public secondary school in West Virginia from joining a girls' athletic team offered by her public secondary school.

RESPONSE: This Defendant admits that the plain language of H.B. 3293 (codified at *West Virginia Code* § 18-2-25d) does not prohibit a cisgender girl student at any public secondary school in West Virginia from joining a girls' athletic team offered by her public secondary school.

REQUEST NO. 36:

Admit that H.B. 3293 prohibits a Bridgeport Middle School transgender girl student from joining a girls' athletic team offered at Bridgeport Middle School.

RESPONSE: This Defendant admits that the plain language of H.B. 3293 (codified at *West Virginia Code* § 18-2-25d) prohibits a Bridgeport Middle School transgender girl student from joining a girls' athletic team offered at Bridgeport Middle School.

REQUEST NO. 37:

Admit that H.B. 3293 prohibits any transgender girl secondary school student located in West Virginia from joining a girls' athletic team offered by her public secondary school.

RESPONSE: This Defendant admits that the plain language of H.B. 3293 (codified at *West Virginia Code* § 18-2-25d) prohibits any transgender girl secondary school student located in West Virginia from joining a girls' athletic team offered by her public secondary school.

REQUEST NO. 38:

Admit that prior to the enactment of H.B. 3293, cisgender boy students at Bridgeport Middle School were prohibited from joining girls' athletic teams offered at Bridgeport Middle School.

RESPONSE: This Defendant admits to the extent that Section 3.8 of 127 C.S.R. 2 is applicable.

REQUEST NO. 39:

Admit that prior to the enactment of H.B. 3293, a cisgender boy student at any public secondary school in West Virginia was prohibited from joining girls' athletic teams offered at his public secondary school.

RESPONSE: This Defendant admits to the extent that Section 3.8 of 127 C.S.R. 2 is applicable.

REQUEST NO. 40:

Admit that prior to the enactment of H.B. 3293, you are not aware of any transgender student athlete participating on an athletic team offered by Bridgeport Middle School.

RESPONSE: This Defendant admits this Request.

REQUEST NO. 41:

Admit that prior to the enactment of H.B. 3293, you are not aware of any transgender student athlete participating on an athletic team offered by a public secondary school in West Virginia.

RESPONSE: This Defendant admits this Request.

REQUEST NO. 42:

Admit that other than Plaintiff B.P.J., you are not aware of a transgender student athlete participating on an athletic team offered by Bridgeport Middle School.

RESPONSE: This Defendant admits this Request.

REQUEST NO. 43:

Admit that other than Plaintiff B.P.J., you are not aware of a transgender student athlete participating on an athletic team offered by a public secondary school in West Virginia.

RESPONSE: This Defendant admits this Request.

REQUEST NO. 44:

Admit that students derive social benefits from participation on athletic teams offered by

public secondary schools in West Virginia.

RESPONSE: Objection. The phrase “derive social benefits” is vague, undefined, and subject to multiple interpretations. Without waiving this objection, this Defendant admits that there are certain benefits to students from participation on athletic teams offered by public secondary schools in West Virginia.

REQUEST NO. 45:

Admit that students derive psychological benefits from participation on athletic teams offered by public secondary schools in West Virginia.

RESPONSE: Objection. The phrase “derive psychological benefits” is vague, undefined, and subject to multiple interpretations. Without waiving this objection, this Defendant admits that there are certain benefits to students from participation on athletic teams offered by public secondary schools in West Virginia.

REQUEST NO. 46:

Admit that interscholastic athletic competition benefits middle school students.

RESPONSE: Objection. The phrase “benefits” is vague, undefined, and subject to multiple interpretations. Without waiving this objection, this Defendant admits that there are certain benefits to middle school students who participate in interscholastic sports.

REQUEST NO. 47:

Admit that middle school students who participate in interscholastic athletics receive benefits regardless whether they win or lose.

RESPONSE: Objection. The phrase “benefits” is vague, undefined, and subject to multiple interpretations. Without waiving this objection, this Defendant admits that there are certain benefits to middle school students who participate in interscholastic sports.

REQUEST NO. 48:

Admit that when you perform your official duties as State Superintendent you are acting on behalf of the State Board of Education.

RESPONSE: This Defendant admits this Request.

REQUEST NO. 49:

Admit that when you perform your official duties as State Superintendent you are acting on behalf of the State of West Virginia.

RESPONSE: This Defendant admits this Request.

REQUEST NO. 50:

Admit that you are a State Actor for purposes of 42 U.S.C. § 1983 when fulfilling duties in your official capacity as the State Superintendent.

RESPONSE: This Defendant admits this Request as he must comply with the law.

REQUEST NO. 51:

Admit that as a member of the State Board of Education, you are required to promulgate rules implementing H.B. 3293 unless enjoined from doing so by a court.

RESPONSE: This Defendant admits this Request as all persons and entities must comply with

the law, unless enjoined from doing so by a court.

REQUEST NO. 52:

Admit that any rules you promulgate pursuant to H.B. 3293 cannot conflict with the plain language of H.B. 3293.

RESPONSE: This Defendant admits this Request all persons and entities must comply with the law, unless enjoined from doing so by a court.

REQUEST NO. 53:

Admit that under any rules you promulgate pursuant to H.B. 3293, students defined as “male” under H.B. 3293 would not be allowed to participate on girls’ athletic teams offered by public secondary schools in West Virginia.

RESPONSE: This Defendant admits this Request as all persons and entities must comply with the law.

REQUEST NO. 54:

Admit that under any rules you promulgate pursuant to H.B. 3293 Plaintiff B.P.J. would not be allowed to participate on girls’ athletic teams offered by public secondary schools in West Virginia.

RESPONSE: This Defendant admits this Request as all persons and entities must comply with the law.

REQUEST NO. 55:

Admit that the West Virginia Secondary School Activities Commission must comply with any rule you promulgate pursuant to H.B. 3293 unless enjoined from doing so by a court.

RESPONSE: This Defendant admits this Request as all persons and entities must comply with the law.

REQUEST NO. 56:

Admit that the Harrison County Board of Education and Harrison County School Superintendent must comply with any rule you promulgate pursuant to H.B. 3293 unless enjoined from doing so by a court.

RESPONSE: This Defendant admits this Request as all persons and entities must comply with the law, unless enjoined from doing so by a court.

REQUEST NO. 57:

Admit that you selected Heather Hutchens to be the person responsible for promulgating rules implementing H.B. 3293.

RESPONSE: This Defendant denies this request as stated; however, this Defendant admits that Heather Hutchens and/or other counsel on behalf of the West Virginia Department of Education are generally tasked with drafting rules.

REQUEST NO. 58:

Admit that you must comply with Title IX of the Education Amendments of 1972, 20 U.S.C. § 1681 *et seq.*

RESPONSE: This Defendant admits this Request as he must comply with the law, unless

enjoined from doing so by a court.

REQUEST NO. 59:

Admit that you must comply with the Equal Protection Clause of the Fourteenth Amendment of the U.S. Constitution.

RESPONSE: This Defendant admits this Request as he must comply with the law, unless enjoined from doing so by a court.

REQUEST NO. 60:

Admit that you are required to enforce H.B. 3293 assuming the Court has not enjoined you from doing so.

RESPONSE: This Defendant denies this Request as *West Virginia Code* § 18-2-25d only requires WVBOE to promulgate rules, including emergency rules, pursuant to *West Virginia Code* § 29A-3B-1 et. seq., to implement the provisions of this section.

STATE SUPERINTENDENT
W. CLAYTON BURCH,

By Counsel,

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IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

B.P.J., by her next friend and mother, HEATHER
JACKSON,

Plaintiff,

v.

Civil Action No. 2:21-cv-00316
Honorable Joseph R. Goodwin

WEST VIRGINIA STATE BOARD OF
EDUCATION, HARRISON COUNTY BOARD OF
EDUCATION, WEST VIRGINIA SECONDARY
SCHOOL ACTIVITIES COMMISSION, W.
CLAYTON BURCH in his official capacity as State
Superintendent, DORA STUTLER, in her official
capacity as Harrison County Superintendent, and
THE STATE OF WEST VIRGINIA,

Defendants,

and

LAINEY ARMISTEAD,

Defendant-Intervenor.

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that a true and correct copy of foregoing “**Defendant State Superintendent W. Clayton Burch’s Responses to Plaintiff’s Second Set of Requests for Admission**” was served upon the following parties through the Court’s Electronic Case Filing (ECF) system and via electronic mail on this day, Thursday, March 10, 2022:

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IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

B.P.J., by her next friend and mother,
HEATHER JACKSON,

Plaintiff,

v.

Civil Action No. 2:21-cv-00316
Hon. Joseph R. Goodwin, District Judge

WEST VIRGINIA STATE BOARD OF
EDUCATION, HARRISON COUNTY BOARD
OF EDUCATION, WEST VIRGINIA
SECONDARY SCHOOL ACTIVITIES
COMMISSION, W. CLAYTON BURCH in his
official capacity as State Superintendent,
DORA STUTLER in her official capacity as
Harrison County Superintendent, PATRICK
MORRISEY in his official capacity as Attorney
General, and THE STATE OF WEST VIRGINIA,

Defendants,

and

LAINEY ARMISTEAD,

Defendant-Intervenor.

**DEFENDANT HARRISON COUNTY BOARD OF EDUCATION’S RESPONSES AND
OBJECTIONS TO PLAINTIFF’S SECOND SET OF REQUESTS FOR ADMISSION**

Pursuant to Rule 36 of the Federal Rules of Civil Procedure, Defendant Harrison County Board of Education (“County Board”) hereby responds and objects to “Plaintiff’s Second Set of Requests for Admission to Defendant Harrison County Board of Education” as follows:

GENERAL OBJECTION: The County Board objects to the definitions of “County Board” and “County Superintendent” as set forth in Plaintiff’s requests for admission. Those definitions are overly broad and outside the permissible scope of discovery under the

Federal Rules of Civil Procedure as the definitions improperly broaden the identity of parties in this case. For instance, the definitions of the “County Board” and the “County Superintendent” also include their “officers, directors, employees, partners, corporate parent, subsidiaries, affiliates, attorneys, accountants, consultants, representatives and agents.” The County Board objects to providing responses pursuant to the broadened definitions of “County Board” and “County Superintendent.” The County Board further objects to the Definitions and Instructions set forth in Plaintiff’s requests to the extent they are inconsistent with the Federal Rules of Civil Procedure or applicable law.

REQUEST NO. 5: Admit that Plaintiff B.P.J. has been diagnosed with gender dysphoria.

RESPONSE: The County Board admits that medical records produced in this case state that Plaintiff B.P.J. has been diagnosed with gender dysphoria.

REQUEST NO. 6: Admit that in 2021 Plaintiff B.P.J. was a member of Bridgeport Middle School’s girls’ cross-country team.

RESPONSE: Admitted.

REQUEST NO. 7: Admit that Plaintiff B.P.J. placed 51 out of 66 competitors in the girls’ middle school cross country Mountain Hollar MS Invitational meet in 2021.

RESPONSE: Upon information and belief, and based on information provided on RunWV.com regarding the results of the race, the County Board admits this request.

REQUEST NO. 8: Admit that Plaintiff B.P.J. placed 123 out of 150 competitors in the girls' middle school cross country Doddridge Invitational meet in 2021.

RESPONSE: Upon information and belief, and based on information provided on RunWV.com regarding the results of the race, the County Board admits this request.

REQUEST NO. 9: Admit that you have not received any complaints associated with Plaintiff B.P.J.'s membership on Bridgeport Middle School's girls' cross country team.

RESPONSE: Admitted.

REQUEST NO. 10: Admit that no middle school girl was harmed as a result of B.P.J.'s participation on Bridgeport Middle School's girls' cross country team in 2021.

RESPONSE: **OBJECTION.** The County Board objects to this request because it is vague. The County Board does not know what Plaintiff means by the term "harmed." Subject to and without waiving the objection, the County Board admits that no student was cut from the Bridgeport Middle School's girls' cross country team in 2021. The County Board otherwise denies this request because it is unclear what Plaintiff is asking.

REQUEST NO. 11: Admit that no middle school girl was injured as a result of Plaintiff B.P.J.'s participation on Bridgeport Middle School's girls' cross country team in 2021.

RESPONSE: **OBJECTION.** The County Board objects to this request because it is vague. The County Board does not know what Plaintiff means by the term "injured." Subject to and without waiving the objection, the County Board admits that no student was cut from the Bridgeport Middle School's girls' cross country team in 2021. The County Board otherwise denies this request because it is unclear what Plaintiff is asking.

REQUEST NO. 12: Admit that no Bridgeport Middle School girl student was prohibited from joining Bridgeport Middle School's girls' cross-country team in 2021.

RESPONSE: Admitted.

REQUEST NO. 13: Admit that Bridgeport Middle School's girls' cross-country team did not turn anyone away from participating due to lack of space on the roster in 2021.

RESPONSE: Admitted.

REQUEST NO. 14: Admit that Plaintiff B.P.J. does not have an unfair athletic advantage over other girls participating on the Bridgeport Middle School girls' cross-country team.

RESPONSE: Even with a reasonable inquiry, the County Board cannot admit or deny this request because the information it knows or can readily obtain is insufficient to enable the County Board to admit or deny the request.

REQUEST NO. 15: Admit that Plaintiff B.P.J. does not have an unfair athletic advantage over girls competing against the Bridgeport Middle School girls' cross-country team.

RESPONSE: Even with a reasonable inquiry, the County Board cannot admit or deny this request because the information it knows or can readily obtain is insufficient to enable the County Board to admit or deny the request.

REQUEST NO. 16: Admit that cross country is a sport that requires "competitive skill" as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board cannot admit or deny this request because "competitive skill" is not defined in H.B. 3293.

REQUEST NO. 17: Admit that cross country is a sport that requires “competitive skill” as that phrase is used in 34 C.F.R. §106.41(b).

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board cannot admit or deny this request because “competitive skill” is not defined in 34 C.F.R. §106.41(b).

REQUEST NO. 18: Admit that cross country is not a “contact sport” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board cannot admit or deny this request because “contact sport” is not defined in H.B. 3293.

REQUEST NO. 19: Admit that cross country is not a “contact sport” as that phrase is used in 34 C.F.R. §106.41(b).

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board admits that “cross country” is not specifically identified as a “contact sport” in 34 C.F.R. §106.41(b).

REQUEST NO. 20: Admit that, but for the injunction issued in this case (Dkt. 67), Plaintiff B.P.J. would not have been permitted to be a member of Bridgeport Middle

School's girls' cross-country team in 2021 because of H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board states as follows: Because, as it is currently drafted, H.B. Bill 3293 (codified at West Virginia Code § 18- 2-25d) applies to public secondary schools and states that “[a]thletic teams or sports designated for females, women, or girls shall not be open to students of the male sex where selection for such teams is based upon competitive skill or the activity involved is a contact sport[,]” because of the definitions set forth in H.B. 3293, and absent the injunction issues in this case, the County Board admits this request.

REQUEST NO. 21: Admit that, but for the injunction issued in this case (Dkt. 67), Plaintiff B.P.J. would not be permitted to be a member of any girls' athletic team offered at Bridgeport Middle School because of H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board states as follows: Because, as it is currently drafted, H.B. Bill 3293 (codified at West Virginia Code § 18- 2-25d) applies to public secondary schools and states that “[a]thletic teams or sports designated for females, women, or girls shall not be open to students of the male sex where selection for such teams is based upon competitive skill or the activity involved is a contact sport[,]” because of the definitions set forth in H.B. 3293, and absent the injunction issued in this case, the County Board admits this request.

REQUEST NO. 22: Admit that H.B. 3293 prohibits Plaintiff B.P.J. from participating on girls' athletic teams at all public secondary schools located in West Virginia.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board states as follows: Because, as it is currently drafted, H.B. Bill 3293 (codified at West Virginia Code § 18- 2-25d) applies to public secondary schools and states that “[a]thletic teams or sports designated for females, women, or girls shall not be open to students of the male sex where selection for such teams is based upon competitive skill or the activity involved is a contact sport[,]” because of the definitions set forth in H.B. 3293, and absent the injunction issued in this case, the County Board admits this request.

REQUEST NO. 23: Admit that the State Board of Education and the State Superintendent must comply with H.B. 3293 unless enjoined from doing so by a court.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board is not in a position to admit or deny this request because it concerns the State Board of Education and State Superintendent's obligations under H.B. 3293.

REQUEST NO. 24: Admit that H.B. 3293 prohibits the State Board of Education and the State Superintendent from adopting or enforcing a policy that would allow B.P.J. to participate on girls' athletic teams at Bridgeport Middle School.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board is not in a position to admit or deny this request because it concerns the State Board of Education and State Superintendent's obligations under H.B. 3293.

REQUEST NO. 25: Admit that the Harrison County Board of Education and the Harrison County School Superintendent must comply with H.B. 3293 unless enjoined from doing so by a court.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board states as follows: Because H.B. 3293 is a West Virginia State law that applies to County Boards of Education, including the County Board and its County Superintendent, because H.B. 3293 provides for private causes of action, and thus imposes liability against County Boards of Education, like the County Board, and while the County Board and its County Superintendent did not devise and have not adopted H.B. Bill 3293 as their own policy, the County Board admits this request because, absent an injunction by a court, the County Board would be compelled and required to enforce H.B. Bill 3293 because it is a mandatory State law that affords the County Board no discretion.

REQUEST NO. 26: Admit that H.B. 3293 prohibits the Harrison County Board of Education and the Harrison County Superintendent from adopting or enforcing a policy that would allow B.P.J. to participate on girls' athletic teams at Bridgeport Middle School.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board states as follows: Because H.B. 3293 is a West Virginia State law that applies to County Boards of Education, including the County Board and its County Superintendent, because H.B. 3293 provides for private causes of action, and thus imposes liability against County Boards of Education, like the County Board, and while the County Board and its County Superintendent did not devise and have not adopted H.B. Bill 3293 as their own policy, the County Board admits this

request because, absent an injunction by a court, the County Board would be compelled and required to enforce H.B. Bill 3293 because it is a mandatory State law that affords the County Board no discretion.

REQUEST NO. 27: Admit that the West Virginia Secondary School Athletic Commission must comply with H.B. 3293 unless enjoined from doing so by a court.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board is not in a position to admit or deny this request because it concerns the West Virginia Secondary School Athletic Commission's obligations under H.B. 3293.

REQUEST NO. 28: Admit that H.B. 3293 prohibits the West Virginia Secondary School Athletic Commission from adopting or enforcing a policy that would allow B.P.J. to participate on girls' athletic teams at Bridgeport Middle School

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board is not in a position to admit or deny this request because it concerns the West Virginia Secondary School Athletic Commission's obligations under H.B. 3293.

REQUEST NO. 29: Admit that there are no athletic teams designated as "coed or mixed," as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), offered at Bridgeport Middle School.

RESPONSE: Denied.

REQUEST NO. 30: Admit that there are no athletic teams designated as "coed or mixed," as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-

25d(c)(1)(C)), that compete interscholastically offered at any public secondary school located in West Virginia.

RESPONSE: Denied.

REQUEST NO. 31: Admit that there are no cross-country teams designated as “coed or mixed,” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), that compete interscholastically offered by any member school of the West Virginia Secondary School Activities Commission.

RESPONSE: **OBJECTION.** The County Board objects to the scope of this request. Subject to and without waiving the objection, the County Board can only answer on behalf of schools in Harrison County, and admits that there are no “co-ed or mixed” cross country teams in Harrison County.

REQUEST NO. 32: Admit that there are no athletic leagues designated as “coed or mixed,” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), that comprise teams from more than one school supervised by the West Virginia Secondary School Activities Commission.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, and even with a reasonable inquiry, the County Board cannot admit or deny this request because the information it knows or can readily obtain is insufficient to enable the County Board to admit or deny the request.

REQUEST NO. 33: Admit that there are no athletic teams designated as “coed or mixed,” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-

25d(c)(1)(C)),” that compete interscholastically offered by any public secondary school under the supervision of the West Virginia State Board of Education.

RESPONSE: **OBJECTION.** The County Board objects to this request because it is vague. Subject to and without waiving the objection, the County Board denies the request because there are “co-ed” teams in Harrison County, but the County Board cannot admit or deny the rest of the request based on how it is phrased.

REQUEST NO. 34: Admit that H.B. 3293 does not prohibit a cisgender girl student at Bridgeport Middle School from joining a girls’ athletic team offered at Bridgeport Middle School.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, and based on the language used in H.B. 3293, the County Board admits this request.

REQUEST NO. 35: Admit that H.B. 3293 does not prohibit a cisgender girl student at any public secondary school in West Virginia from joining a girls’ athletic team offered by her public secondary school.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, and based on the language used in H.B. 3293, the County Board admits this request.

REQUEST NO. 36: Admit that H.B. 3293 prohibits a Bridgeport Middle School transgender girl student from joining a girls’ athletic team offered at Bridgeport Middle School.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County

Board states as follows: Because, as it is currently drafted, H.B. Bill 3293 (codified at West Virginia Code § 18- 2-25d) applies to public secondary schools and states that “[a]thletic teams or sports designated for females, women, or girls shall not be open to students of the male sex where selection for such teams is based upon competitive skill or the activity involved is a contact sport[,]” because of the definitions set forth in H.B. 3293, and absent the injunction issued in this case, the County Board admits this request.

REQUEST NO. 37: Admit that H.B. 3293 prohibits any transgender girl secondary school student located in West Virginia from joining a girls’ athletic team offered by her public secondary school.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board states as follows: Because, as it is currently drafted, H.B. Bill 3293 (codified at West Virginia Code § 18- 2-25d) applies to public secondary schools and states that “[a]thletic teams or sports designated for females, women, or girls shall not be open to students of the male sex where selection for such teams is based upon competitive skill or the activity involved is a contact sport[,]” because of the definitions set forth in H.B. 3293, and absent the injunction issued in this case, the County Board admits this request.

REQUEST NO. 38: Admit that prior to the enactment of H.B. 3293, cisgender boy students at Bridgeport Middle School were prohibited from joining girls’ athletic teams offered at Bridgeport Middle School.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County

Board admits that there is a West Virginia Secondary School Activities Commission rule that may apply to this situation.

REQUEST NO. 39: Admit that prior to the enactment of H.B. 3293, a cisgender boy student at any public secondary school in West Virginia was prohibited from joining girls' athletic teams offered at his public secondary school.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board admits that there is a West Virginia Secondary School Activities Commission rule that may apply to this situation.

REQUEST NO. 40: Admit that prior to the enactment of H.B. 3293, you are not aware of any transgender student athlete participating on an athletic team offered by Bridgeport Middle School.

RESPONSE: Admitted.

REQUEST NO. 41: Admit that prior to the enactment of H.B. 3293, you are not aware of any transgender student athlete participating on an athletic team offered by a public secondary school in West Virginia.

RESPONSE: Admitted.

REQUEST NO. 42: Admit that other than Plaintiff B.P.J., you are not aware of a transgender student athlete participating on an athletic team offered by Bridgeport Middle School.

RESPONSE: Admitted.

REQUEST NO. 43: Admit that other than Plaintiff B.P.J., you are not aware of a transgender student athlete participating on an athletic team offered by a public secondary school in West Virginia.

RESPONSE: Admitted.

REQUEST NO. 44: Admit that students derive social benefits from participation on athletic teams offered by public secondary schools in West Virginia.

RESPONSE: Admitted.

REQUEST NO. 45: Admit that students derive psychological benefits from participation on athletic teams offered by public secondary schools in West Virginia.

RESPONSE: Admitted.

REQUEST NO. 46: Admit that interscholastic athletic competition benefits middle school students.

RESPONSE: Admitted.

REQUEST NO. 47: Admit that middle school students who participate in interscholastic athletics receive benefits regardless whether they win or lose.

RESPONSE: Admitted.

REQUEST NO. 48: Admit that but for the injunction issued in this case, the Harrison County School Board and schools within the Harrison County School District would comply with H.B. 3293.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County

Board states as follows: Because H.B. 3293 is a West Virginia State law that applies to County Boards of Education, including the County Board and its County Superintendent, because H.B. 3293 provides for private causes of action, and thus imposes liability against County Boards of Education, like the County Board, and while the County Board and its County Superintendent did not devise and have not adopted H.B. Bill 3293 as their own policy, the County Board admits this request because, absent an injunction by a court, the County Board would be compelled and required to enforce H.B. Bill 3293 because it is a mandatory State law that affords the County Board no discretion.

REQUEST NO. 49: Admit that but for the injunction in this case (Dkt. 67) the Harrison County School Board and schools within the Harrison County School District would not take any actions that violated H.B. 3293.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board states as follows: Because H.B. 3293 is a West Virginia State law that applies to County Boards of Education, including the County Board and its County Superintendent, because H.B. 3293 provides for private causes of action, and thus imposes liability against County Boards of Education, like the County Board, and while the County Board and its County Superintendent did not devise and have not adopted H.B. Bill 3293 as their own policy, the County Board admits this request because, absent an injunction by a court, the County Board would be compelled and required to enforce H.B. Bill 3293 because it is a mandatory State law that affords the County Board no discretion.

REQUEST NO. 50: Admit that, but for the injunction in this case (Dkt. 67), the Harrison County School Board and Bridgeport Middle School would not have permitted Plaintiff

B.P.J. to try out for the Bridgeport Middle School's girls' cross-country team in 2021 because of H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board states as follows: Because H.B. 3293 is a West Virginia State law that applies to County Boards of Education, including the County Board and its County Superintendent, because H.B. 3293 provides for private causes of action, and thus imposes liability against County Boards of Education, like the County Board, and while the County Board and its County Superintendent did not devise and have not adopted H.B. Bill 3293 as their own policy, the County Board admits this request because, absent an injunction by a court, the County Board would be compelled and required to enforce H.B. Bill 3293 because it is a mandatory State law that affords the County Board no discretion.

REQUEST NO. 51: Admit that, but for the injunction in this case (Dkt. 67), the Harrison County School Board and Bridgeport Middle School would not have allowed Plaintiff B.P.J. to participate on the Bridgeport Middle School's girls' cross-country team in 2021 because of H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board states as follows: Because H.B. 3293 is a West Virginia State law that applies to County Boards of Education, including the County Board and its County Superintendent, because H.B. 3293 provides for private causes of action, and thus imposes liability against County Boards of Education, like the County Board, and while the County Board and its County Superintendent did not devise and have not adopted H.B. Bill 3293 as their own policy, the County Board admits this

request because, absent an injunction by a court, the County Board would be compelled and required to enforce H.B. Bill 3293 because it is a mandatory State law that affords the County Board no discretion.

REQUEST NO. 52: Admit that, but for the injunction in this case (Dkt. 67), the Harrison County School Board and Bridgeport Middle School would not permit Plaintiff B.P.J. to try out for any girls' athletic team offered at Bridgeport Middle School because of H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board states as follows: Because H.B. 3293 is a West Virginia State law that applies to County Boards of Education, including the County Board and its County Superintendent, because H.B. 3293 provides for private causes of action, and thus imposes liability against County Boards of Education, like the County Board, and while the County Board and its County Superintendent did not devise and have not adopted H.B. Bill 3293 as their own policy, the County Board admits this request because, absent an injunction by a court, the County Board would be compelled and required to enforce H.B. Bill 3293 because it is a mandatory State law that affords the County Board no discretion.

REQUEST NO. 53: Admit that, but for the injunction issued in this case (Dkt. 67), the Harrison County School Board and Bridgeport Middle School would not permit Plaintiff B.P.J. to be a member of any girls' athletic team offered at Bridgeport Middle School because of H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County

Board states as follows: Because H.B. 3293 is a West Virginia State law that applies to County Boards of Education, including the County Board and its County Superintendent, because H.B. 3293 provides for private causes of action, and thus imposes liability against County Boards of Education, like the County Board, and while the County Board and its County Superintendent did not devise and have not adopted H.B. Bill 3293 as their own policy, the County Board admits this request because, absent an injunction by a court, the County Board would be compelled and required to enforce H.B. Bill 3293 because it is a mandatory State law that affords the County Board no discretion.

REQUEST NO. 54: Admit that Plaintiff B.P.J.’s gender is identified as “male” in the West Virginia Education Information System (“WVEIS”).

RESPONSE: Admitted.

REQUEST NO. 55: Admit that you have the ability to change Plaintiff B.P.J.’s gender in WVEIS to “female.”

RESPONSE: **OBJECTION.** The County Board objects to the request because it seeks information that is not relevant to any party’s claim or defense and is not proportional to the needs of the case. Subject to and without waiving the objection, the County Board admits that it has the ability to change data in WVEIS.

REQUEST NO. 56: Admit that H.B. 3293 allows a student to bring an action against you for alleged violations of H.B. 3293.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board admits this request.

REQUEST NO. 57: Admit that you are required to regulate athletic activities offered by public secondary schools in Harrison County. See Code of West Virginia §18-2-25.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board admits that the provisions of West Virginia Code §18-2-25 require it to regulate athletic activities of public secondary schools in Harrison County.

REQUEST NO. 58: Admit that you are required to control interscholastic athletic events in which Bridgeport Middle School participates. See Code of West Virginia §18-2-25.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board admits that the provisions of West Virginia Code §18-2-25 require it to control athletic activities of public secondary schools in Harrison County.

REQUEST NO. 59: Admit that you are required supervise interscholastic athletic events in which Bridgeport Middle School participates. See Code of West Virginia §18-2-25.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board admits that the provisions of West Virginia Code §18-2-25 require it to supervise athletic activities of public secondary schools in Harrison County.

REQUEST NO. 60: Admit that you are required regulate interscholastic athletic events in which Bridgeport Middle School participates. See Code of West Virginia §18-2-25.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County

Board admits that the provisions of West Virginia Code §18-2-25 require it to regulate athletic events in which Bridgeport Middle School participates.

REQUEST NO. 61: Admit that Bridgeport Middle School is a member school of the West Virginia Secondary School Activities Commission.

RESPONSE: Admitted.

REQUEST NO. 62: Admit that you have delegated control over interscholastic athletic events in Harrison County to the West Virginia Secondary School Activities Commission.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board admits that it has delegated some, but not all, control over interscholastic athletic events in Harrison County to the West Virginia Secondary School Activities Commission.

REQUEST NO. 63: Admit that you have delegated supervision over interscholastic athletic events to the West Virginia Secondary School Activities Commission.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board admits that it has delegated some, but not all, supervision over interscholastic athletic events to the West Virginia Secondary School Activities Commission.

REQUEST NO. 64: Admit that you have delegated regulation of interscholastic athletic events to the West Virginia Secondary School Activities Commission.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County

Board admits that it has delegated some, but not all, regulation of interscholastic athletic events to the West Virginia Secondary School Activities Commission.

REQUEST NO. 65: Admit that the State Board of Education controls you. See Code of West Virginia §18-2-5.

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board denies this request because West Virginia Code §18-2-5 states that “the State Board of Education shall exercise general supervision of the public schools of the state, and shall promulgate rules[.]”

REQUEST NO. 66: Admit that you receive federal financial assistance.

RESPONSE: Admitted.

REQUEST NO. 67: Admit that you must comply with Title IX of the Education Amendments of 1972, 20 U.S.C. §1681 *et seq.*

RESPONSE: **OBJECTION.** The County Board objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, the County Board admits this request.

Dated this the 10th day of March, 2022.

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IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

B.P.J., by her next friend and mother,
HEATHER JACKSON,

Plaintiff,

v.

Civil Action No. 2:21-cv-00316
Hon. Joseph R. Goodwin, District Judge

WEST VIRGINIA STATE BOARD OF
EDUCATION, HARRISON COUNTY BOARD
OF EDUCATION, WEST VIRGINIA
SECONDARY SCHOOL ACTIVITIES
COMMISSION, W. CLAYTON BURCH in his
official capacity as State Superintendent,
DORA STUTLER in her official capacity as
Harrison County Superintendent, PATRICK
MORRISEY in his official capacity as Attorney
General, and THE STATE OF WEST VIRGINIA,

Defendants,

and

LAINEY ARMISTEAD,

Defendant-Intervenor.

CERTIFICATE OF SERVICE

I hereby certify that on the 10th day of March, 2022, I electronically filed the foregoing Certificate of Service of “Defendant Harrison County Board of Education’s Responses and Objections to Plaintiff’s Second Set of Requests for Admission” with the Clerk of the Court using the CM/ECF system, and a true and exact copy of such filing was sent by email to the following counsel of record:

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IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

B.P.J., by her next friend and mother,
HEATHER JACKSON,

Plaintiff,

v.

Civil Action No. 2:21-cv-00316
Hon. Joseph R. Goodwin, District Judge

WEST VIRGINIA STATE BOARD OF
EDUCATION, HARRISON COUNTY BOARD
OF EDUCATION, WEST VIRGINIA
SECONDARY SCHOOL ACTIVITIES
COMMISSION, W. CLAYTON BURCH in his
official capacity as State Superintendent,
DORA STUTLER in her official capacity as
Harrison County Superintendent, PATRICK
MORRISEY in his official capacity as Attorney
General, and THE STATE OF WEST VIRGINIA,

Defendants,

and

LAINEY ARMISTEAD,

Defendant-Intervenor.

**DEFENDANT SUPERINTENDENT DORA STUTLER’S RESPONSES AND
OBJECTIONS TO PLAINTIFF’S SECOND SET OF REQUESTS FOR ADMISSION**

Pursuant to Rule 36 of the Federal Rules of Civil Procedure, Defendant Superintendent Dora Stutler (“Superintendent Stutler”) hereby responds and objects to “Plaintiff’s Second Set of Requests for Admission to Defendant Harrison County Superintendent Dora Stutler” as follows:

GENERAL OBJECTION: Superintendent Stutler objects to the definitions of “County Board” and “County Superintendent” as set forth in Plaintiff’s requests for admission.

Those definitions are overly broad and outside the permissible scope of discovery under the Federal Rules of Civil Procedure as the definitions improperly broaden the identity of parties in this case. For instance, the definitions of the “County Board” and the “County Superintendent” also include their “officers, directors, employees, partners, corporate parent, subsidiaries, affiliates, attorneys, accountants, consultants, representatives and agents.” Superintendent Stutler objects to providing responses pursuant to the broadened definitions of “County Board” and “County Superintendent.” Superintendent Stutler further objects to the Definitions and Instructions set forth in Plaintiff’s requests to the extent they are inconsistent with the Federal Rules of Civil Procedure or applicable law.

REQUEST NO. 5: Admit that Plaintiff B.P.J. has been diagnosed with gender dysphoria.

RESPONSE: Superintendent Stutler admits that medical records produced in this case state that Plaintiff B.P.J. has been diagnosed with gender dysphoria.

REQUEST NO. 6: Admit that in 2021 Plaintiff B.P.J. was a member of Bridgeport Middle School’s girls’ cross-country team.

RESPONSE: Admitted.

REQUEST NO. 7: Admit that Plaintiff B.P.J. placed 51 out of 66 competitors in the girls’ middle school cross country Mountain Hollar MS Invitational meet in 2021.

RESPONSE: Upon information and belief, and based on information provided on RunWV.com regarding the results of the race, Superintendent Stutler admits this request.

REQUEST NO. 8: Admit that Plaintiff B.P.J. placed 123 out of 150 competitors in the girls' middle school cross country Doddridge Invitational meet in 2021.

RESPONSE: Upon information and belief, and based on information provided on RunWV.com regarding the results of the race, Superintendent Stutler admits this request.

REQUEST NO. 9: Admit that you have not received any complaints associated with Plaintiff B.P.J.'s membership on Bridgeport Middle School's girls' cross country team.

RESPONSE: Admitted.

REQUEST NO. 10: Admit that no middle school girl was harmed as a result of B.P.J.'s participation on Bridgeport Middle School's girls' cross country team in 2021.

RESPONSE: **OBJECTION.** Superintendent Stutler objects to this request because it is vague. Superintendent Stutler does not know what Plaintiff means by the term "harmed." Subject to and without waiving the objection, Superintendent Stutler admits that no student was cut from the Bridgeport Middle School's girls' cross country team in 2021. Superintendent Stutler otherwise denies this request because it is unclear what Plaintiff is asking.

REQUEST NO. 11: Admit that no middle school girl was injured as a result of Plaintiff B.P.J.'s participation on Bridgeport Middle School's girls' cross country team in 2021.

RESPONSE: **OBJECTION.** Superintendent Stutler objects to this request because it is vague. Superintendent Stutler does not know what Plaintiff means by the term "injured." Subject to and without waiving the objection, Superintendent Stutler admits that no student was cut from the Bridgeport Middle School's girls' cross country team in 2021. Superintendent Stutler otherwise denies this request because it is unclear what Plaintiff is asking.

REQUEST NO. 12: Admit that no Bridgeport Middle School girl student was prohibited from joining Bridgeport Middle School's girls' cross-country team in 2021.

RESPONSE: Admitted.

REQUEST NO. 13: Admit that Bridgeport Middle School's girls' cross-country team did not turn anyone away from participating due to lack of space on the roster in 2021.

RESPONSE: Admitted.

REQUEST NO. 14: Admit that Plaintiff B.P.J. does not have an unfair athletic advantage over other girls participating on the Bridgeport Middle School girls' cross-country team.

RESPONSE: Even with a reasonable inquiry, Superintendent Stutler cannot admit or deny this request because the information she knows or can readily obtain is insufficient to enable Superintendent Stutler to admit or deny the request.

REQUEST NO. 15: Admit that Plaintiff B.P.J. does not have an unfair athletic advantage over girls competing against the Bridgeport Middle School girls' cross-country team.

RESPONSE: Even with a reasonable inquiry, Superintendent Stutler cannot admit or deny this request because the information she knows or can readily obtain is insufficient to enable Superintendent Stutler to admit or deny the request.

REQUEST NO. 16: Admit that cross country is a sport that requires "competitive skill" as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, Superintendent Stutler cannot admit or deny this request because "competitive skill" is not defined in H.B. 3293.

REQUEST NO. 17: Admit that cross country is a sport that requires “competitive skill” as that phrase is used in 34 C.F.R. §106.41(b).

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, Superintendent Stutler cannot admit or deny this request because “competitive skill” is not defined in 34 C.F.R. §106.41(b).

REQUEST NO. 18: Admit that cross country is not a “contact sport” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, Superintendent Stutler cannot admit or deny this request because “contact sport” is not defined in H.B. 3293.

REQUEST NO. 19: Admit that cross country is not a “contact sport” as that phrase is used in 34 C.F.R. §106.41(b).

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, Superintendent Stutler admits that “cross country” is not specifically identified as a “contact sport” in 34 C.F.R. §106.41(b).

REQUEST NO. 20: Admit that, but for the injunction issued in this case (Dkt. 67), Plaintiff B.P.J. would not have been permitted to be a member of Bridgeport Middle

School's girls' cross-country team in 2021 because of H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, Superintendent Stutler states as follows: Because, as it is currently drafted, H.B. Bill 3293 (codified at West Virginia Code § 18- 2-25d) applies to public secondary schools and states that “[a]thletic teams or sports designated for females, women, or girls shall not be open to students of the male sex where selection for such teams is based upon competitive skill or the activity involved is a contact sport[,]” because of the definitions set forth in H.B. 3293, and absent the injunction issued in this case, Superintendent Stutler admits this request.

REQUEST NO. 21: Admit that, but for the injunction issued in this case (Dkt. 67), Plaintiff B.P.J. would not be permitted to be a member of any girls' athletic team offered at Bridgeport Middle School because of H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, Superintendent Stutler states as follows: Because, as it is currently drafted, H.B. Bill 3293 (codified at West Virginia Code § 18- 2-25d) applies to public secondary schools and states that “[a]thletic teams or sports designated for females, women, or girls shall not be open to students of the male sex where selection for such teams is based upon competitive skill or the activity involved is a contact sport[,]” because of the definitions set forth in H.B. 3293, and absent the injunction issued in this case, Superintendent Stutler admits this request.

REQUEST NO. 22: Admit that H.B. 3293 prohibits Plaintiff B.P.J. from participating on girls' athletic teams at all public secondary schools located in West Virginia.

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, Superintendent Stutler states as follows: Because, as it is currently drafted, H.B. Bill 3293 (codified at West Virginia Code § 18- 2-25d) applies to public secondary schools and states that “[a]thletic teams or sports designated for females, women, or girls shall not be open to students of the male sex where selection for such teams is based upon competitive skill or the activity involved is a contact sport[,]” because of the definitions set forth in H.B. 3293, and absent the injunction issued in this case, Superintendent Stutler admits this request.

REQUEST NO. 23: Admit that the State Board of Education and the State Superintendent must comply with H.B. 3293 unless enjoined from doing so by a court.

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, Superintendent Stutler is not in a position to admit or deny this request because it concerns the State Board of Education and State Superintendent's obligations under H.B. 3293.

REQUEST NO. 24: Admit that H.B. 3293 prohibits the State Board of Education and the State Superintendent from adopting or enforcing a policy that would allow B.P.J. to participate on girls' athletic teams at Bridgeport Middle School.

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, Superintendent Stutler is not in a position to admit or deny this request because it concerns the State Board of Education and State Superintendent's obligations under H.B. 3293.

REQUEST NO. 25: Admit that the Harrison County Board of Education and the Harrison County School Superintendent must comply with H.B. 3293 unless enjoined from doing so by a court.

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, Superintendent Stutler states as follows: Because H.B. 3293 is a West Virginia State law that applies to County Boards of Education, including the Harrison County Board of Education (“County Board”) and its County Superintendent, because H.B. 3293 provides for private causes of action, and thus imposes liability against County Boards of Education, like the County Board, and while the County Board and its County Superintendent did not devise and have not adopted H.B. Bill 3293 as their own policy, Superintendent Stutler admits this request because, absent an injunction by a court, the County Board and the County Superintendent would be compelled and required to enforce H.B. Bill 3293 because it is a mandatory State law that affords the County Board and the County Superintendent no discretion.

REQUEST NO. 26: Admit that H.B. 3293 prohibits the Harrison County Board of Education and the Harrison County Superintendent from adopting or enforcing a policy that would allow B.P.J. to participate on girls’ athletic teams at Bridgeport Middle School.

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, Superintendent Stutler states as follows: Because H.B. 3293 is a West Virginia State law that applies to County Boards of Education, including the County Board and its County Superintendent, because H.B. 3293 provides for private causes of action, and thus imposes liability against County Boards of Education, like the County Board, and while the County Board and its County

Superintendent did not devise and have not adopted H.B. Bill 3293 as their own policy, Superintendent Stutler admits this request because, absent an injunction by a court, the County Board and the County Superintendent would be compelled and required to enforce H.B. Bill 3293 because it is a mandatory State law that affords the County Board and the County Superintendent no discretion.

REQUEST NO. 27: Admit that the West Virginia Secondary School Athletic Commission must comply with H.B. 3293 unless enjoined from doing so by a court.

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, Superintendent Stutler is not in a position to admit or deny this request because it concerns the West Virginia Secondary School Athletic Commission's obligations under H.B. 3293.

REQUEST NO. 28: Admit that H.B. 3293 prohibits the West Virginia Secondary School Athletic Commission from adopting or enforcing a policy that would allow B.P.J. to participate on girls' athletic teams at Bridgeport Middle School

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, Superintendent Stutler is not in a position to admit or deny this request because it concerns the West Virginia Secondary School Athletic Commission's obligations under H.B. 3293.

REQUEST NO. 29: Admit that there are no athletic teams designated as "coed or mixed," as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), offered at Bridgeport Middle School.

RESPONSE: Denied.

REQUEST NO. 30: Admit that there are no athletic teams designated as “coed or mixed,” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), that compete interscholastically offered at any public secondary school located in West Virginia.

RESPONSE: Denied.

REQUEST NO. 31: Admit that there are no cross-country teams designated as “coed or mixed,” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), that compete interscholastically offered by any member school of the West Virginia Secondary School Activities Commission.

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the scope of this request. Subject to and without waiving the objection, Superintendent Stutler can only answer on behalf of schools in Harrison County, and admits that there are no “co-ed or mixed” cross country teams in Harrison County.

REQUEST NO. 32: Admit that there are no athletic leagues designated as “coed or mixed,” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), that comprise teams from more than one school supervised by the West Virginia Secondary School Activities Commission.

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, and even with a reasonable inquiry, Superintendent Stutler cannot admit or deny this request because the information she knows or can readily obtain is insufficient to enable Superintendent Stutler to admit or deny the request.

REQUEST NO. 33: Admit that there are no athletic teams designated as “coed or mixed,” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)),” that compete interscholastically offered by any public secondary school under the supervision of the West Virginia State Board of Education.

RESPONSE: **OBJECTION.** Superintendent Stutler objects to this request because it is vague. Subject to and without waiving the objection, Superintendent Stutler denies the request because there are “co-ed” teams in Harrison County, but Superintendent Stutler cannot admit or deny the rest of the request based on how it is phrased.

REQUEST NO. 34: Admit that H.B. 3293 does not prohibit a cisgender girl student at Bridgeport Middle School from joining a girls’ athletic team offered at Bridgeport Middle School.

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, and based on the language used in H.B. 3293, Superintendent Stutler admits this request.

REQUEST NO. 35: Admit that H.B. 3293 does not prohibit a cisgender girl student at any public secondary school in West Virginia from joining a girls’ athletic team offered by her public secondary school.

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, and based on the language used in H.B. 3293, Superintendent Stutler admits this request.

REQUEST NO. 36: Admit that H.B. 3293 prohibits a Bridgeport Middle School transgender girl student from joining a girls' athletic team offered at Bridgeport Middle School.

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, Superintendent Stutler states as follows: Because, as it is currently drafted, H.B. Bill 3293 (codified at West Virginia Code § 18- 2-25d) applies to public secondary schools and states that “[a]thletic teams or sports designated for females, women, or girls shall not be open to students of the male sex where selection for such teams is based upon competitive skill or the activity involved is a contact sport[,]” because of the definitions set forth in H.B. 3293, and absent the injunction issued in this case, Superintendent Stutler admits this request.

REQUEST NO. 37: Admit that H.B. 3293 prohibits any second (sic) school transgender girl student located in West Virginia from joining a girls' athletic team offered by her public secondary school.

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, Superintendent Stutler states as follows: Because, as it is currently drafted, H.B. Bill 3293 (codified at West Virginia Code § 18- 2-25d) applies to public secondary schools and states that “[a]thletic teams or sports designated for females, women, or girls shall not be open to students of the male sex where selection for such teams is based upon competitive skill or the activity involved is a contact sport[,]” because of the definitions set forth in H.B. 3293, and absent the injunction issued in this case, Superintendent Stutler admits this request.

REQUEST NO. 38: Admit that prior to the enactment of H.B. 3293, cisgender boy students at Bridgeport Middle School were prohibited from joining girls' athletic teams offered at Bridgeport Middle School.

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, Superintendent Stutler admits that there is a West Virginia Secondary School Activities Commission rule that may apply to this situation.

REQUEST NO. 39: Admit that prior to the enactment of H.B. 3293, a cisgender boy student at any public secondary school in West Virginia was prohibited from joining girls' athletic teams offered at his public secondary school.

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, Superintendent Stutler admits that there is a West Virginia Secondary School Activities Commission rule that may apply to this situation.

REQUEST NO. 40: Admit that prior to the enactment of H.B. 3293, you are not aware of any transgender student athlete participating on an athletic team offered by Bridgeport Middle School.

RESPONSE: Admitted.

REQUEST NO. 41: Admit that prior to the enactment of H.B. 3293, you are not aware of any transgender student athlete participating on an athletic team offered by a public secondary school in West Virginia.

RESPONSE: Admitted.

REQUEST NO. 42: Admit that other than Plaintiff B.P.J., you are not aware of a transgender student athlete participating on an athletic team offered by Bridgeport Middle School.

RESPONSE: Admitted.

REQUEST NO. 43: Admit that other than Plaintiff B.P.J., you are not aware of a transgender student athlete participating on an athletic team offered by a public secondary school in West Virginia.

RESPONSE: Admitted.

REQUEST NO. 44: Admit that students derive social benefits from participation on athletic teams offered by public secondary schools in West Virginia.

RESPONSE: Admitted.

REQUEST NO. 45: Admit that students derive psychological benefits from participation on athletic teams offered by public secondary schools in West Virginia.

RESPONSE: Admitted.

REQUEST NO. 46: Admit that interscholastic athletic competition benefits middle school students.

RESPONSE: Admitted.

REQUEST NO. 47: Admit that middle school students who participate in interscholastic athletics receive benefits regardless whether they win or lose.

RESPONSE: Admitted.

REQUEST NO. 48: Admit that when enforcing West Virginia State law you act on behalf of the State of West Virginia.

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, Superintendent Stutler admits this request.

REQUEST NO. 49: Admit that when enforcing West Virginia State law you are a State Actor for purposes of 42 U.S.C. § 1983.

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, Superintendent Stutler admits this request.

REQUEST NO. 50: Admit that you are required to enforce H.B. 3293 assuming the Court has not enjoined you from doing so.

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, Superintendent Stutler states as follows: Because H.B. 3293 is a West Virginia State law that applies to County Boards of Education, including the County Board and its County Superintendent, because H.B. 3293 provides for private causes of action, and thus imposes liability against County Boards of Education, like the County Board, and while the County Board and its County Superintendent did not devise and have not adopted H.B. Bill 3293 as their own policy, Superintendent Stutler admits this request because, absent an injunction by a court, the County Board and the County Superintendent would be compelled and required to enforce H.B. Bill 3293 because it is a mandatory State law that affords the County Board and the County Superintendent no discretion.

REQUEST NO. 51: Admit that you are required to ensure that the Harrison County Board of Education enforces H.B. 3293 assuming the Court has not enjoined it from doing so.

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, Superintendent Stutler states as follows: Because H.B. 3293 is a West Virginia State law that applies to County Boards of Education, including the County Board and its County Superintendent, because H.B. 3293 provides for private causes of action, and thus imposes liability against County Boards of Education, like the County Board, and while the County Board and its County Superintendent did not devise and have not adopted H.B. Bill 3293 as their own policy, Superintendent Stutler admits this request because, absent an injunction by a court, the County Board and the County Superintendent would be compelled and required to enforce H.B. Bill 3293 because it is a mandatory State law that affords the County Board and the County Superintendent no discretion.

REQUEST NO. 52: Admit that you are required to ensure that Bridgeport Middle School enforces H.B. 3293 assuming the Court has not enjoined it from doing so.

RESPONSE: **OBJECTION.** Superintendent Stutler objects to the extent this request is seeking a legal conclusion. Subject to and without waiving the objection, Superintendent Stutler states as follows: Because H.B. 3293 is a West Virginia State law that applies to County Boards of Education, including the County Board and its County Superintendent, because H.B. 3293 provides for private causes of action, and thus imposes liability against County Boards of Education, like the County Board, and while the County Board and its County Superintendent did not devise and have not adopted H.B. Bill 3293 as their own policy,

Superintendent Stutler admits this request because, absent an injunction by a court, the County Board and the County Superintendent would be compelled and required to enforce H.B. Bill 3293 because it is a mandatory State law that affords the County Board and the County Superintendent no discretion.

Dated this the 10th day of March, 2022.

STEPTOE & JOHNSON PLLC
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of Education and Dora Stutler*

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

B.P.J., by her next friend and mother,
HEATHER JACKSON,

Plaintiff,

v.

Civil Action No. 2:21-cv-00316
Hon. Joseph R. Goodwin, District Judge

WEST VIRGINIA STATE BOARD OF
EDUCATION, HARRISON COUNTY BOARD
OF EDUCATION, WEST VIRGINIA
SECONDARY SCHOOL ACTIVITIES
COMMISSION, W. CLAYTON BURCH in his
official capacity as State Superintendent,
DORA STUTLER in her official capacity as
Harrison County Superintendent, PATRICK
MORRISEY in his official capacity as Attorney
General, and THE STATE OF WEST VIRGINIA,

Defendants,

and

LAINEY ARMISTEAD,

Defendant-Intervenor.

CERTIFICATE OF SERVICE

I hereby certify that on the 10th day of March, 2022, I electronically filed the foregoing Certificate of Service of “Defendant Harrison County Superintendent Dora Stutler’s Responses and Objections to Plaintiff’s Second Set of Requests for Admission” with the Clerk of the Court using the CM/ECF system, and a true and exact copy of such filing was sent by email to the following counsel of record:

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**IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION**

B.P.J. by her next friend and mother, HEATHER JACKSON,

Plaintiff,

v.

WEST VIRGINIA STATE BOARD OF EDUCATION, HARRISON COUNTY BOARD OF EDUCATION, WEST VIRGINIA SECONDARY SCHOOL ACTIVITIES COMMISSION, W. CLAYTON BURCH in his official capacity as State Superintendent, DORA STUTLER in her official capacity as Harrison County Superintendent, and THE STATE OF WEST VIRGINIA,

Defendants,

and

LAINY ARMISTEAD,

Defendant-Intervenor.

Civil Action No. 2:21-cv-00316

Hon. Joseph R. Goodwin

**RESPONSES TO PLAINTIFF’S SECOND SET OF REQUESTS FOR ADMISSION
TO DEFENDANT, STATE OF WEST VIRGINIA**

Pursuant to Federal Rules of Civil Procedure 33 and 36 and the applicable Local Rules of the Southern District of West Virginia and this Court, the Defendant, State of West Virginia (the “State”), provides these responses to Plaintiff’s Second Set of Requests for Admission to Defendant, State of West Virginia (“Second Set of RFAs”).

GENERAL OBJECTIONS

The State objects to the definitions of the terms “Cisgender,” “Gender Identity,” “Transgender,” and “Transgender Girl” in the Second Set of RFAs’ instructions. Those terms have no definitive legally recognized definition, and those terms do not have an agreed or stipulated meaning in this matter. Any requests for admissions based on these disputed and unproven definitions would necessarily be admissions as to Plaintiff’s definitions, which the State declines to do at this point in the litigation.

Objecting further, Plaintiff's instructions state: "3. GENDER IDENTITY is synonymous with the meaning used in Plaintiff's First Amended Complaint, paragraphs 19-23." Yet those paragraphs do not contain any definition of the term "gender identity." Accordingly, the instructions for the Second Set of RFAs, even if otherwise acceptable, are vague and unclear.

Further objecting, the Defendant State objects to the definition of "YOU," "YOUR," and "YOURS." As previously discussed in this case, the State of West Virginia alone intervened and was then added as a named defendant via the Amended Complaint, and the Attorney General represents only the State of West Virginia. The Attorney General does not represent any of the other entities or individuals listed in the definition of "YOU, YOUR or YOURS" in these requests and cannot speak on behalf of those entities and individuals here. Accordingly—and consistent with other discovery responses in this matter—any responses are on behalf of the State only.

Further objecting, to the extent that the RFAs ask that the Defendant State admit to its awareness, it is unclear how "awareness" is meant to be applied to the State of West Virginia as (i) "awareness" is distinct from "knowledge" and (ii) the State is an entity which does not have "awareness" as that term is typically understood. Any RFAs seeking such an admission are unclear and consequently seem inappropriate.

Further objecting, the Defendant State objects to any instructions which go beyond Federal Rule 36 and will follow that rule in the event the instructions conflict or go beyond that rule.

RESPONSES TO REQUESTS FOR ADMISSION

Defendant State of West Virginia incorporates by reference all of the foregoing objections into each of the responses below. Any admission in the responses below are made without waiver of the foregoing objections.

REQUEST NO. 5: Admit that Plaintiff B.P.J. has been diagnosed with gender dysphoria.

RESPONSE: The State objects to this request as it is vague in the sense that the term "diagnosed" suggests a medical diagnosis. The assertion of a diagnosis of gender dysphoria relates to a subjective psychological diagnosis, and it is the State's understanding that the standards for such diagnosis vary and that different medical providers reach such a diagnosis differently. Further responding, the State denies for lack of knowledge. The State acknowledges and admits that there are medical records that record and reflect a diagnosis of gender dysphoria for BPJ that was provided by Dr. Montano and that there has been deposition testimony consistent with these records, but denies all other requests included within this Request.

REQUEST NO. 6: Admit that in 2021 Plaintiff B.P.J. was a member of Bridgeport Middle School's girls' cross-country team.

RESPONSE: The State admits this Request.

REQUEST NO. 7: Admit that Plaintiff B.P.J. placed 51 out of 66 competitors in the girls' middle school cross country Mountain Hollar MS Invitational meet in 2021.

RESPONSE: The State denies this Request for lack of knowledge. The State has no knowledge of the source of this information or the validity of such information.

REQUEST NO. 8: Admit that Plaintiff B.P.J. placed 123 out of 150 competitors in the girls' middle school cross country Doddridge Invitational meet in 2021.

RESPONSE: The State denies this Request for lack of knowledge. The State has no knowledge of the source of this information or the validity of such information.

REQUEST NO. 9: Admit that you have not received any complaints associated with Plaintiff B.P.J.'s membership on Bridgeport Middle School's girls' cross country team.

RESPONSE: The State objects to this request as it would not be the recipient of such complaints. Without waiver of the foregoing, the State admits this Request.

REQUEST NO. 10: Admit that no middle school girl was harmed as a result of B.P.J.'s participation on Bridgeport Middle School's girls' cross country team in 2021.

RESPONSE: The State objects to this request as the term "harmed" is vague and has multiple meanings. Without waiver of the foregoing, the State denies for lack of knowledge and further states that it is perhaps unknowable what effect B.P.J.'s participation on Bridgeport Middle School's girls' cross country team in 2021 has had on other participants on that team, participants on other teams, or on others who wanted to participate in this or other events but were dissuaded from such participation or otherwise felt harmed in some way, psychologically or otherwise. Further responding, the State has no knowledge of any physical harm to any middle school girl as a result of Plaintiff B.P.J.'s participation on Bridgeport Middle School's girls' cross country team in 2021.

REQUEST NO. 11: Admit that no middle school girl was injured as a result of Plaintiff B.P.J.'s participation on Bridgeport Middle School's girls' cross country team in 2021.

RESPONSE: The State objects to this request as the term "injured" is vague and has multiple meanings. Without waiver of the foregoing, the State denies for lack of knowledge and further states that it is perhaps unknowable what effect B.P.J.'s participation on Bridgeport Middle School's girls' cross country team in 2021 has had on other participants on that team, participants on other teams, or on others who wanted to participate in this or other events but were dissuaded from such participation or otherwise felt injured in some way, psychologically or otherwise. Further responding, the State has no knowledge of any physical injury to any middle school girl as a result of Plaintiff B.P.J.'s participation on Bridgeport Middle School's girls' cross country team in 2021.

REQUEST NO. 12: Admit that no Bridgeport Middle School girl student was prohibited from joining Bridgeport Middle School's girls' cross-country team in 2021.

RESPONSE: The State denies this Request for lack of knowledge. This type of information is not within the knowledge of the State.

REQUEST NO. 13: Admit that Bridgeport Middle School's girls' cross-country team did not turn anyone away from participating due to lack of space on the roster in 2021.

RESPONSE: The State denies this Request for lack of knowledge. This type of information is not within the knowledge of the State.

REQUEST NO. 14: Admit that Plaintiff B.P.J. does not have an unfair athletic advantage over other girls participating on the Bridgeport Middle School girls' cross-country team.

RESPONSE: The State objects to this Request as the use of the word "over" makes the meaning of this request unclear. Without waiving the foregoing, the State denies this Request. As expert witness testimony has or will show, biological boys statistically have an athletic advantage over biological girls, even at 11 years of age. The State views this as an unfair advantage. Because B.P.J. is a biological boy, B.P.J. does have an advantage.

REQUEST NO. 15: Admit that Plaintiff B.P.J. does not have an unfair athletic advantage over girls competing against the Bridgeport Middle School girls' cross-country team.

RESPONSE: The State objects to this Request as the use of the word "over" makes the meaning of this request unclear. Without waiving the foregoing, the State denies this Request. As expert witness testimony has or will show, biological boys statistically have an athletic advantage over biological girls, even at 11 years of age. The State views this as an unfair advantage. Because B.P.J. is a biological boy, B.P.J. does have an advantage.

REQUEST NO. 16: Admit that cross country is a sport that requires "competitive skill" as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: The State admits this Request.

REQUEST NO. 17: Admit that cross country is a sport that requires "competitive skill" as that phrase is used in 34 C.F.R. § 106.41(b).

RESPONSE: The State admits this Request.

REQUEST NO. 18: Admit that cross country is not a "contact sport" as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: The State admits this Request.

REQUEST NO. 19: Admit that cross country is not a "contact sport" as that phrase is used in 34 C.F.R. § 106.41(b).

RESPONSE: The State admit this Request.

REQUEST NO. 20: Admit that, but for the injunction issued in this case (Dkt. 67), Plaintiff B.P.J. would not have been permitted to be a member of Bridgeport Middle School's girls' cross-country team in 2021 because of H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: The State objects to this Request relative to the terms “permitted” and “because of.” Further responding, the State admits that H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)) directs that biological males, such as B.P.J., are not eligible to be members of any athletic teams designated for females, such as Bridgeport Middle School’s girls’ cross-country team.

REQUEST NO. 21: Admit that, but for the injunction issued in this case (Dkt. 67), Plaintiff B.P.J. would not be permitted to be a member of any girls’ athletic team offered at Bridgeport Middle School because of H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)).

RESPONSE: The State objects to this Request relative to the terms “permitted” and “because of.” Further responding, the State admits that H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(2)) directs that biological males, such as B.P.J., are not eligible to be members of any athletic teams designated for females, including girls’ athletic teams offered at Bridgeport Middle School.

REQUEST NO. 22: Admit that H.B. 3293 prohibits Plaintiff B.P.J. from participating on girls’ athletic teams at all public secondary schools located in West Virginia.

RESPONSE: The State admits this Request.

REQUEST NO. 23: Admit that the State Board of Education and the State Superintendent must comply with H.B. 3293 unless enjoined from doing so by a court.

RESPONSE: The State admits this Request.

REQUEST NO. 24: Admit that H.B. 3293 prohibits the State Board of Education and the State Superintendent from adopting or enforcing a policy that would allow B.P.J. to participate on girls’ athletic teams at Bridgeport Middle School.

RESPONSE: The State denies that H.B. 3293 contains an express prohibition to this effect, but, responding further, admits that the State Board and State Superintendent must comply with the statute.

REQUEST NO. 25: Admit that the Harrison County Board of Education and the Harrison County School Superintendent must comply with H.B. 3293 unless enjoined from doing so by a court.

RESPONSE: The State admits this Request.

REQUEST NO. 26: Admit that H.B. 3293 prohibits the Harrison County Board of Education and the Harrison County Superintendent from adopting or enforcing a policy that would allow B.P.J. to participate on girls’ athletic teams at Bridgeport Middle School.

RESPONSE: The State denies that H.B. 3293 contains an express prohibition to this effect, but, responding further, admits that the County Board and Harrison County Superintendent must comply with the statute.

REQUEST NO. 27: Admit that the West Virginia Secondary School Athletic Commission must comply with H.B. 3293 unless enjoined from doing so by a court.

RESPONSE: The State admits this Request.

REQUEST NO. 28: Admit that H.B. 3293 prohibits the West Virginia Secondary School Athletic Commission from adopting or enforcing a policy that would allow B.P.J. to participate on girls' athletic teams at Bridgeport Middle School.

RESPONSE: The State denies that H.B. 3293 contains an express prohibition to this effect, but, responding further, admits that the West Virginia Secondary School Activities Commission must comply with the statute.

REQUEST NO. 29: Admit that there are no athletic teams designated as "coed or mixed," as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), offered at Bridgeport Middle School.

RESPONSE: The State denies this Request based on the testimony of the County Board that some teams are coed or mixed.

REQUEST NO. 30: Admit that there are no athletic teams designated as "coed or mixed," as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), that compete interscholastically offered at any public secondary school located in West Virginia.

RESPONSE: The State denies this Request based on the testimony of the West Virginia Secondary Schools Activities Commission that some teams are coed or mixed.

REQUEST NO. 31: Admit that there are no cross-country teams designated as "coed or mixed," as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), that compete interscholastically offered by any member school of the West Virginia Secondary School Activities Commission.

RESPONSE: The State denies this Request for lack of knowledge. This information is not within the knowledge of the State. The State understands that the Plaintiff is seeking this information directly from the State Board and West Virginia Secondary School Activities Commission, which are in a position to respond to this inquiry.

REQUEST NO. 32: Admit that there are no athletic leagues designated as "coed or mixed," as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), that comprise teams from more than one school supervised by the West Virginia Secondary School Activities Commission.

RESPONSE: The State denies this Request for lack of knowledge. This information is not within the knowledge of the State. The State understands that the Plaintiff is seeking this information directly from the State Board and West Virginia Secondary School Activities Commission, which are in a position to respond to this inquiry.

REQUEST NO. 33: Admit that there are no athletic teams designated as “coed or mixed,” as that phrase is used in H.B. 3293 (codified at Code of West Virginia §18-2-25d(c)(1)(C)), that compete interscholastically offered by any public secondary school under the supervision of the West Virginia State Board of Education.

RESPONSE: The State denies this Request based on the testimony of the West Virginia Secondary Schools Activities Commission that some teams are coed or mixed.

REQUEST NO. 34: Admit that H.B. 3293 does not prohibit a cisgender girl student at Bridgeport Middle School from joining a girls’ athletic team offered at Bridgeport Middle School.

RESPONSE: The State objects as the terms utilized in this Request are not included in H.B. 3293, and therefore the State denies this Request. Without waiver of the foregoing, the State admits that H.B. 3293 does not prohibit a biological girl student at Bridgeport Middle School from joining a girls’ athletic team offered at Bridgeport Middle School.

REQUEST NO. 35: Admit that H.B. 3293 does not prohibit a cisgender girl student at any public secondary school in West Virginia from joining a girls’ athletic team offered by her public secondary school.

RESPONSE: The State objects as the terms utilized in this Request are not included in H.B. 3293, and therefore the State denies this Request. Without waiver of the foregoing, the State admits that H.B. 3293 does not prohibit a biological girl student at any secondary school in West Virginia from joining a girls’ athletic team offered at the public secondary school where such biological girl attends.

REQUEST NO. 36: Admit that H.B. 3293 prohibits a Bridgeport Middle School transgender girl student from joining a girls’ athletic team offered at Bridgeport Middle School.

RESPONSE: The State objects to this Request as H.B. 3293 does not use the term “transgender girl,” and therefore the State denies this Request. Without waiver of the foregoing, the State admits that H.B. 3293 prohibits a biological boy attending Bridgeport Middle School from joining a girls’ athletic team offered at Bridgeport Middle School.

REQUEST NO. 37: Admit that H.B. 3293 prohibits any transgender girl secondary school student located in West Virginia from joining a girls’ athletic team offered by her public secondary school.

RESPONSE: The State objects to this Request as H.B. 3293 does not use the term “transgender girl,” and therefore the State denies this Request. Without waiver of the foregoing, the State admits that H.B. 3293 prohibits a biological boy attending a secondary school in West Virginia from joining a girls’ athletic team offered at the school where such biological boy attends.

REQUEST NO. 38: Admit that prior to the enactment of H.B. 3293, cisgender boy students at Bridgeport Middle School were prohibited from joining girls' athletic teams offered at Bridgeport Middle School.

RESPONSE: The State objects to this Request as it appears to seek a legal opinion on the legal question of whether a biological boy was permitted to participate on a girls' athletic team under West Virginia law prior to the enactment of H.B. 3293. The following cases may contain legal analysis which may have been used to address this issue: *Gregor v. W. Virginia Secondary Sch. Activities Comm'n*, No. 2:20-CV-00654, 2020 WL 5997057, at *1 (S.D.W. Va. Oct. 9, 2020); *Israel by Israel v. W. Virginia Secondary Sch. Activities Comm'n*, 182 W. Va. 454, 388 S.E.2d 480 (1989). Further objecting. Accordingly, the State denies this Request.

REQUEST NO. 39: Admit that prior to the enactment of H.B. 3293, a cisgender boy student at any public secondary school in West Virginia was prohibited from joining girls' athletic teams offered at his public secondary school.

RESPONSE: The State objects to this Request as it appears to seek a legal opinion on the legal question of whether a biological boy was permitted to participate on a girls team under West Virginia law prior to the enactment of H.B. 3293. The following cases may contain legal analysis which may have been used to address this issue: *Gregor v. W. Virginia Secondary Sch. Activities Comm'n*, No. 2:20-CV-00654, 2020 WL 5997057, at *1 (S.D.W. Va. Oct. 9, 2020); *Israel by Israel v. W. Virginia Secondary Sch. Activities Comm'n*, 182 W. Va. 454, 388 S.E.2d 480 (1989). Further objecting, this seeks the answer to a hypothetical question. Accordingly, the State denies this Request.

REQUEST NO. 40: Admit that prior to the enactment of H.B. 3293, you are not aware of any transgender student athlete participating on an athletic team offered by Bridgeport Middle School.

RESPONSE: To the extent that the State is capable of having "awareness," the State admits that, prior to the enactment of H.B. 3293, the State was not aware of any biological male students claiming to identify as female, any biological female students claiming to identify as male, or any students describing themselves as "transgender" participating on an athletic team offered by Bridgeport Middle School.

REQUEST NO. 41: Admit that prior to the enactment of H.B. 3293, you are not aware of any transgender student athlete participating on an athletic team offered by a public secondary school in West Virginia.

RESPONSE: To the extent that the State is capable of having "awareness," the State admits that, prior to the enactment of H.B. 3293, the State was not aware of any biological male students claiming to identify as female, any biological female students claiming to identify as male, or any students describing themselves as "transgender" participating on an athletic team offered by a public secondary school in West Virginia.

REQUEST NO. 42: Admit that other than Plaintiff B.P.J., you are not aware of a transgender student athlete participating on an athletic team offered by Bridgeport Middle School.

RESPONSE: To the extent that the State is capable of having “awareness,” the State admits that, other than Plaintiff B.P.J., it is not aware of any biological male students claiming to identify as female, any biological female students claiming to identify as male, or any students describing themselves as “transgender” participating on an athletic team offered by Bridgeport Middle School.

REQUEST NO. 43: Admit that other than Plaintiff B.P.J., you are not aware of a transgender student athlete participating on an athletic team offered by a public secondary school in West Virginia.

RESPONSE: To the extent that the State is capable of having “awareness,” the State admits that, other than Plaintiff B.P.J., it has no awareness of any biological male students identifying as female, any biological female students identifying as male, or any students describing themselves as “transgender” participating on an athletic team offered by a public secondary school in West Virginia.

REQUEST NO. 44: Admit that students derive social benefits from participation on athletic teams offered by public secondary schools in West Virginia.

RESPONSE: The State objects to this Request as it is vague, overbroad and speculative in that it seeks to include all students and the State would have to speculate as to whether any or all students “derive social benefits” and what are “social benefits.” Without waiver of the foregoing, the State states that it is likely that some students who participate in athletic teams feel that they have benefited in some fashion or fashions and it is likely that some students who participate in athletic teams feel that they have not so benefited.

REQUEST NO. 45: Admit that students derive psychological benefits from participation on athletic teams offered by public secondary schools in West Virginia.

RESPONSE: The State objects to this Request as it is vague, overbroad and speculative in that it seeks to include all students and the State would have to speculate as to whether any or all students “derive psychological benefits” and what are “psychological benefits.” Without waiver of the foregoing, the State states that it is likely that some students who participate in athletic teams feel that they have benefited in some fashion or fashions and it is likely that some students who participate in athletic teams feel that they have not so benefited.

REQUEST NO. 46: Admit that interscholastic athletic competition benefits middle school students.

RESPONSE: The State objects to this Request as it is vague, overbroad and speculative in that it seeks to include all students and what constitutes a benefit for students. Further, the State would have to speculate as to whether it benefits any or all middle school students. Without waiver of the foregoing, the State states that it is likely that interscholastic athletic competition benefits some middle school students in some fashion or fashions but also may not benefit other students.

REQUEST NO. 47: Admit that middle school students who participate in interscholastic athletics receive benefits regardless whether they win or lose.

RESPONSE: The State objects to this Request as it is vague, overbroad and speculative in that it seeks to include all participating students and what constitutes a benefit for students. Each student would likely have an opinion unique to that student. Further, the State would have to speculate as to the answer for each and every child. Further objecting, the terms “win” or “lose” are somewhat vague and may or may not apply to all athletic situations. Without waiver of the foregoing, the State states that it is likely that some middle school students who participate in interscholastic athletics feel that they receive benefits regardless whether they outright “win” or “lose” and that others do not.

Respectfully,

STATE OF WEST VIRGINIA,

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Motivational climate and goal orientations as predictors of perceptions of improvement, satisfaction and coach ratings among tennis players

Article in *Scandinavian Journal of Medicine and Science in Sports* · January 2000

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Motivational climate and goal orientations as predictors of perceptions of improvement, satisfaction and coach ratings among tennis players

Balaguer I, Duda JL, Crespo M. Motivational climate and goal orientations as predictors of perceptions of improvement, satisfaction and coach ratings among tennis players.

Scand J Med Sci Sports 1999; 9: 381–388. © Munksgaard, 1999

One purpose of this work was to study the relationship of goal orientations and the perceived motivational climate created by the coach in relation to 219 competitive Spanish tennis players: a) perceived improvement in different facets of the game, b) satisfaction with their competitive results, overall level of play, and coach, and c) ratings of their coach. The second purpose was to examine whether the dependent variables were best predicted by the perceived situationally emphasized goal structure created by the coach and/or the athletes' dispositional goal perspective. Intermediate (N=70), advanced (N=124), and professional (N=25) level players completed Spanish versions of the TEOSQ and the PMCSQ-2 and items assessing perceived improvement specific to tennis, satisfaction and coach ratings. The results were consistent with the tenets of goal perspective theory and provide further support for the promotion of a task-involving atmosphere in sport.

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Key words: motivational climate; goal orientations; performance improvement; coaching; tennis

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During this past decade, goal perspective theory (1–3) has played an important role in the study of achievement motivation in sport (4–6). This theory holds that there are two primary goal perspectives operating in this achievement activity (namely, task and ego involvement), which relate to different ways of defining success and judging one's competence. When task-involved, perceived ability is self-referenced and emphasis is placed on task mastery, the exertion of effort, and development of one's skills or knowledge of the activity. When ego-involved, individuals are concerned with demonstrating normatively referenced high ability and, thus, perceive a successful event when they think that they have surpassed others or performed equally with less effort.

Researchers (1–3) suggest that social situations created by significant others (such as teachers, coaches, parents) can impact the probability of whether an athlete will be task- or ego-involved when she participates in sport. Environments that are highly competitive (within and between teams) entail the public

evaluation of skills, emphasize normatively based feedback which favors the highly able, and/or are punitive when mistakes are made are more likely to be perceived as ego-involving (7, 8). In contrast, situations emphasizing effortful involvement over outcome, personal improvement, and collective contributions tend to be viewed as task-involving.

It is assumed that whether an athlete is task- and/or ego-involved in sport is also impacted by dispositional goal perspectives or her/his degree of task and ego orientation. According to Nicholls (3), these "individual differences in proneness to the different types of involvement" (p. 95) are orthogonal and sport research has supported his assertion (6).

The literature to date suggests that an examination of goal perspectives (whether operationalized as dispositional goal orientations, and/or the perceived motivational climate) provides insight into variations in the motivational processes of individuals involved in athletic activities. For example, task and ego orientations have been found to differentially predict ath-

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letes' perceptions of the purposes of sport, beliefs about the causes of success, enjoyment of and interest in the activity, sportspersonship attitudes, participation motives, and anxiety and coping strategies in a conceptually consistent manner (6, 9, 10). Further, perceptions of the motivational environment operating on sport teams have been linked to variability in enjoyment, satisfaction with team membership, intrinsic motivation, beliefs about the determinants of success, self-efficacy, and perceived functions of sport participation (6). In general, and consistent with theoretical tenets (1–3), this work has indicated that a focus on task-involved goals is associated with adaptive motivation-related cognitions, emotional responses, and beliefs in the sport context (5).

Less attention, however, has been given to examining the potential impact of goal perspectives on performance and other variables fundamental to persistence in sport and physical activities (6). This is particularly true in the context of skilled athletic performance (11). Currently, in the goal perspective literature, there is an interesting debate regarding whether the motivation-related advantages of task involvement (and disadvantage of ego involvement) hold for samples including elite competitors (11–13). One purpose of this study was to extend previous work and examine the relationship of the perceived motivational climate created by the coach and dispositional goal orientations to intermediate, advanced, and professional level tennis players': 1) perceived improvement in the technical, tactical, physical and psychological facets of their tennis performance, 2) satisfaction with their recent competitive results, level of play, and degree of individualized training provided by their coach, and 3) ratings of their coach in reference to an ideal (preferred) coach and the importance of the coach with respect to the athlete's learning and improvement. These variables would be critical if we are interested in the likelihood of skilled athletes staying with a particular coach and the probability of their persisting and improving in the sport in question.

This study also examined the degree to which the dependent variables of interest were a function of dispositional goal orientations, the perceived situational goal structure, or both factors. Duda and Nicholls (14) have argued that, as these variables are more dispositional and stable in nature, overall attitudes toward and views about sport will primarily be predicted by athletes' goal orientations. Perceptions and cognitive responses tied to the sport context at hand (or, especially in the case of younger athletes; 15) are expected to be best predicted by the perceived motivational climate operating in the particular athletic context. Cognizant of Duda and Nicholls' (14) suggestions and recognizing that the current sample was composed of adolescents, we hypothesized that vari-

ations in perceptions of the motivational climate would emerge as the best predictor of indices of perceived improvement, satisfaction, and coach ratings examined in this study. More specifically, we expected that the tennis players would perceive greater improvement in dimensions of their game, be more satisfied with their results, level of play and coach's individualized training, indicate a greater preference for their coach, and rate their coach as more important in the athletes' development when the atmosphere created by their coach is deemed more task-involving.

Method

Sample. A total of 219 tennis players (73 female and 116 male) from clubs throughout Spain participated voluntarily in this study. Their mean age was 15.6 ± 2.1 years and mean years of tennis experience was 7.3 ± 2.7 years. The subjects ranged in skill level representing the intermediate (32.1%), advanced (56.6%), and professional (11.3%) levels of tennis competition.

Assessments and procedure. In the training setting, the subjects were given (by the third author or a trained assistant) a multi-section inventory containing measures of the perceived situationally emphasized goal perspective in their training environment, goal orientations, and items assessing perceived improvement specific to tennis, satisfaction and coach ratings. The inventory took approximately 30 min to complete.

Situational goal perspectives. The players responded to a Spanish version (16) of the Perceived Motivational Climate in Sport Questionnaire (7, 17) specific to tennis. The instrument contained 23 items examining the degree to which the climate created by the coach was deemed to be more or less task- and ego-involving. Each item was preceded by the stem "In my training group or team". Mean scale scores for the task- and ego-involving climate scales were calculated.

Goal orientations. The Spanish version (18) of the Task and Ego Orientation in Sport Questionnaire (19) was used to assess the tennis players' dispositional proneness for task and ego involvement in their sport. In previous work, this instrument was found to exhibit acceptable factorial validity and internal reliability. When completing the Spanish version of the TEOSQ, subjects were requested to think of when they felt most successful in tennis. Mean scale scores were calculated for both the task and ego orientation scales.

Perceived improvement, satisfaction, and coach ratings. The tennis players' evaluation of their personal level of improvement in the technical, tactical, physical, and psychological aspects of the game and overall results was examined. The areas of improvement

Motivational climate in tennis

Table 1. Descriptive statistics (M, SD and range for all the variables)

	M	SD	Range
Motivational climate			
Task-involving	3.99	0.55	2.45–5
Ego-involving	2.62	0.70	1.09–5
Goal orientations			
Task orientation	4.32	0.57	2–5
Ego orientation	3.26	0.86	1–5
Perceived improvement:			
Technical	5.77	0.96	1–7
Tactical	5.37	1.00	2–7
Physical	5.50	1.23	1–7
Psychological	4.98	1.33	1–7
Satisfaction with:			
Results this year	4.45	1.57	1–7
Level of play	4.85	1.37	1–7
The coach	5.66	1.39	1–7
Coach ratings:			
Coach like I want to have	3.93	0.89	1–5
Importance of coach in training process	4.42	0.76	2–5

were evaluated on a 7-point Likert scale ranging from 1="I have gotten worse" to 7="I have gotten much better." The athletes' level of satisfaction with their competitive results during the current year, level of play, and degree of individualized instruction provided by their coach was indicated on a 7-point Likert scale ranging from 1="very dissatisfied" to 7="very satisfied." In regard to the tennis players' opinion of his/her coach, each athlete rated: a) whether his/her current coach is like the one the athlete would prefer to have (responses were provided on a 5-point Likert scale ranging from 1="doesn't coincide at all with the coach I would like to have" to 7="is my ideal coach") and b) the perceived importance of the coach in regard to the athlete's learning and improvement (responses were provided on a 5-point Likert

scale ranging from 1="not important at all" to 5="extremely important").

Results

The descriptive statistics for each of the variables assessed in this study are presented in Table 1. The tennis players, as a group, perceived the motivational climate on their team /in their training group to be highly task-involving. They also endorsed task-oriented goals in tennis. In general, the athletes felt that they were improving in their game, especially in regard to the technical aspects. They were satisfied with their competitive results, level of play and, in particular, the degree of individualized training provided by their coach and rated this individual in a positive manner overall.

Simple correlations (Table 2) indicated that tennis players who perceived that their coaches created a more task-involving environment also perceived they had improved in regard to the tactical, technical and psychological facets of their game. Perceptions of a task-involving environment were also significantly and positively associated with satisfaction with one's coach, level of play and match results. On the other hand, a perceived ego-involving environment was linked to greater dissatisfaction with the coach and positively correlated to reported satisfaction with level of play (Table 2). In regard to the coach ratings, when tennis players viewed their training/team environment as more task-involving, they also perceived that their coach was like the one they would prefer to have and felt their coach played a significant role in their learning and improvement. The coach rating variables were significantly and negatively correlated with perceptions of an ego-involving climate.

Task orientation was positively correlated with reported satisfaction with the individualized teaching

Table 2. Simple correlations between perceptions of the motivational climate and goal orientations with perceived improvement, satisfaction and coach ratings

	Climate		Orientation	
	Task	Ego	Task	Ego
Perceived improvement:				
Technical	0.14*	-0.10	0.05	-0.01
Tactical	0.13*	-0.03	0.11	-0.01
Physical	0.02	0.07	0.11	0.08
Psychological	0.26***	-0.05	0.09	0.06
Satisfaction with:				
Results this year	0.23**	-0.16*	0.14*	0.00
Level of Play	0.23**	0.13*	0.12	0.03
The coach	0.41***	-0.41***	0.25***	-0.02
Coach ratings:				
Coach like I want to have	0.32***	-0.33***	0.26***	-0.05
Importance of coach in training process	0.32***	-0.35***	0.39***	0.03

* $P < 0.05$; ** $P < 0.005$; *** $P < 0.001$.

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and support provided by one's coach and competitive results (Table 2). When tennis players endorsed a strong task orientation, they were also more likely to indicate that their coach is like the one they would prefer to have and is more important in terms of their development in tennis.

In order to determine whether indices of perceived individual improvement, satisfaction, and ratings of the coach were best predicted by dispositional goal orientations (i.e., task and ego orientation), perceptions of the motivational climate (i.e., perceived task-involving and ego-involving climate), or both factors, we performed a series of hierarchical stepwise regressions. In the first analysis, dispositional goal orientations (task and ego) were entered in Step 1 of the regression equation and motivational climate (task climate and ego climate) was entered in Step 2. A subsequent hierarchical stepwise procedure entered the perceived motivational climate in Step 1 and dispositional goal orientations in Step 2.

Subjective performance

As shown in Table 3, perceptions of the motivational climate emerged as a significant predictor of psychological improvement regardless of which step this variable was entered in the regression analysis. More specifically, perceptions of a task-involving training environment (created by the coach) corresponded to greater perceived improvement in the psychological facets of one's tennis game. The amount of variance accounted for, however, was limited (7%). Goal orientations did not emerge as significant predictors of any of the indices of subjective performance.

Level of satisfaction

With respect to the satisfaction variables, the perceived motivational climate emerged as the major predictor. Although the percentage of variance accounted for was low (5–6%), perceptions of a task-

Table 3. Percentage of variance accounted for in indices of perceived improvement

Step	Variable	Beta	RsQCh	RsQCu	F-value	P
Technical						
1	Ego orientation	–0.01				
	Task orientation	–0.07	0.00	0.00	0.12	0.88
2	Ego climate	–0.03				
	Task climate	0.18	0.02	0.02	2.50	0.08
1	Ego climate	–0.03				
	Task climate	0.18	0.02	0.02	2.28	0.10
2	Ego orientation	–0.01				
	Task orientation	–0.07	0.00	0.02	0.36	0.70
Tactical						
1	Ego orientation	–0.01				
	Task orientation	0.06	0.01	0.01	0.87	0.42
2	Ego climate	0.01				
	Task climate	0.07	0.00	0.01	0.36	0.69
1	Ego climate	0.01				
	Task climate	0.07	0.01	0.01	0.99	0.37
2	Ego orientation	–0.01				
	Task orientation	0.06	0.00	0.01	0.25	0.78
Physical						
1	Ego orientation	0.04				
	Task orientation	0.12	0.01	0.01	1.34	0.26
2	Ego climate	0.09				
	Task climate	–0.02	0.01	0.02	0.76	0.47
1	Ego climate	0.09				
	Task climate	–0.02	0.01	0.01	0.80	0.45
2	Ego orientation	0.04				
	Task orientation	0.12	0.01	0.02	1.30	0.28
Psychological						
1	Ego climate	0.07				
	Task orientation	–0.08	0.01	0.01	1.19	0.31
2	Ego climate	–0.00				
	Task orientation	0.30	0.07	0.08	7.24	0.001
1	Ego climate	0.00				
	Task orientation	0.30	0.07	0.07	7.77	0.001
2	Ego climate	0.07				
	Task orientation	–0.08	0.01	0.08	0.76	0.47

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Table 4. Percentage of variance accounted for the indices of satisfaction and coach ratings among tennis players

Step	Variable	Beta	RsQCh	RsQCu	F-value	P
Satisfaction with results						
1	Ego orientation	0.02				
	Task orientation	0.04	0.03	0.03	2.64	0.07
2	Ego climate	-0.13				
	Task climate	0.16	0.04	0.07	4.02	0.02
1	Ego climate	-0.13				
	Task climate	0.16	0.06	0.06	6.59	0.00
2	Ego orientation	0.02				
	Task orientation	0.04	0.00	0.06	0.20	0.82
Satisfaction with level of play						
1	Ego orientation	0.04				
	Task orientation	-0.03	0.01	0.01	1.11	0.33
2	Ego climate	-0.08				
	Task climate	0.22	0.05	0.06	4.76	0.01
1	Ego climate	-0.08				
	Task climate	0.22	0.05	0.05	5.74	0.00
2	Ego orientation	0.04				
	Task orientation	-0.03	0.00	0.05	0.21	0.81
Satisfaction with the coach						
1	Ego orientation	0.07				
	Task orientation	0.03	0.08	0.08	8.31	0.00
2	Ego climate	-0.34				
	Task climate	0.28	0.18	0.26	24.42	0.00
1	Ego climate	-0.34				
	Task climate	0.28	0.26	0.26	34.04	0.00
2	Ego orientation	0.07				
	Task orientation	0.03	0.01	0.27	0.75	0.47
Coach I prefer						
1	Ego orientation	-0.00				
	Task orientation	0.12	0.09	0.09	9.40	0.00
2	Ego climate	-0.26				
	Task climate	0.17	0.09	0.18	11.03	0.00
1	Ego climate	-0.27				
	Task climate	0.17	0.17	0.172	20.19	0.00
2	Ego orientation	-0.00				
	Task orientation	0.12	0.01	0.18	1.16	0.31
Importance of coach in training						
1	Ego orientation	0.07				
	Task orientation	0.25	0.15	0.15	17.60	0.00
2	Ego climate	-0.25				
	Task climate	0.13	0.07	0.22	8.94	0.00
1	Ego climate	-0.25				
	Task climate	0.13	0.17	0.17	20.16	0.00
2	Ego orientation	0.07				
	Task orientation	0.25	0.05	0.22	6.64	0.00

involving climate positively related to greater satisfaction with one's competitive tennis results and level of play (Table 4). An examination of the beta weight indicated that perceptions of ego climate were negatively associated with satisfaction with one's match results. In terms of the tennis players' degree of satisfaction with the degree of individualized training provided by their current coach, greater satisfaction was positively linked to perceptions of a task-involving environment and negatively related to a perceived ego-involving atmosphere ($R^2=.18-.26$).

Ratings of the coach

Motivational climate, mainly a perceived ego-involving environment, emerged as the primary predictor of the ratings of the coach (Table 4). The variance accounted for (17%) was considered statistically significant and meaningful (20). In relation to the conceptualization of their coach as an ideal one, tennis players revealed a greater preference for their present coach if their coach-created training environment was high in task-involving features and low in its ego-in-

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volving characteristics. Moreover, when the climate was more task-involving and less ego-involving, the athletes rated their coach as being more significant to their development in tennis (i.e., their learning and improvement). Goal orientations also emerged as a significant predictor of the players' ratings of whether their current coach is like the one they would prefer to have and the importance of the coach in regard to their tennis. In this case, task orientation was positively related to the players' evaluations of their coach.

Discussion

A major focus of this research was to determine whether variations in dispositional and situational goal perspectives correspond to tennis players' estimations of the growth in their game and attitudes toward their coach in a conceptually consistent manner. Perceptions of the motivational climate were primarily linked to the indices of subjective performance. However, the perceived situational goal structure emerged as a significant predictor of perceived improvement in the psychological dimension only. In particular, when the environment created by the coach was deemed more task-involving, the tennis players felt that they were progressing more in the psychological facet of their game. This result is consistent with previous work which has found an emphasis on task goals to be positively associated with the reported salience of mental skills training, the amount of practice of mental skills, and the use of mental skills to counter performance-related stress among intercollegiate athletes (21, 22).

The tennis players' reported satisfaction with their competitive results for the year and current level of play was negatively associated with a perceived ego-involving climate and, in particular, positively associated with perceptions of a task-involving atmosphere. These findings make sense if we consider the characteristics and motivational implications of an environment which is viewed as being more task-involving and less ego-involving. Such a coach-created climate should promote more task involvement among the tennis players which, in turn, means that they will be more self-referenced and mastery-focused in how they conceive their ability and judge success. As task-involved conceptions of ability and subjective success are more within the athlete's personal control, such a perspective should foster a more positive outlook on one's competitive record as well as the athlete's current performance level.

When entered first in the regression analysis, perceptions of the motivational climate accounted for a significant amount of variance in the tennis players' satisfaction with the degree of individualized instruction exhibited by their coach. More specifically, when

the environment created by the coach was deemed more task-involving and less ego-involving, the athletes were more satisfied with the amount of teaching and personalized treatment they were receiving. This result is in agreement with recent work by Balaguer et al. (23), who found that athletes felt that their coaches *engaged* in more teaching and instruction and provided greater social support when they viewed the motivational climate as promotive of task involvement. The present finding also is compatible with the work of Smith and colleagues (24, 25). They demonstrated that athletes who played for coaches who had undergone coach effectiveness training (CET) (and, thus, instructed to use more positive reinforcement, provide less punishment and do more teaching) rated their coaches as better teachers and indicated a greater desire to play for such coaches than control group athletes. Chaumeton and Duda (26) have argued that the principles of CET are endemic to a task-involving motivational climate.

In a similar vein, the perceived motivational atmosphere induced by the coach also emerged as the best predictor of the tennis players' degree of preference for their present coach. That is, when the athletes deemed the atmosphere to be more task-involving, and especially, less ego-involving, they reported that their current coach was closer to their "ideal" coach.

If entered before dispositional goal perspectives, perceptions of the motivational climate accounted for more variance in the athletes' rating of the significance of the coach to their learning and performance improvement. Once again, a more positive evaluation was tied to a perceived coach-created environment which is stronger in its task-involving features and less pronounced in its ego-involving attributes. However, dispositional goal orientations (namely, task orientation) added significant variance in the prediction of the tennis players' appraisal of the coach's importance to their progress in tennis. This finding is consonant with research by Walling and Duda (27) in the physical education (PE) context. They reported a link between task orientation and the belief that having an effective PE teacher is an important determinant of students' success.

The adopted goal perspective in achievement situations is presumed to be dependent on individual differences in proneness to task and ego involvement as well as the situational goal structure at hand. Whether the person or situational dimension is most salient depends on a number of factors, such as the contextual-specificity of the variables being predicted and age group sampled. In accordance with the suggestions of Duda and Nicholls (14) and Treasure and Roberts (15), it was hypothesized that perceptions of the motivational climate would emerge as the major predictor of the current sample of tennis players' perceived performance improvement in tennis, satisfac-

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tion with how one is doing in tennis, and contentment with and the evaluation of one's tennis coach. In general, the present findings supported this hypothesis (although limited support emerged for the indices of subjective performance). Only in the case of the athletes' rating of the relevance of the coach to the athletes' training and development did dispositional goal perspectives also emerge as a significant, albeit less important, predictor. The latter result can be explained by the observation that this particular variable seemed to encompass a belief (i.e., that a coach's contribution is pertinent to one's achievement in a sport) as well as a situation-specific evaluation (i.e., I am satisfied with my coach's influence on my tennis development). Beliefs have been found to be more closely associated with dispositional differences in goal perspectives than perceptions of the prevailing motivational atmosphere operating in one's sport (e.g., 7, 14).

The overall results concerning the superior prediction provided by perceptions of the motivational climate have important applied implications. Recent research (28) has indicated that the situationally emphasized goal structure can be modified in sport and that such interventions have a theoretically consonant effect on indices of motivation. It is reasonable to assume that it is easier to alter situational in contrast to dispositional goal perspectives. That is, we would expect that there is a need to change the former to impact the latter over time (3, 5, 9).

It should be noted, however, that perceptions of the motivational climate and goal orientations captured a limited amount of variance in facets of performance improvement ($R^2=.01-.07$) and reported satisfaction with match results and personal level of play ($R^2=.05-.06$). It appears that other factors, besides dispositional and situationally emphasized goal perspectives, influence subjective ratings of performance and satisfaction with competitive outcomes and one's tennis play among the present sample of athletes (e.g., the athlete's objective level of tennis talent, and the difficulty of the competition the athlete has faced).

Situationally emphasized goals were a better predictor of the three items which related to the coach ($R^2=.17-.26$) than the other dependent variables examined in this study. As suggested above, we would expect a greater interdependence between athletes' perceptions of the goal perspectives manifested at the contextual level and their evaluation of the major determinant of that climate, namely the coach.

As a whole, the present findings are in accordance with the tenets of goal perspective theory (1-3) and previous sport research (5, 9, 10), and provide further support regarding the motivational advantages of a task-involving atmosphere. Some researchers have argued that the promotion of task involvement (and curtailing of ego involvement) may not be an appropriate

strategy at the higher levels of athletic competition (11), while others, such as Pensgaard and Roberts (29) in their work involving Norwegian Olympic athletes, have noted the adaptive qualities of a task-involving climate. This study's results suggest that climates which are more task-involving and less ego-involving may be more beneficial for skilled athletes (at least in their own minds). Slightly over two-thirds of the current sample were at the advanced level of tennis proficiency or beyond. It should be noted that MANOVA revealed no differences in the variables of interest in this study as a function of competitive level. Further, the observed relationships between perceptions of the motivational climate, goal orientations, and the items assessing perceived improvement, satisfaction, and coach ratings did not significantly vary among the intermediate, advanced, and professional level tennis players.

In future research, it would be interesting to examine the predictive utility of dispositional and contextual goals to current *and* subsequent objective indices of competitive performance (11) among such skilled groups of athletes. Additionally, subsequent work might look at the capacity for perceptions of the motivational climate and goal orientations to discriminate between those younger, talented athletes who continue to participate and move up the competitive ladder and those who do not (30).

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Scientific Statement

Considering Sex as a Biological Variable in Basic and Clinical Studies: An Endocrine Society Scientific Statement

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Abbreviations: ACTH, adrenocorticotrophic hormone; AT₂R, angiotensin type 2 receptor; BMI, body mass index; cAMP, cyclic adenosine monophosphate; CKD, chronic kidney disease; CRF, corticotropin-releasing factor; CVD, cardiovascular disease; dMRI, diffusion magnetic resonance imaging; fMRI, functional magnetic resonance imaging; FCG, Four Core Genotypes (model); GMV, gray matter volume; GPCR, G-protein coupled receptor; HPA, hypothalamic-pituitary-adrenal; KYN, kynurenine; LC, locus coeruleus; MIH, Müllerian inhibitory hormone; PAR, pseudoautosomal region; PKA, protein kinase A; PTSD, posttraumatic stress disorder; RAAS, renin-angiotensin-aldosterone system; rs-fMRI, resting state functional magnetic resonance imaging; sMRI, structural magnetic resonance imaging; UCN, urocortin.

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Abstract

In May 2014, the National Institutes of Health (NIH) stated its intent to “require applicants to consider sex as a biological variable (SABV) in the design and analysis of NIH-funded research involving animals and cells.” Since then, proposed research plans that include animals routinely state that both sexes/genders will be used; however, in many instances, researchers and reviewers are at a loss about the issue of sex differences. Moreover, the terms *sex* and *gender* are used interchangeably by many researchers,

further complicating the issue. In addition, the sex or gender of the researcher might influence study outcomes, especially those concerning behavioral studies, in both animals and humans. The act of observation may change the outcome (the “observer effect”) and any experimental manipulation, no matter how well-controlled, is subject to it. This is nowhere more applicable than in physiology and behavior. The sex of established cultured cell lines is another issue, in addition to aneuploidy; chromosomal numbers can change as cells are passaged. Additionally, culture medium contains steroids, growth hormone, and insulin that might influence expression of various genes. These issues often are not taken into account, determined, or even considered. Issues pertaining to the “sex” of cultured cells are beyond the scope of this Statement. However, we will discuss the factors that influence sex and gender in both basic research (that using animal models) and clinical research (that involving human subjects), as well as in some areas of science where sex differences are routinely studied. Sex differences in baseline physiology and associated mechanisms form the foundation for understanding sex differences in diseases pathology, treatments, and outcomes. The purpose of this Statement is to highlight lessons learned, caveats, and what to consider when evaluating data pertaining to sex differences, using 3 areas of research as examples; it is not intended to serve as a guideline for research design.

Key Words: brain-gut, cardiovascular disease, chromosome complement, gender, sex differences, steroid hormones

Sex is an important biological variable that must be considered in the design and analysis of human and animal research. The terms *sex* and *gender* should not be used interchangeably. Sex is dichotomous, with sex determination in the fertilized zygote stemming from unequal expression of sex chromosomal genes. By contrast, gender includes perception of the individual as male, female, or other, both by the individual and by society; both humans and animals have sex, but only humans have gender. Both sexes produce estrogens, androgens, and progestins; there are no male- or female-specific sex hormones, *per se*, although these steroids are present in substantially different levels in males and females. Sex differences are caused by 3 major factors—sex hormones, genes, and environment. To understand disease mechanisms and exploit sex differences in protection or exacerbation of diseases, one needs to determine the relative contribution of factors, including observer effect (1), causing sex differences. Here—using 3 broad research areas as examples—the roles of sex differences in brain anatomy, brain-gut axis, and cardiovascular disease are discussed. Contemporary brain imaging methods show age- and sex-related differences in brain size, global and regional gray matter volume, white matter connectivity, and neuroanatomic regulation of appetite and satiety; while these differences are seen in large population-based studies, there is tremendous individual overlap, but such group-level findings do not inform findings, physiology, or pathology at the individual level. Sex differences in disorders of the brain-gut axis, obesity, type 2 diabetes,

and metabolic syndrome are caused by differential actions of brain-gut peptide and steroid hormones. The activation, signaling, and pharmacotherapy responses of the components of the hypothalamic-pituitary-adrenal (HPA) axis differ between the sexes. Heart and kidney functions are linked. Age, hormones, and sex biases seen in cardiovascular and chronic kidney diseases also differentially influence pharmacologic responses in men and women. Thus, sex differences pervade biology and medicine, and while not discussed in this Statement, must be considered in virtually all areas of biomedical research.

Section I

Sex Versus Gender

Much of the American public is surprisingly prudish about the word *sex*; it has now become commonplace to use the seemingly more genteel term *gender* when one really means *sex*. In *Moritz v Commissioner of Internal Revenue* (469 F.2d 466 [1972]), Ruth Bader Ginsburg (subsequently, The Honorable Ruth Bader Ginsburg) argued against discrimination “on the basis of sex” not “on the basis of gender,” thus clearly, knowledgeably, and presciently understanding that “sex” does not equal “gender.” In a decision 48 years later (*Bostock v Clayton County*, 590 US, decided June 15, 2020), the United States Supreme Court separately ruled against discrimination on the basis of gender. *Gender* is often misused as a synonym for *sex*—for example, when filling out forms for various activities, we are routinely

asked to check a box labeled “gender,” but the only available options are boxes labeled “M” and “F.” But *sex* is not the same thing as *gender* and using these terms as equivalents obfuscates differences that are real and important in society in general and biomedical research in particular.

Biological Sex: The Definition of Male and Female

Sex is a biological concept. Asexual reproduction (cloning) is routine in microorganisms and some plants, but most vertebrates and all mammals have 2 distinct sexes. Even single-cell organisms have “mating types” to facilitate sexual reproduction. Only cells belonging to different mating types can fuse together to reproduce sexually (2, 3). Sexual reproduction allows for exchange of genetic information and promotes genetic diversity. The classical biological definition of the 2 sexes is that females have ovaries and make larger female gametes (eggs), whereas males have testes and make smaller male gametes (sperm); the 2 gametes fertilize to form the zygote, which has the potential to become a new individual. The advantage of this simple definition is first that it can be applied universally to any species of sexually reproducing organism. Second, it is a bedrock concept of evolution, because selection of traits may differ in the 2 sexes. Thirdly, the definition can be extended to the ovaries and testes, and in this way the categories—female and male—can be applied also to individuals who have gonads but do not make gametes.

In mammals, numerous sexual traits (gonads, genitalia, etc) that typically differ in males and females are tightly linked to each other because one characteristic leads to sex differences in other traits. The type of gonads is controlled by the presence of XX or XY chromosomes, and gonadal secretions in turn regulate formation of female or male reproductive tissues, and characteristics that differ in typical males or females. These characteristics include external genitalia, uterus and oviducts, sperm ducts, and secondary sexual characteristics such as facial hair and pitch of voice. However, many people cannot make either eggs or sperm, yet are recognized as female or male based on other physical characteristics; people who do not have either ovaries or testes are rare. For individuals that possess a combination of male- and female-typical characteristics, these clusters of traits are sufficient to classify most individuals as either biologically male or female. For example, a person with testes and a penis, who cannot make sperm, is usually classified as a biological male, as long as the person does not possess female features such as a vagina, ovaries, or uterus. Based on evidence presented, to define male and female individuals in general society, we expand the defining characteristics of sex to include nongonadal traits, as well as classical gonadal traits.

A simple biological definition of male and female, satisfactory to all people, is elusive. In human societies, the terms *female* and *male* can have several meanings, as they refer both to a person’s biological sex and to their social roles. Most people learn to discriminate males and females from an early age, but often not based on biological traits (4). For example, behaviors such as pair-bonding, sexual activity, offspring defense and care, and mate/partner selection (5) involve complex interplay between sex steroid hormones and peptide hormones (oxytocin and arginine vasopressin); these behaviors are encouraged differently in women and men, which influences their role in the society and culture in which they live to behave as “females” or “males.” While these factors have little impact on their biological sex, they can have profoundly different outcomes in the behavior and health of an individual. Biological sex is dichotomous because of the different roles of each sex in reproduction. For scientific research, it is important to define biological sex and distinguish it from other meanings.

Sex Chromosomes and Biological Sex Determination

Among mammals and many other taxa, males are characterized as the heterogametic sex (6), having 2 different sex chromosomes, X and Y, whereas females are homogametic (XX). By contrast birds, many reptiles, and some other organisms have Z and W chromosomes (7). In these organisms, the female is the heterogametic sex (ZW) and males are homogametic (ZZ). Some adult fish and reptiles can also change sex in response to environmental factors (8, 9), and even the adult mouse gonad can undergo partial sex reversal when specific genes are deleted (10, 11). Human biological sex is often assessed by examining the individual’s complement of sex chromosomes as determined by karyotypic analysis: males are XY and females are XX. Karyotypic sex is actually a surrogate for genetic sex, determined by the presence of the *SRY* gene on the Y chromosome (12, 13). However, karyotypic analysis may be misleading, as there are well-described 46,XX males (with testes). Most of these individuals carry a short segment of the Y chromosome that includes *SRY* transferred to an X chromosome, but up to 10% lack an *SRY* gene (14, 15). Similarly, there are 46,XY females, who have *SRY* but also have a duplication of *DAX1* (dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1) (16).

Sex Determination and Sex Differentiation

In mammals, sex determination begins with the inheritance of XX or XY chromosomes, which are the only factors that are different in XX and XY zygotes. Thus, all phenotypic sex differences, including gonadal development, stem originally from the unequal effects of XX and XY

sex chromosomes. Phenotypic sex differences develop in XX and XY embryos as soon as transcription begins. The categories of X and Y genes that are unequally represented or expressed in male and female mammalian zygotes, which could cause phenotypic sex differences, fall into 3 main categories (17).

1. *Y genes causing male-specific effects.* These Y-linked genes do not have homologous genes on the X chromosome. The most important Y-linked gene is *SRY*, the testis-determining gene, which encodes the *SRY* transcription factor expressed during embryonic life in the bipotential gonadal ridge; *SRY* activates downstream autosomal genes such as *SOX9* to cause formation of a testis (18). In the absence of *SRY*, autosomal and X chromosome genes (*WNT-4*, *DAX-1*, *FOXL2*, *COUP-TFII*, and *RSPO1*) are activated to cause formation of an ovary (19–22). Both testicular and ovarian development are subject to active genetic regulation (12, 13, 16). Pathways downstream of *SRY* inhibit ovary-determining pathways, and ovary-determining pathways also inhibit pathways for testis development. Once the testes form, they secrete sex hormones that act widely throughout the body to cause male differentiation of nongonadal tissues. Other Y genes also have male-specific effects (for example, those required for spermatogenesis) (23, 24).
2. *X gene dosage or parental imprint.* Because XX nongermline cells inactivate one X chromosome (25, 26), it was long thought that both XX and XY cells have only one active X chromosome, with little inherent difference in expression related to the number of X chromosomes. The inactivated regions of the X chromosome are “coated” with large noncoding RNA transcribed from the X-inactive specific transcript (*XIST*) gene, part of the XIC (X inactivation center) located on Xq13 (27, 28). But some genes escape X inactivation (termed as *X escapees*), and therefore are expressed more in XX than XY cells, resulting in imbalance or incomplete dosage compensation (29). About 23% of human X-linked genes are more abundantly expressed in XX cells than XY cells in many tissues (30, 31). Recent evidence from mouse studies suggests that the inherent male-female difference in expression of X genes leads to significant sex differences in disease phenotypes. For example, sex differences in placental *Ogt* expression are associated with sex differences in prenatal vulnerability to stress (32). X escapee *Kdm6a*, a histone demethylase, contributes to sex differences in mouse models of bladder cancer (33), autoimmune disease (34), and Alzheimer disease (35). Similarly, variations in human *KDM6A* are associated with prognosis of bladder cancer or cognitive decline in female patients (33). The dose of another X escapee histone demethylase, *Kdm5c*,

contributes to sex differences in adiposity and body weight in mice, and variations in *KDM5C* in humans are associated with body mass (36).

Sex differences may also arise from genes in the pseudoautosomal regions (PARs) of the sex chromosomes, small regions of sequence similarity on the X and Y chromosomes that allow for X and Y chromosome pairing during meiosis. Both XX and XY cells have 2 PARs, implying equivalent effects of XX and XY PARs. Paradoxically, the process of X inactivation appears to spill over into the PAR and reduce expression on one X chromosome only in XX cells, leading to greater expression of PAR genes in XY cells compared to XX cells in the human transcriptome (30). A third potential source of X-linked imbalance stems from parentally imprinted genes in XX cells, which have one X chromosome from each parent and thus are influenced by any imprint on X genes from either parent. XY cells only receive imprints from the mother, and thus differ phenotypically from XX cells (37).

3. *XX mosaicism.* Female mammals are a mosaic of cells of 2 types: those expressing the X chromosome from the father (Xp), or from the mother (Xm) because of X inactivation (25). In contrast, XY individuals will lack this diversity within cell types in each organ because only one X (Xm) chromosome and only the maternal imprint of X genes will be expressed in each cell. The mosaicism in females means that in genetically diverse populations, the effects of disease-promoting X-linked alleles, inherited from one parent, will be muted in XX cells because half of the cells will have a different allele (38), and genomic imprints from each parent will only be expressed in half of the cells. In general, XX tissues are thought to have less extreme phenotypes than XY tissues, because the effects of extremely deleterious or beneficial alleles or imprints are buffered by the diversity of X alleles and imprints. For example, hemophilia A and hemophilia B (clotting factor VIII and IX deficiencies, respectively), are X-linked diseases that affect men, whereas most women are asymptomatic carriers.

Sexual Differentiation Caused by Gonadal and Nongonadal Hormones

In mammals, the process of reproductive system development requires the action of hormones (peptide/gonadotropins and steroids) from the pituitary gland, the adrenal cortex, and the gonads. Testicular development leads to secretion of Müllerian inhibitory hormone (MIH, also termed anti-Müllerian hormone, AMH), a glycopeptide, and testosterone, which affects many sex differences in nongonadal tissues (39). In contrast to the fetal testis, the fetal ovary makes minimal steroid hormones

(40), and ovarian function is not needed for development of the female reproductive system, as evidenced by the normal female anatomy of individuals with Turner syndrome, who have 45,X gonadal dysgenesis. The pioneering work of Alfred Jost suggested that 2 classes of testicular hormones are involved in sexual differentiation. First, testicular androgens drive the differentiation of the fetal external genitalia from female morphology to that of the male and are required for the differentiation of embryonic Wolffian ducts into male internal reproductive structures (41, 42). Androgens, secreted by Leydig cells, are required for the differentiation of embryonic Wolffian ducts into male internal reproductive structures (epididymis, vas deferens, ejaculatory ducts, prostate, and seminal vesicles), and drive the differentiation of the undifferentiated external genitalia toward male morphology. Second, the testis produces locally acting MIH that causes involution of the Müllerian ducts, which would otherwise develop into the fallopian tubes, uterus, and cervix (43, 44).

It was long thought that only the involution of the Müllerian ducts was an active process, with the Wolffian ducts simply involuting in the absence of androgens. Recent evidence from mice indicates that Wolffian involution is also an active process controlled by the transcription factor COUP-TFII (22, 45), but the nature of any factors stimulating COUP-TFII remains unknown (22). Some aspects of gonadal differentiation are active throughout life,

preventing ovarian follicle cells from transdifferentiating into “testis-like” cells (11). MIH is secreted by Sertoli cells and androgenic steroid hormones, usually testosterone, are secreted by Leydig cells. Testosterone and its more potent derivative dihydrotestosterone are responsible for the development of the male external genitalia (46). Androgens from adrenal glands and alternative pathway androgen biosynthesis in the human placenta can influence virilization of the developing fetus (47, 48). The adrenals of adult primates also produce abundant androgens, profoundly influencing phenotypes, so that not all sex steroids are gonadal (see Boxes 1 and 2). Although the term *sexual differentiation* is usually applied to the development of sex differences in genitalia and other organs such as the brain in the growing fetus; sex differences also occur later in life during the mini-puberty of infancy (49), puberty, the female menstrual cycle, menopause in women, and andropause in men. The actions of gonadal and nongonadal hormones as well as sex and autosomal chromosome gene products in adult people causes many sex differences in health and disease.

Influence of Gonadal Steroid Hormones and Nongonadal Hormones in Brain Development

Differentiation of the brain by gonadal hormones is implemented during a restricted critical window, which is operationally defined by the onset of copious androgen

Box 1. Steroidogenesis in gonadal and nongonadal tissues

All biologically active sex steroids, whether gonadal or nongonadal in origin, are derived from cholesterol by the process of steroidogenesis. Two steroidogenic steps must be considered (for details see (50)). First, the cholesterol side-chain cleavage enzyme, P450_{scc} (CYP11A1) initiates steroidogenesis by converting cholesterol to pregnenolone; expression of P450_{scc} renders a tissue “steroidogenic,” that is, able to make steroids de novo (51). The gonads, adrenals, and placenta express abundant P450_{scc} and produce the familiar circulating endocrine steroids, but the brain, skin, and some other organs also express low levels of P450_{scc} and produce steroids involved in paracrine actions. Brain steroidogenesis has been studied mainly in fetal rodents, with little information in other systems (52). Many nonsteroidogenic tissues (liver, kidney, fat, breast, heart) do not express P450_{scc} but express other steroidogenic enzymes that modify steroids taken up from the circulation. Fat and breast express CYP19A1 (aromatase), permitting local production of estradiol from circulating 19-carbon (C19) steroids; this estradiol is important in breast cancer but is not a gonadal steroid. Similarly, prostate and genital skin express several enzymes leading to dihydrotestosterone, accounting for the failure of “androgen deprivation therapy” by gonadectomy in prostate cancer. Not all gonadal steroids are sex steroids, as both the ovary and testis secrete some “upstream” steroids that are precursors of the classic sex steroids. For example, dehydroepiandrosterone (DHEA) does not bind to sex steroid receptors, but it can be converted into testosterone and estrone. Second, synthesis of all sex steroids requires P450_{c17} (CYP17A1), which catalyzes 17 α -hydroxylation and the 17,20 lyase activity that changes 21-carbon steroids to C19 precursors of androgens and estrogens. P450_{c17} is abundantly expressed in the gonads of all vertebrates and in the adrenals of most vertebrates other than rodents, but the rodent *Cyp17A1* gene is silenced by tissue-specific methylation (53). Consequently, rodents make only miniscule amounts of adrenal C19 steroids and also use corticosterone instead of cortisol as their glucocorticoid. In most mammals, P450_{c17} has low 17,20 lyase activity, so that their adrenals produce rather small amounts of C19 steroids, but primate P450_{c17} has abundant 17,20 lyase activity, generating abundant C19 androgen precursors (DHEA, DHEA-sulfate, androstenedione) (47, 48). Furthermore, production of these C19 steroids proceeds by different pathways in rodents and primates: primates favor the “ Δ 5 pathway,” through DHEA, whereas rodents favor the “ Δ 4 pathway” through 17OH-progesterone (17OHP) (50). Primate adrenals also produce a true androgen, 11-keto-testosterone (54), profoundly influencing phenotypes (apocrine odor; female sexual hair). Thus, not all sex steroids are gonadal: ~ 50% of the circulating androgens in adult women are of adrenal origin.

Box 2. Gonadectomy and sex steroids

Many animal studies employ gonadectomy to eliminate the actions of sex steroids (estrogens, androgens, progestins). If using this approach, the investigator must consider whether nongonadal tissues will produce sufficient sex steroids to influence the study. The gonads produce most but not all circulating sex steroids; furthermore, some tissues produce steroids that act locally and do not enter the circulation, hence absence of a measurable steroids in blood does not ensure absence of its action in the target tissue. Both sexes produce all steroids and their metabolites, hence there are no male- or female-specific sex hormones, *per se*. In male mammals, testosterone release is highly pulsatile in nature (49, 55) and in laboratory mice, strain-dependent variations in androgen levels are reported (56). In female rodents, circulating levels of estradiol, testosterone, and DHT are highest in proestrus phase; a comprehensive analyses of sex steroids in intact and gonadectomized rodents can be found elsewhere (57). Circulating concentrations of testosterone in adult women are similar to those of boys in early puberty, and estradiol concentrations in men are similar to those in mid-cycle women, but the tenfold higher concentrations of testosterone obscure its effects. Rodents are widely used in research, but they differ from primates in several important aspects of steroidogenesis (see Box 1), and hence must be used with caution in studies seeking to model aspects of human physiology that might be influenced by steroids. These differences include: (i) In humans, substantial amounts of circulating sex steroids are bound to sex hormone-binding globulin (SHBG), whereas this carrier protein is not present in rodent circulation (58). (ii) Dehydroepiandrosterone (DHEA) and androstenedione, 19-carbon (C19) precursors for testosterone and estrone, that do not bind to sex steroid receptors, are secreted from the adrenal glands, the ovary and testis in humans, but not rodents (59). Thus, not all gonadal steroids are sex steroids. (iii) The rodent ovarian corpus luteum produces progesterone throughout pregnancy but in human pregnancy the corpus luteum involutes early in the second trimester, after which the placenta produces the progesterone needed to suppress uterine contractility, permitting term pregnancy. (iv) Adrenal-specific methylation of rodent *Cyp17A1* prohibits their adrenal synthesis of C19 precursors of sex steroids; however, changes in methylation status can occur under conditions of pathology. (v) As a further consequence of adrenal *Cyp17A1* methylation, rodents utilize corticosterone as their glucocorticoid, whereas almost all other vertebrates use cortisol. (vi) Rodent adrenals use high-density lipoproteins (HDL) taken up via scavenger receptor B1 (SRB1), as their principal source of cholesterol for steroidogenesis, whereas primates use low-density lipoproteins (LDL) taken up by receptor-mediated endocytosis. (vii) Several genes encoding steroidogenic enzymes are duplicated; rodents and primates differ in which copy(ies) of these genes are expressed: *CYP21*; *HSD3B*, *HSD17B*, *AKR1-3*. Such differences may affect laboratory results in unanticipated fashions. (viii) In rodents, nonsteroidogenic tissues such as the gut, liver, kidney, fat, breast, heart, thymus, skin, and the placenta have all been shown to make steroids. Thus, gonadectomy may eliminate most, but not all, circulating sex steroids, depending on the species being studied and may not reveal much about the paracrine effects of sex steroids present in the tissue(s) under investigation. Nonetheless, gonadectomy is an invaluable research tool that helps unequivocally confirm the influence of gonadal hormones in sex differences.

production from the fetal testis. Human fetal androgen production begins at 8 to 10 weeks postconception and in rodents is closer to parturition, at embryonic days 16 to 18, with birth following 2 to 4 days later. An important effect of this androgen surge is to masculinize the rodent brain. Steady but pulsatile release of the gonadotropins luteinizing hormone and follicle stimulating hormone from the pituitary gland support continuous steroidogenesis and production of sperm (60). In female rodents, the feminization of the brain proceeds in the absence of exposure to high levels of androgens or their aromatized byproducts, estrogens, a developmental strategy highly analogous to that used for masculinization of the gonads, reproductive tract, and secondary sexual characteristics, with the exception that estrogens are actively downregulated in male rodents. In human females, gonadotropins from the pituitary gland regulate ova development, induction of ovulation, and stimulation of estradiol and progesterone from the ovaries (49). An important feature of this developmental strategy is the existence of a sensitive period in female rodents (61). Male rodents must be exposed to high levels of

androgens during the critical period; if exposure occurs too early or too late it will be ineffective at inducing masculinization. However, females are also sensitive to androgens during a restricted period of development, hence a sensitive period in rodents. In males, the critical period closes shortly after androgen exposure because the cellular and molecular processes of masculinization have been initiated and cannot be reversed; the train has left the station. In both primates and rodents this process is largely prenatal, but female rodents remain sensitive to androgen exposure into the first postnatal week. Injecting a newborn female rodent with androgens will initiate the process of masculinization, thus she is still sensitive. After the first week, the feminization process cannot be overridden by androgens and thus the sensitive period has closed. The existence of the sensitive period in females is useful as a research tool—it is important in understanding the potential impact of exposure to endocrine-disrupting compounds or other cellular agents of masculinization that act in an analogous manner to androgen exposure in modulating female brain development. There is evidence for a later sensitive

period for brain feminization mediated by small increases in estrogens (62); this topic warrants further investigation. The closing of the sensitive period in primates, especially humans, remains poorly understood, but it appears to end prenatally, similar to the critical period in rodents. The sources of androgens that females can be exposed to during the sensitive period include from: (i) experimental interventions; (ii) male littermates in animals; (iii) or human adrenals carrying genetic mutations in the steroidogenic pathway (as in congenital adrenal hyperplasia).

Given that the critical and sensitive periods for sexual differentiation are defined by the production and response to gonadal steroids, it is not surprising that steroids are the primary drivers of developmental origins of sex differences in brain (and probably other tissues) and behavior. But how do steroids achieve this? The first step in any investigation is often to identify the active steroid metabolite(s). In rodents, circulating fetal testicular testosterone enters the fetal brain where it can serve as a direct precursor for estradiol synthesis via aromatase (*Cyp19A1*) (see Box 1). Fetal and adult neurons can aromatize testosterone to estradiol in a nonrandom distribution: neurons of the hypothalamus, preoptic area, and amygdala are particularly active for local estradiol synthesis, whereas the hippocampus and parts of the cortex, midbrain, and spinal cord are also active at a lower level (63). For most reproductive endpoints, it is the local actions of estradiol that drive neural phenotype toward masculinization, which to some seems counterintuitive, given that estradiol is so often referred to as a “female” hormone (64), and further highlights that it is impossible to completely eliminate the effects of sex steroids, especially in the brain, by simple gonadectomy (see Box 2). Developing rodent embryos sequester maternal estrogens by binding to circulating alpha-fetoprotein, which is present only during the critical/sensitive period; when it is genetically deleted, all the offspring are masculinized (65). However, in humans, sex hormone-binding protein, not alpha-fetoprotein, is the major serum glycoprotein that binds androgens and estrogens with an undetermined role in fetal sexual development (66, 67).

In rodents, there is abundant evidence that gonadal androgens are metabolized to estrogens in the brain and mediate “masculinizing” effects on the brain; similar evidence in primates is limited. In primates, the principal masculinizing agents are androgens, not estrogens, and although there is alpha-fetoprotein present in fetal circulation, it has a weak binding affinity for estradiol (68), and instead it plays a much broader role in brain and body development (69). The conclusion of no strong role for estrogens in humans is based on individuals with dysfunctional aromatase or androgen receptors. Males lacking aromatase still identify as men,

while XY individuals with complete androgen insensitivity identify as women (70). The disparity between the principal differentiating hormones in primates versus rodents suggests that findings may not be easily extrapolated, and it is important to specify both the hormone and species under investigation. To discern whether the biological basis of sexual differentiation of brain and behavior differs between primates and rodents, one needs to identify mechanisms by which steroids transduce signals to modify the trajectory of the nervous system. While those mechanisms are incompletely understood, a few general principles are clear. First, there is no unified mechanism that applies broadly across the brain, with the exception that androgens and estrogens are the primary drivers of masculinization during a restricted developmental window. Similar masculinizing effects of testicular androgens may also occur during puberty (71). Second, all aspects of neural development are capable of being “organized” or programmed by sex steroids. This includes cell genesis, migration, myelination, dendritic and axonal growth and branching, synapse formation, synapse elimination, and neurochemical differentiation. Effects are not limited to neurons, with both astrocytes and microglia also exhibiting morphological sex differences. Third, each discrete brain region, nucleus, or subnucleus appears to have unique mechanisms of cellular masculinization. In some brain regions, such as the preoptic area, there are multiple separate mechanisms at play simultaneously. Sex steroids act in both paracrine and endocrine manners to influence structural development and function (72, 73).

Biological Basis of Diversity in Sexual/Gender Development and Orientation

Given the complexities of the biology of sexual determination and differentiation, it is not surprising that there are dozens of examples of variations or errors in these pathways associated with genetic mutations that are now well known to endocrinologists and geneticists (74); in medicine, these situations are generally termed *disorders of sexual development* (DSD) or *differences in sexual development* (75). DSD includes genetic disorders in the sexual determination pathway (76), disorders of steroidogenesis (50, 77), disorders of steroid hormone action, especially androgen insensitivity syndrome (78), and less well-defined “developmental field defects” (79), such as Mayer-Rokitansky-Küster-Hauser syndrome (80). The study of genes and factors underlying DSD and the diagnosis and management of the various forms of DSD is a complex and rapidly evolving area of endocrinology: clinical management is complex (81) and requires both contemporary molecular genetics (82) and well-integrated interdisciplinary care (83).

Gender includes perception of the individual as male, female, or other, both by the individual and by society. *Gender identity* is a psychological concept that refers to an individual's self-perception; while associations between gender identity, neuroanatomic, genetic, and hormone levels exist, a clear causative biological underpinning of gender identity remains to be demonstrated. Both animals and human beings have biological sex, but only humans have evident self-awareness that allows them to express gender; self-awareness in animals has not been investigated in this context. Gender also includes differences that males and females experience in their social and physical environments, which can have differentiating effects on the sexes. Human social environments are poorly modeled in laboratory animals and thus animal studies are usually limited to addressing sex differences. For centuries, the concept of male and female did not distinguish between biological sex differences and those caused by consistent differences in the environments. Thus *sex differences* are those caused by biological factors, whereas *gender differences* reflect a complex interplay of psychological, environmental, cultural, and biological factors (Fig. 1).

At birth, individuals are assigned a sex or gender ("natal gender"), almost always based on the appearance of the

external genitalia. In most individuals, the various biological determinants of sex are consistent with one another, and this biological sex is also consistent with the individual's self-perception—the sex and gender are concordant. However, a substantial minority of people who do not have DSD have some degree of variation in their self-perception of their gender, which may differ from their biological sex; this is usually termed *gender incongruence* (84). The term *gender disorder* has been replaced with the term *gender dysphoria* which describes the distress that an individual might feel as a consequence of having gender incongruence. *Transgender* (often called *trans*) refers to individuals who do not identify themselves as being of their natal gender, whereas *cisgender* (*cis*) people do not experience gender incongruence (85). Readers are also referred to Endocrine Society's 2017 Clinical Practice Guideline and Transgender Health Fact Sheet (84). Estimates of the prevalence of male-to-female transgender individuals among general populations range from 0.5% to 1.3% and estimates for female-to-male transgender individuals range from 0.4% to 1.2% (85). State level population-based surveys indicate that 0.6 % of US adults (25-64 years of age) and 0.7% of adolescents and young adults (13-24 years of age) identify as transgender. Other studies of US high school

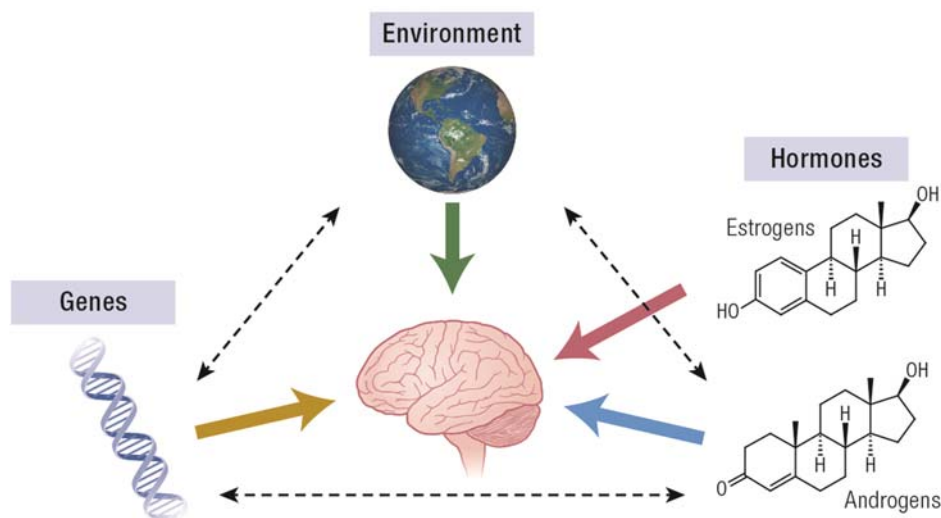


Figure 1. Simplified view of the factors influencing sex differences in the brain. Three broad groups of factors influence the sexually dimorphic brain, as indicated by the broad, colored arrows. 1) Genes and genetic factors that influence the brain include both those on sex chromosomes and autosomes, and include both the DNA itself (represented by the classic double helix) but also chemical modification of DNA (eg, methylation) and modifications of proteins associated with DNA to form chromatin, including histones, and also changes in proteins that bind to DNA. 2) Hormones clearly influence sexual dimorphism in the brain; these are represented by the principal sex steroids, estradiol and testosterone, but also include other steroid and protein hormones (progestins, MIH, oxytocin, prolactin, etc). 3) The environment includes a wide spectrum of influences, including perinatal nutrition and familial support, socioeconomic and demographic factors, intrinsic factors of brain development, age, and gender, and larger environmental factors, such as education, profession, and societal expectations (the "gendered environment"). In addition to each class of factor influencing the brain (bold arrows), the human brain also reciprocally influences each of these groups of factors. Furthermore, each group of factors influences the other, as represented by the dotted arrows. Some examples include: the environment influences genes via epigenomics and genes influence the environment by population sizes and domains; the environment influences hormones by seasonal variations and the actions of xenobiotics, and hormones influence the environment by promoting reproduction and consumption of foodstuffs; genes directly influence hormones by regulating their production and action, and many hormones, including all steroid hormones, regulate gene transcription.

students suggest a prevalence of 1.8% to 2.7% of being gender nonconforming or transgender (86-88). However, several factors may influence reported prevalence of gender dysphoria: (i) small sample sizes; (ii) differences in assessment techniques leading to incomplete ascertainment of gender dysphoric individuals; (iii) unwillingness of some individuals to respond fully and honestly, especially in older studies or studies deriving from locales where gender incongruence is a social taboo; (iv) differences in the subjects ages. *Sexual orientation*, not to be confused with gender identity, refers to the group of persons to whom an individual is sexually attracted; both cisgender and transgender individuals may be hetero-, homo-, or bi-sexual (89).

Although gender is strongly influenced by environmental and cultural forces, it is unknown if the choice to function in society in male, female, or other role(s) is also affected by biological factors (89-91). A general issue is that the association of sex, gender, or sexual orientation with specific brain structures, or with other biological variables, does not establish whether the biological variables are causes or consequences or noncausal correlates of the behavioral characteristics or function of the individuals studied. Three areas of biological difference have been studied fairly extensively: neuroanatomy, genetics, and hormones. Studies have reported differences in the hypothalamic INAH3 nucleus in men vs women and in homosexual vs heterosexual men (92, 93). Although initially controversial, others have confirmed sex differences in INAH3 numbers, not in size or densities, whereas no evidence for sexual dimorphism of any other INAH structures are reported (94). Studies in people with gender dysphoria found that the phenotypes of specific brain structures, such as the bed nucleus of the stria terminalis, of transgender women and transgender men differ from cisgender men and women, with partial, but incomplete sex reversal of sexually dimorphic structures (95). Brain networks involved in one's body perception, (pregenual anterior cingulate cortex, temporo-parietal junction, and fusiform body area) differ in individuals with gender dysphoria compared with cisgender individuals (96-98). Neuroimaging shows that testosterone treatment resulted in functional and structural changes in brain areas associated with self-referential and own body perception (99). Transgender men have thicker medial prefrontal cortex than cis men. Testosterone treatment does not change prefrontal cortex thickness in transgender men, but it has other effects on cortical thickness, connectivity, and fractional anisotropy (99).

Genetics may play a role in gender identity (100): monozygotic twins have 39% concordance for gender dysphoria (101). Attempts to identify specific genes governing gender identity have been plagued by small numbers of subjects and low statistical significance; no

specific gene has been reproducibly identified. However, such studies have suggested associations with genes encoding steroidogenic enzymes and sex steroid receptors, and it is generally agreed that androgens play an important but not determinative role. For example, many 46,XX individuals with severe virilizing congenital adrenal hyperplasia (steroid 21-hydroxylase deficiency) are exposed to intrauterine testosterone concentrations typical of those in normal male fetuses and consequently have severely virilized external genitalia; nevertheless, most have a female gender identity, but about 5% to 10% of such individuals have gender dysphoria, an atypical gender identity (89, 102, 103), or atypical sexual orientation and gender behavior (104, 105). Similarly, about half of 46,XY individuals with defects in androgen synthesis who were raised as females revert to a male gender role (106). The biological underpinnings of sexual orientation and gender identity are apparently related but are not the same (107). Thus, there is ample but incomplete evidence for biological substrates—neuroanatomic, genetic, and hormonal—for gender orientation, making this an important area of ongoing research.

Hormonal Versus Sex Chromosome Effects

Sex differences are caused by 3 major factors—sex hormones, genes on sex chromosomes/autosomes, and environment (Fig. 1). To understand disease mechanisms in both sexes and exploit sex differences in protection or exacerbation of diseases, it is important to determine the relative contribution of each of these factors in causing sex differences (17). Many sex differences caused by gonadal hormones have been discovered by measurements of sex steroids and gonadotropins during human development, and in animals by similar measurements or by interventional methods, such as gonadectomy, hormone administration, or the expression of synthetic enzymes or receptors in transgenic mice. Sex steroids play an integral part in many physiological processes (Box 1). Whereas the gonads are the major site of sex steroid synthesis, the adrenals, placenta, brain, and skin can also initiate steroidogenesis, and steroid-modifying enzymes are found elsewhere, especially in liver and fat, permitting synthesis of sex steroid hormones in multiple other sites (50). Thus, animal gonadectomy may provide information about endocrine effects of gonadal steroid hormones but cannot address tissue-specific paracrine effects (Box 2). Moreover, gonadectomy cannot mimic low pre-pubertal levels or physiological conditions in which hormone levels decrease, such as aging or menopause. Manipulations of human gonadal hormones are routinely used in contraception and in the management of sex steroid-dependent cancers (eg, breast, prostate). When

a sex difference is discovered in human disease, and modeled in animals, the investigation of possible hormonal causation of the sex difference is usually the first option considered.

To detect effects of sex chromosomes that cause sex differences, one can compare people who have differences in their sex chromosomes, revealing effects of X or Y chromosome number (108-110). These results strongly suggest direct sex chromosomal contributions to sex differences in cell function. Comparison of brains of XY patients with complete androgen insensitivity (who are phenotypically female), with brains of control XY males and XX females, suggests that cortical thickness and functional connectivity between the limbic regions and the cortex are influenced not only by testosterone actions, but by sex chromosome factors as well (111). However, changes in the sex chromosome ploidy also alter gonadal hormones, so it can be difficult to isolate sex chromosome effects not mediated by gonadal hormone effects. Circulating human embryonic/fetal sex steroid concentrations are poorly characterized, and the tissue concentrations are almost totally unknown. Another approach is to use mice to identify genes on the X or Y chromosome that act outside of the gonads to cause sex differences, and then seek evidence that the orthologous human genes cause human sex differences. Controlled experiments are possible in which XX or XY mice with comparable gonadal hormones can be compared. A frequently used model is the Four Core Genotypes (FCG) model, in which the testis-determining mouse *Sry* gene is deleted from the Y chromosome (creating the Y⁻ or “Y minus” chromosome) and inserted as a transgene on chromosome 3 (*Sry*+) (Fig. 2 and Box 3) (112). The utility and limitations of these models have been extensively discussed (113, 114).

Considering Sex and/or Gender as Variables in Health and Disease

Women and men differ in many physiological and psychological variables. It is important to establish the mechanisms causing such differences in health and disease, and to consider sex-related variables in studies of human health and disease. These variables include, but are not limited to, sex- and gender-related factors. The inability to control all variables in human studies means that it may be impossible to determine the relative roles of environment and biology in causing a difference between women and men, when both types of variable can influence the trait. Furthermore, while “gender expression/behavior” can be observed, “gender identity” can only be known by what an individual states. Thus, gender identity, *per se*, cannot be studied in animals. In human studies, it is unethical to selectively manipulate specific biological and environmental variables, and most currently available data derive

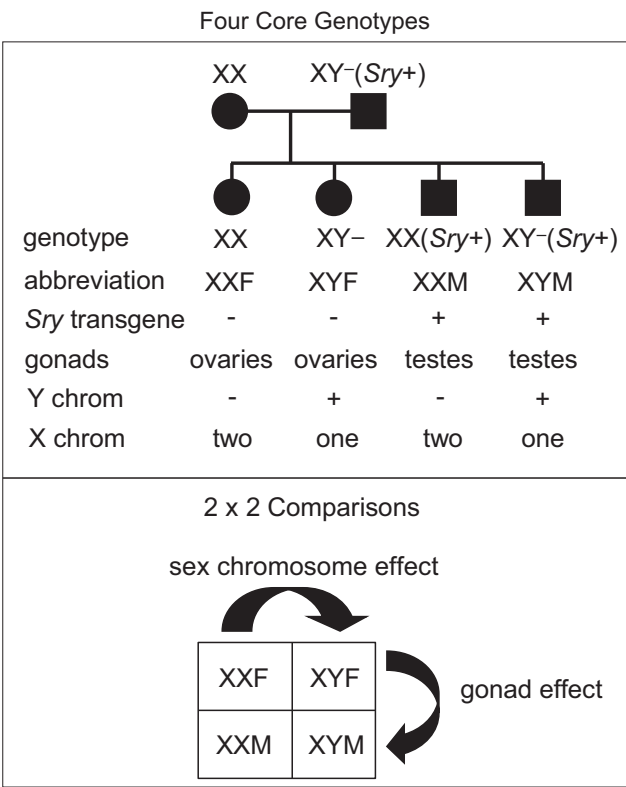


Figure 2. Schematic diagram of the Four Core Genotypes mouse model. The testis-determining gene *Sry* is deleted from the Y chromosome, producing the Y⁻ chromosome. An *Sry* transgene is inserted onto chromosome 3. Thus, the type of gonad is no longer linked to the sex chromosomes. The model produces XX and XY mice with *Sry* and testes, and XX and XY mice without *Sry*, with ovaries. Sex differences in phenotype can be attributed to an effect of gonadal hormones, comparing mice with ovaries and testes, or to an effect of sex chromosomes, comparing XX and XY mice with the same type of gonad. [Modified with permission from Arnold AP & Chen X. *Front Neuroendocrinol*, 2009; 30(1) © Elsevier Inc. (112)].

from studies comparing groups of men with groups of women. It is therefore difficult to disentangle the specific contribution of sex-related genes, hormones, gender-related variables, and other variables that contribute to being female or male. Because sex has long been defined by gonadal type, the list of sex-influencing factors has been primarily associated with gonadal hormones, especially estrogens, progestins, and androgens (121). However, some phenotypic sex differences develop before the gonads differentiate as testes or ovaries (122), so other factors also contribute to sex differences (123) but are seldom considered.

Sex is an essential part of vertebrate biology, but gender is a human phenomenon; sex often influences gender, but gender cannot influence sex. Studies of animal physiology must consider sex as a variable (124), with sex steroids (of both gonadal and nongonadal origins), sex chromosomes, and other factors contributing to sex differences in many physiologic processes. Similarly, studies of human physiology and disease must also consider sex for the same reason (125) and its disorders must

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Box 3. Investigating sex chromosome complement versus gonadal hormones in health and disease: the four core genotypes (FCG) model

The FCG model allows for discriminating hormonal vs sex chromosome effects in animals. Gonadal males (XY⁻(Sry⁺)), bred to XX gonadal females, produce 4 types of offspring: XY⁻ and XX mice with the Sry transgene and testes, and XY⁻ and XX gonadal females lacking the Sry gene (Fig. 2). Thus, it is possible to compare XX and XY mice with the same type of gonad, in 2 separate comparisons. Differences between XX and XY are attributed to effects of sex chromosome genes acting on nongonadal tissues. To determine if this sex chromosome effect is caused by X or Y genes, a second model is studied, the XY* model (113, 114). This model produces genotypes that are similar to XO, XX, XY, and XXY. An effect of number of X chromosomes is discovered by comparing XO and XX, or XY and XXY. An effect of the Y chromosome genes is discovered by comparing XO and XY, or XX and XXY. These mouse models have been used to demonstrate sex chromosome effects causing sex differences in a wide variety of phenotypes and disease models, including brain and behavioral phenotypes, metabolism, autoimmune, cardiovascular and pulmonary diseases, Alzheimer disease, aging, and cancer (35, 113, 115). These models have facilitated discovery of several disease phenotypes in which the number of X chromosomes contributes to sex differences (116), and a smaller number of sex-biasing effects of Y genes (117). Sex chromosome effects occur in the same disease systems alongside sex-biasing effects of gonadal hormones, such that the 2 effects can synergize to increase the amount of sex difference, or counterbalance each other to reduce a sex difference. Moreover, genes encoded on the Y chromosome can have gene-specific effects, and/or effects that overlap with those of X genes (118). In the cardiovascular system and associated physiological/disease states, sex chromosomes and gonadal hormones can have opposing effects. Estrogens generally protect from cardiac ischemia/reperfusion injury and other cardiovascular diseases, reducing disease in female relative to male mice. However, studies of ischemia/reperfusion injury in gonadectomized FCG mice reveal that the XX sex chromosome complement is associated with worse outcomes, relative to XY (119). In another study, sex chromosome effects in angiotensin II-induced hypertension showed that arterial pressure was greater in gonadectomized XX mice than in gonadectomized XY mice (120). Sex chromosome complement also influences the development of abdominal aortic aneurysms, fat metabolism and adiposity, plasma lipids and lipoprotein levels (particularly HDL-C) (115)).

also consider gender. However, human gender is a spectrum from feminine to gender-neutral to masculine, and also likely includes individuals who do not fit readily on a simple linear continuum (84). Studies addressing the endocrine care of transgender youth during the time of their potential gender transition (84, 89) find that they have a higher prevalence of stress-associated mental health disorders such as depression and anxiety, which can be ameliorated by gender-affirming endocrine treatment (126). It is essential to recognize these sex and gender differences as our health care systems endeavor to develop “individualized medicine.”

Despite the fact that biological sex is such a fundamental source of intraspecific variation in anatomy and physiology, much basic and clinical science has tended to focus studies on one sex (typically male). Few studies have done side-by-side testing for sex differences at baseline and in experimental models of human diseases (127-129). Studies in laboratory animals that manipulate biological (eg, genes and hormones) and environmental variables (eg, housing conditions, diet, physical activity, etc) demonstrate that many variables can affect sex-related aspects of an animal's physiology. However, laboratory rodents may show male-female differences caused by different housing conditions, which could be misinterpreted as being caused directly by biological differences without environmental mediation. In studies concerning animal behavior, the sex and gender of the researcher conducting behavioral measures may also influence outcomes (130). Thus, for reproducibility and proper interpretation of the data, at the minimum, it is important to state the precise housing

conditions, anesthetics, analgesics (different effects in sexes), doses, surgical manipulations, diet, sex, strain, species, and age of animals used, as well as sex/gender of the researcher(s) performing experiments.

Having laid the foundation for several factors that contribute to sex versus gender, this Statement will use 3 areas of research as examples (not as a literature review) where human and animal sex differences are well known. First, sex differences in specific brain regions of healthy men and women are increasingly being documented along with differences in brain connectomes; these will be discussed in detail in Section II. Second, stress-related pathophysiologies are known to affect twice as many women as men. However, few studies systematically include study designs to ascertain function or mechanisms that may be similar or different between males and females. Hormones and signaling pathways that contribute to sex-specific differences in stress-based pathophysiologies will be discussed in Section III. Similarly, sex differences in manifestation of cardiovascular and renal diseases are well recognized and will be discussed in Section IV.

Section II

Developmental Origins of Sex Differences in Brain Anatomy, Function, and Behavior

Sex differences in the human brain are a topic of intense popular and scientific interest. Several scientific observations motivate the search for sex differences in brain structure

and function. First, the act of sexual reproduction requires that the male and female animals show qualitatively different reproductive behaviors. The stereotyped emergence of these reproductively critical and sexually differentiated behavior reflects biologically programmed (or “innate”) sex differences in the organization of those brain circuits that support the motivational and consummatory phases of copulatory behavior (131). Second, the fact that males and females make different biological investments in reproduction—eg, the risks of pregnancy in mammals are borne entirely by the female—sets up sex differences in the behavioral strategies that optimize reproductive fitness (132). Sexual selection based on sex-biased behavioral strategies is predicted to drive the evolution of sex differences in those brain circuits that are responsible for sexually selected behaviors. Third, males and females can show consistent sex biases in broader behavioral domains beyond those that directly relate to reproductive strategies. In our own species for example, there are highly consistent sex differences in the prevalence of physical aggression and violence (both male-biased) (133), as well as extensively documented sex differences in risk for different mental disorders (134).

In this section, we will first describe the main neuroimaging techniques commonly used in comparisons of brain anatomy, connectivity, function, and subnetwork organizations. We then review the key aspects of sex-biased brain anatomy and connectivity that have been revealed by these techniques; sex differences in stimulus-based or task-based functional magnetic resonance imaging (fMRI) studies are not addressed here. Next, we discuss specific disease states that appear to have different outcomes in the 2 sexes due to baseline differences in the “connectome” and animal models used in neuroimaging. Finally, we will address some important caveats and controversies in the field of brain imaging.

Brain Imaging Techniques

Modern neuroimaging methods make it possible to characterize diverse aspects of brain structure, function, and connectivity in vivo. This large toolbox of methods has been used to examine sex differences in brain organization at several levels of analysis. These techniques aim to analyze, map, and visualize regional and inter-regional (connectomic) features of the brain at macroscopic (systems-level) and mesoscopic (neural circuit architecture) levels in order to illuminate brain organization in health and disease (135). Of note, cellular-level details are beyond the resolution of most in vivo brain imaging techniques.

Sex differences in global and regional brain anatomy can be measured in vivo using structural magnetic resonance imaging (sMRI). Several considerations have made

sMRI an especially popular technique in the study of brain sex differences in humans. First, sMRI allows a quick and spatially comprehensive screen of the entire brain that can quantify thousands of morphometric properties simultaneously in vivo across a large number of individuals. These characteristics not only facilitate testing for sex differences outside defined regions of interest, but also allow longitudinal measurements that can track the emergence of brain sex differences over development (136, 137). Second, because sMRI considers structure rather than function, it can leverage evolutionary conservation of the basic mammalian brain plan (138), and it is therefore particularly well-suited for cross-species investigation of sex differences in humans and animals. Thus, a critical role for sMRI research in the study of brain sex differences is to screen for brain regions that can then be prioritized for closer analysis using more resource-intensive assays that are typically applied in a regionally selective manner.

Complimenting sMRI, other in vivo neuroimaging techniques such as diffusion MRI (dMRI), resting state functional MRI (rs-fMRI), and fMRI provide unprecedented insights into tissue microstructure and brain connectivity. fMRI maps brain circuitry based on stimulus- or task-based brain functional responses. In contrast, rs-fMRI, by measuring changes in blood flow in the brain generated by signals dependent on blood-oxygen-levels, helps explore the brain’s functional organization by providing insights into intrinsic brain activity without requiring participants to be trained in specific tasks, thereby eliminating task performance as a confounder (139, 140). dMRI measures the differential patterns of water diffusivity in biological tissue revealing details of tissue microstructure, especially in white matter (141). Fiber tractography on dMRI enables mapping the fiber architecture of the brain, and subsequently, the network organization of the brain through structural connectomes (142–144). A brain connectome is an extensive map of the white matter structural or functional connections of the brain, created using dMRI or rs-fMRI (145). Modeling efforts, such as the Human Connectome Project, and the use of connectome-based predictive modeling, have provided an integrative, in-depth, and multilevel understanding of the structural and functional connectivity (regions that get coactivated) of the neuronal networks (146, 147).

Sex Differences in Global and Regional Brain Anatomy

It is well established that men have an average total brain volume that is approximately 10% greater than that of women (148, 149). A similar sex difference in average

human brain volume (~8%) appears to be present at birth (150) and is sustained throughout childhood and adolescence (151). The sex differences for total brain volume also hold for the 2 main subdivisions of brain tissue—gray matter and white matter—despite these 2 brain compartments following very different developmental trajectories (151, 152) (Fig. 3).

The robust sex difference in brain volume identified through human sMRI research cannot be fully explained by the fact that brain volume is positively correlated with height (average height is greater in men than in women). Statistical control for body size diminishes, but does not remove, sex differences in total brain volume (149), and boys also show greater average brain volume than girls during early adolescent development, at a time when girls are taller than boys (153). Thus, available literature supports a consistent picture in which there is overlap between the distribution of brain size in men and women, but the mean of this distribution is significantly greater in men than women. The medium effect size of sex on brain volume exists above and beyond sex differences in stature. However, it is important to note that no known functional sex differences associate with the sex difference in overall brain size. Sex differences in overall brain size, and their developmental timing, are both theoretically and methodologically important when considering: (i) whether neuroanatomical sex differences are conserved across species; (ii) whether there are sex differences in regional brain anatomy above and beyond sex differences in overall brain size; and (iii) whether

there is concordance between sex differences in brain size and any observed associations between brain size and putative biological causes of sex differences, such as gonadal or sex chromosome status (see below).

The patterning of sex differences in behavior and mental illness risk across the lifespan suggest that sex differences in human brain organization are likely to vary across different brain sub-systems or regions, and potentially also across different developmental periods. Structures in human gray matter compartments mediate neural computation and information processing—in contrast to axon-rich white matter compartments that are primarily involved in connectivity between different brain regions (see “Sex Differences in Brain Network Organization: The Brain Connectome,” below). Here, we focus on sMRI studies that have tested for sex differences in regional gray matter volume (regional GMV) after controlling for sex differences in overall brain size. Regional GMV sex differences that survive statistical correction for total brain volume variation are of special interest because they exist beyond global sex differences in brain size. We emphasize GMV rather than other morphometric properties of the brain such as cortical thickness, sulcation, or the shape of subcortical structures (144, 154), because GMV provides a common metric that can be examined across cortical and subcortical structures, with equal applicability to humans and mice. Independent large-scale human sMRI studies in biobanks have identified a reproducible pattern of sex differences in regional GMV using sample sizes that are

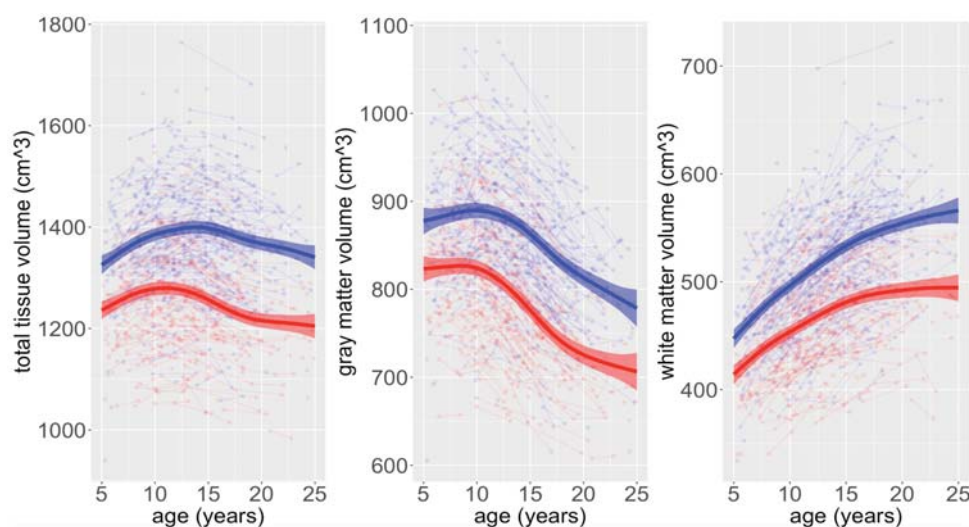


Figure 3. Developmental trajectories for total brain tissue volume, gray matter volume, and white matter volume in men and women over Development. Person-level data are shown for women (red) and men (blue) as points, with lines linking measures from the same person over time. Note the large interindividual variation in volumes within each sex, and the overlap of these distributions, between the sexes. Superimposed on these person-level data are group-level best fit volume trajectories (bold lines with shaded 95% confidence intervals). The developmental window covered is 5 to 25 years of age. For all plots, there are statistically significant sex differences in both trajectory shape (ie, sex differences in the tempo of volume change, $P < 0.00001$), and trajectory “height” (ie, sex differences in absolute volume across ages, $P < 0.00001$). [Adapted with permission from Giedd JN et al. *Neuropsychopharmacology*, 2015; 40 © Springer Nature (153)].

significantly larger than those used in earlier work (148, 149, 155). A structural neuroimaging study involving >2000 individuals demonstrated that higher regional expression of sex-linked genes was coupled with greater GMV in men relative to women (155). These studies, by different laboratories, using different datasets and different techniques for sMRI analysis, find a largely overlapping regional pattern of GMV sex differences after correction for sex differences in total brain volume. These independent replications of regional sex differences in GMV are also in agreement with meta-analytic studies (156). Together, these studies show that, in adulthood, regional GMV is (on average): (i) greater in women than men within superior parietal, dorsolateral frontal, and anterior cingulate cortices; and (ii) greater in men than women within occipital, fusiform, and parahippocampal cortices as well as the amygdala and putamen. Furthermore, while these studies lack temporally resolved developmental maps of male-female differences in regional GMV throughout the brain, there is extensive evidence from focused studies of particular structures that neuroanatomical sex differences can vary dynamically over development, such as observed with amygdala volume and shape (156).

The rapidly expanding body of sMRI research on regional GMV sex differences in the murine brain shows important overlaps and differences with findings from human studies (137, 157). These murine sMRI studies—which are most commonly conducted *ex vivo* at a spatial resolution of <100 μm throughout the whole brain—have been able to confirm the identification of all classically sexually dimorphic nuclei of male-biased volume from prior histological research, including the bed nucleus of the stria terminalis and medial amygdala (137, 157). These brain regions play a predominant role in modulating social and goal-directed behaviors, pain, and cardiovascular control, all of which are conserved among mammalian species and subject to sexually dimorphic outcomes. By allowing a full-brain screen, murine sMRI has also newly identified a reproducible set of regions with greater GMV in females, including the cerebellar cortex, ventral thalamus, and somatosensory cortex (137, 157). Furthermore, a longitudinal sMRI study in mice found that the set of regions with male-biased GMV can be detected by early postnatal life (with some accentuating over puberty), whereas regions of female-biased GMV in murine adulthood appear to emerge in adolescence (137). To date, there are no studies that formally seek to compare the spatiotemporal patterning of regional GMV sex differences in humans and mice, although existing work already suggests some potential homologies, including foci of greater cerebellar cortex GMV in females vs males by adulthood (137, 148) and the adolescent accentuation of male-biased amygdala volume (158, 159).

An important technical challenge in assessing the degree of anatomical homology between regions of sex-biased brain anatomy in humans and mice is that most of the best-established and histologically validated foci of sex-biased brain volume in mice (eg, bed nucleus stria terminalis, medial preoptic nucleus of the hypothalamus) are hard to image in humans due to their small size and intrinsic tissue contrast properties.

Sex Differences in Brain Network Organization: The Brain Connectome

The structural or functional brain network is represented by a “connectome,” wherein the structural or functional connectivity between coactivated regions is encoded either through fiber tracts or functional co-activations (160). These connectomes can be studied at the level of subnetworks like visuospatial, auditory, cognitive control, or macro-scale level through global measures of network segregation, integration, and efficiency, to obtain functional associations (161).

A study of 949 individuals (aged 8–22 years; 428 males and 521 females) showed that on average, there are significant differences between the sexes in their structural connectomes (Fig. 4) (162). On average, men had greater within-hemispheric connectivity, as well as enhanced network segregation, whereas between-hemispheric connectivity and network integration predominated in women (Fig. 4A), but these differences were most prominent during adolescence (Fig. 4B–4D). However, an opposite trend was seen for cerebellar connections, which developed differently between human males and females in adolescence and adulthood. The structural connectivity findings were consistent with a behavioral study conducted on the parent cohort (the above-mentioned imaging study was performed on a subset of participants), with women outperforming men on attention, word and face memory, and social cognition tasks, and men performing better on spatial processing and motor and sensorimotor speed tasks (163). An analysis of the Human Connectome Project rs-fMRI data identified age and sex as independent variables that contributed to differences in functional connectivity (164). In brains of men, functional connectivity was more clustered locally in all lobes, except in the cerebellum, whereas the brains of women showed a higher clustering coefficient at the whole-brain level. Thus, brains of men were classified as more segregated and brains of women as more integrated, which agrees with the structural connectivity findings (162). In connectomes, the identification of subnetwork properties (165) can reveal how the complex functional and behavioral repertoire emerges from the simultaneous processes of segregated neuronal clusters and their

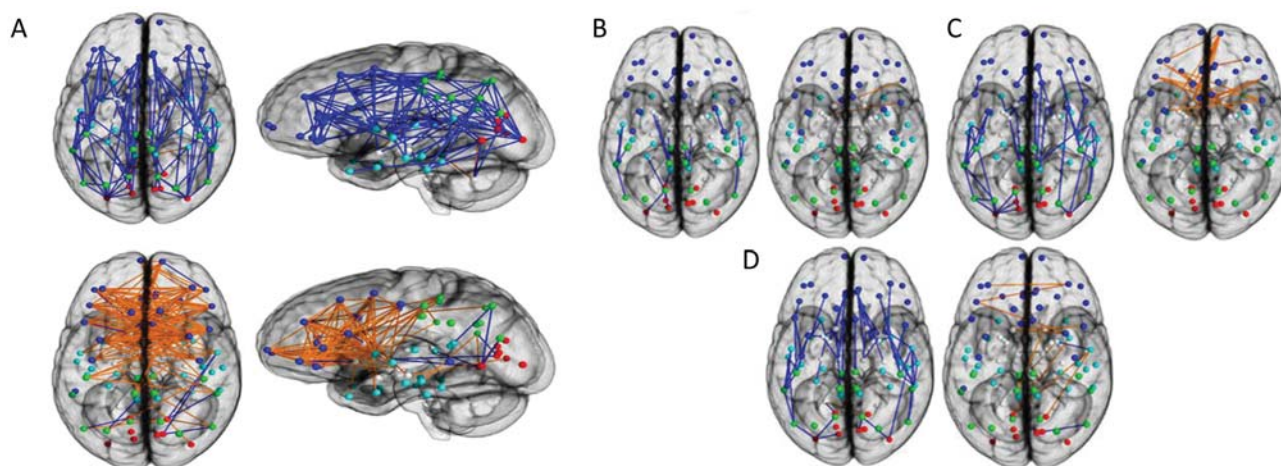


Figure 4. Sex differences in structural connectomes across development. Connectomes representing the white matter structural connectivity in the brain, with nodes indicating the brain regions and edges between the nodes representing the structural connectivity between the nodes. Node colors representing respective brain regions are as follows: dark blue, frontal; cyan, temporal; green, parietal; red, occipital; white, subcortical. The depicted edges shown are those that survived permutation testing at $P = 0.05$. **A**, shows increased intrahemispheric connectivity in men (Upper, in blue) and increased inter-hemispheric connectivity in women (Lower, in orange) on average. **B-D**: Connectivity differences shown in **A** separated by age groups are shown: **B**, under 13 years, **C**, adolescent (13-18 years), and **D**, young adults (18-22 years). Left image: Men/Boys; Right image: Women/Girls. [Adapted with permission from Ingahlhalikar M et al. *Proc Natl Acad Sci U S A*, 2014; 111(2) © National Academy of Sciences (163)].

integration during complicated cognitive tasks (166, 167). Consistent with the behavioral findings on sex differences, men had increased connectivity between motor and sensory (auditory) systems, along with increased connectivity in the fronto-parietal and cingulo-opercular systems that are traditionally associated with complex reasoning and control, whereas women had higher connectivity between reward, memory, and sensory (auditory) systems (163, 168). Better spatial skills in men and improved memory and social cognition skills in women have been reported in behavioral literature (169, 170).

It is important to point out that observed group-level differences in brain structure, function, or connectivity in men and women may reflect the influence of several extraneous factors. For example, in a set of elegant studies, brains of men were imaged to ascertain the contribution of performing complex spatial navigation tasks as part of their daily work on gray matter volume. These studies found that posterior hippocampi of London taxi drivers were significantly larger compared with controls (171), although the work did not address sex differences. Driving a taxi in London before the era of digital maps/navigation systems required extensive training and learning to navigate complex routes before being given a license to operate. In a subsequent study, comparison between London taxi drivers and bus drivers matched and controlled for age, education, intellectual, and stress levels, as well as years of driving experience, showed that taxi drivers had greater GMV in the posterior and less volume in the anterior hippocampi compared with bus drivers (172). Interestingly, years of

navigation experience associated with hippocampal volume in taxi drivers alone, but they were significantly worse at acquiring or retrieving novel visuo-spatial information than bus drivers. Importantly, no differences in other GMV, including the caudate nucleus, were found between the taxi and bus drivers; the caudate nucleus is associated with a myriad of cognitive and emotional functions. These studies illustrate brain plasticity and that professional work and years of performing certain tasks can result in brain structural, volume, and connectivity differences that may have little to do with sex or gender per se, but more with training, social environments, and behaviors. In other studies, GMV changes were greater in professional musicians, or after induced training (juggling for 3 months), and in early bilinguals, and white matter volume changes were found in adults learning a second language, irrespective of sex, when reported (173-176). These findings suggest that brain structure retains its plasticity and controlling for factors other than sex or gender are key in interpreting data on structural volumes and associated functions.

The above-mentioned existing datasets did not collect the requisite information on self-report of gender, thereby precluding retrospective analysis of gender in these cases. As identifying correspondence between behavioral scores and the regions that are involved in the manifestation of that behavior remains challenging, analyses of subnetworks pertaining to functional and behavioral domains can help elucidate a brain-behavior correspondence. The detailed description of sex differences in brain organization at the group level, and concerted efforts to specify

the role of sex-biased biological factors in shaping such sex differences, is of fundamental importance (177) and also provides a crucial adjunct for indispensable studies on environmental and wider societal contributions to sex-biased brain development. Such studies should be undertaken jointly using structural and functional connectivity. These studies elucidate the various ways in which sex differences in brain microstructure and connectivity can be investigated.

Sex Differences in Structural and Functional Brain Regions in Obesity

The hypothalamus has long been known as the “center” where peripheral and neural signals converge in the regulation of food intake and energy homeostasis in both sexes. Advances in neuroimaging studies have helped identify activation of several distinct brain regions comprising brain networks in response to eating in men and women. Behavioral and sociocultural factors may play a role in the observed sex differences in ingestive behaviors, appetite, and cravings related to obesity (178). Women report higher prevalence of maladaptive ingestive behaviors such as binge eating, food cravings, and “food addiction,” and the lifetime prevalence of disordered eating behaviors are about 3 times higher in women than in men (179, 180). Women also experience episodes of food cravings of greater intensity (181, 182), and greater frequency (183–185), and are less able to suppress food cravings than men (184, 186). Despite the wealth of data indicating that women experience disproportionately higher rates of food cravings, stress eating, and eating disorders than men, the reasons for these differences are incompletely understood (184, 187).

Regulation of food intake entails both homeostatic and nonhomeostatic factors (188). Homeostatic regulation balances energy needs with energy consumption, whereas nonhomeostatic regulation—in particular hedonic regulation and food addiction—involves reward-seeking behaviors that drive humans and animals to consume food beyond their metabolic needs, leading to the development of obesity (189–191). These findings have directed attention toward the extended reward system in obesity-related research, which consists mainly of basal ganglia regions and is involved in dopamine signaling and addiction-like behaviors (192). The extended reward system is composed of 6 interconnected brain networks—salience, central autonomic, basal ganglia, somatosensory, executive control, and emotional regulation (192).

Functional MRI studies have found that, in response to food images, obese individuals show greater activation than normal-weight individuals in regions associated with

reward anticipation, dopamine signaling, and addiction-like behaviors (193–196). Greater activity in brain regions of the extended reward network may drive obesity-related behaviors, such as greater responses to food odors and food consumption (197–199). Recent meta-analyses have further supported the role of the brain in disrupting the balance between energy consumption and expenditure. This combination of increased activity in regions associated with reward-driven behaviors and decreased activity in regions moderating top-down control of appetite may lead to consumption of excess calories (188).

Furthermore, sex-specific activations in response to food intake have been observed in cognitive, emotional, and reward-related regions (200–202). For example, obese men had greater activation than obese women in the supplementary motor area, precentral gyrus, fusiform gyrus, and inferior parietal lobule, which are associated with motor control, visuospatial attention, and responding to salient new or alerting stimuli (203). In this same study, obese women showed greater activation than obese men in the caudate and parahippocampal gyrus, regions implicated in reward processing and memory (203). Using graph theory to define the underlying architecture of brain structural connectivity obtained from diffusion tensor imaging, sex differences were observed in the topological measures of centrality (which determine the degree of information flow in specific brain regions) in regions of reward and salience networks in women, and in reward and sensorimotor networks in men (204). Resting state fMRI studies have found sex differences and commonalities in body mass index (BMI)-related connectivity associated with specific defined regions of interest in the reward network (205). For example, women had increased associations between BMI and increased connectivity in the right globus pallidus and bilateral putamen. In men, BMI was associated with increased connectivity in the medial frontal cortex. A study of sex differences in response to visual and auditory food cues found that women experience greater activation in lateral and dorsolateral prefrontal and parietal cortical regions involved in cognitive planning and executive guidance and evaluation of behavior, compared with men (202). When viewed together, these studies highlight the importance of investigating sex differences in obesity-related alterations in the core and extended reward networks.

Although many single-sex studies of fMRI and obesity have been published, with the majority having all-female subjects, few studies have specifically investigated sex differences in brain function and structure in obesity. Despite the literature supporting sex differences in the brain, including in regions implicated in reward behaviors and energy homeostasis, few comprehensive reviews of sexually dimorphic brain signatures related to obesity have

been performed. A recent meta-analysis using an activation likelihood estimation approach to evaluate comparisons in functional responses to stimuli by obesity and by sex revealed differential sex- and BMI-related activations in reward anticipation and response, in shaping food-related memories, and in generating top-down control of appetitive processes. Together, these findings have important implications for sex-specific obesity treatments.

Models to Study Sex Differences in Normal Brain Structure and During Pathophysiology

Studies of sex differences offer important considerations for personalized medicine. The prevalence, clinical presentation, and symptomatic progression of many neurological and psychiatric disorders are remarkably different between the sexes. In addition to common X-lined mental retardation syndromes, men have a greater prevalence of neuropsychiatric disorders such as autism, attention-deficit/hyperactivity disorder (ADHD), and Tourette syndrome (206), whereas women have a greater prevalence of mood and eating disorders (207, 208). From the perspective of developmental disorders, the differences in the developmental trajectories of the sexes perhaps represent different vulnerabilities of maturing brain circuitry, leading to differences in symptoms, onset, and severity of neurological disorders. There are also sex differences in the risk factors, average age of onset, and prevalence of late-life dementias, as well as cerebrovascular disease (209). Additionally, in traumatic brain injuries, where the network organization of the brain is affected by the injury, such as the corpus callosum region, sex differences in inter-hemispheric connectivity and brain subnetworks may influence the impact of injury, and hence subsequent recovery. Thus, sex differences in brain connections are crucial to identify, as they may elucidate mechanisms in disease risk and potential treatment and recovery (210).

Most models of sex-biased mammalian brain development are based on experimental data from rodents (now largely from mice, but previously also from guinea pigs and rats). One of the most systematic dissociations of gonadal and chromosomal contributions to sex-biased anatomical brain organization in mammals is provided by a recent sMRI study of adult mice from the FCG model (112, 211). By combining sMRI with behavioral assays, these studies determined the contribution of sex chromosomes and gonads to adult mouse brain structure and function (211). This study revealed: (i) an effect of sex chromosomes on regional GMV in the cerebellar cortex and olfactory bulb; and (ii) an effect of gonads on regional GMV in the parietotemporal cortex and the bed nucleus of the stria terminalis. Some of these effects overlapped

with regions of normal sex differences in murine GMV (eg, cerebellar cortex and bed nucleus of the stria terminalis), and some brain regions were anatomically sensitive to both effects (basal forebrain and periaqueductal gray matter). Sex-chromosome effects on regional gray matter anatomy have also been reported by complementary sets of sMRI studies in both mice and humans that compare groups of euploid individuals with groups carrying X-chromosome aneuploidy (157, 212). Finally, in both mice (137) and humans (155), the spatial patterning of sex differences in regional GMV in adulthood appears to be preferentially aligned with the spatial patterning of sex-chromosome gene expression—which points toward a potential role of sex-linked genes in the establishment of maintenance of regional GMV sex differences. These studies emphasize the need for integrative models that view biological contribution to sex-biased brain development as a developmental dance of coordinated influences from both gonads and sex chromosomes.

Caveats and Critiques Relating to Neuroimaging of Brain Sex Differences

While several sMRI studies apparently establish that there are highly reproducible male-female differences in regional gray matter volume after controlling for variation in total brain size in humans, this conclusion should be considered in the light of several important caveats and critiques to avoid misinterpretation. First, all sMRI phenotypes that show reproducible and statistically significant sex differences also show a considerable overlap between men and women. This overlap is illustrated by total brain volume: total brain volume averages 10% greater in men than women, but many women have a total brain volume above the 30th centile for male brain volume, and many men have a total brain volume below the 30th centile for female brain volume (149). Sex differences in brain structure and organization are present across the lifespan and vary based on age, so inferences should be drawn cautiously. Thus, while total brain size shows a robust mean difference between men and women, an individual's total brain volume is a weak predictor of biological sex. These 2 facts arise because biological sex is only one source of variation in brain size (149), and other factors/variables that influence total brain size are unknown and/or hard to model statistically (Fig. 1). By extension, because sources of anatomical variation can differ between brain regions—the same individual can have GMV values that appear to be “sex-typical” in one region, but “sex-atypical” in another (when typical and atypical are defined by an individual's percentile position relative to the distribution of population-level trait variation in each sex) (213). This interpretation offers one

potential explanation for the observation that an individual brain can show varying degrees of GMV “sex-typicality” in different brain regions (relative to the population distribution). Alternative explanations have been proposed, including regional variations in programs of sex-biased development such that one individual’s brain may be considered a “mosaic” of male and female parts regardless of their chromosomal and/or gonadal sex (213).

Second, although sex differences in regional GMV are highly reproducible in humans and mice, these meso-anatomical sex differences *cannot* be assumed to correlate with behavioral sex differences. The functional relevance of neuroanatomical sex differences is hard to establish experimentally in humans, but correlations between anatomical and behavioral sex differences could be modeled in humans using several feasible study designs. To date, however, very few studies have directly tested for such structure-function correlations in humans (161), and this is an important priority area for future research. Several other challenges will need to be addressed in future work for any given sex-biased sMRI phenotype, including which aspects of behavior to measure and how to consider properly all possible configurations of brain-behavior association in 2 groups (eg, varying intercepts and/or regression slopes across groups). Moreover, some sex-biased sMRI phenotypes, such as trajectories of anatomical change, can only be estimated from group-level data, which complicates comparisons with interindividual variation in behavior. More fundamentally, however, regional GMV sex differences may be useful for understanding the brain basis for sex-biased behavior without GMV variation itself being the behaviorally relevant marker. For example, sex differences in mean regional GMV may help to define brain circuits that subserve sex-biased behaviors through their molecular, cellular, or connectivity features rather than through their volume *per se*. It is also important to entertain the possibility that sex differences in the anatomical organization of a given brain system may actually serve to equilibrate function between the sexes despite each sex having a categorically different genetic starting point.

Third, in addition to the functional considerations above, full understanding of a given sex bias in regional brain anatomy requires a mechanistic account that can link observed anatomical sex differences back to specific genetic and/or environmental factors that differ between men and women. It is usually impossible to disentangle biological sex differences from those which could be the result of environmental influences during development, differences in gender, and in sexual orientation

(Fig. 1). Strict causal tests for mechanistic models of sex-biased brain development are very hard to achieve in humans, although several informative approaches have been pursued including: (i) modeling sMRI data using normative variation in hypothalamic-pituitary-gonadal axis maturation or function (214); (ii) applying sMRI methods to cohorts undergoing gender-reassignment (215); and (iii) studying how sMRI features differ between typically developing groups and those affected by medical disorders involving the sex chromosomes (eg, sex chromosome aneuploidies) or sex steroids (eg, androgen insensitivity, congenital adrenal hyperplasia) (215, 216). However, the opportunistic and correlational nature of these approaches places considerable limits on the inferential power of mechanistic studies of human sex-biased brain development. Moreover, as challenging as it is to study chromosomal or gonadal factors in humans, it is even harder to address empirically the many plausible hypotheses about the potential for experiential and societal influences to differentially shape brain development in both sexes (121) or genders.

Section III

Sex Differences in Molecular Mechanisms Underlying Brain-Gut Disorders

The brain and the gut communicate with each other in a bidirectional way through parallel and interacting channels, involving immune, endocrine, and neural signaling mechanisms (217). The brain is able to modulate gut permeability, motility, intestinal transit, and microbial function via the autonomic nervous system (217), and the gut in turn sends signals to the brain to modulate behavior, in rodents (218). This brain-gut communication is especially critical in mediating stress responses and in stress-based disorders. In psychiatric and other neurological diseases, there are notable sex differences that point to different underlying neurobiological mechanisms in men vs women (219–221). Despite their clear documentation, these sex differences have largely been ignored, in order to develop broadly applicable pharmacotherapies that come at a considerable cost, especially for women’s health (222, 223). Sex biases in psychiatric risk are particularly instructive as they are developmentally patterned in a manner that is highly reproducible across different cultural settings and historical epochs: early-onset neurodevelopmental and gut disorders are more prevalent in boys than girls, while the opposite sex-bias is seen for adolescent-emergent mood disorders (134, 224). Brain-gut disorders are more prevalent in women than men, but this may be due to underreporting by men due to social stigma associated with several of these

disorders. The etiologies and risk factors for several brain-gut disorders differ between the sexes, yet study designs include predominantly male sex. In this section, we discuss the possibilities that shared and distinct mechanisms operate in males and females resulting in similar as well as distinct manifestation of symptoms for a given disease/disorder.

Sex-Related Differences in Obesity

Although prevalence rates for obesity are at unprecedented levels in all ages (225) and are almost equal in men and women (except when stratified by race or ethnicity) (226), recent surveys indicate an increase in the incidence of obesity in adults and sex differences in the associations between weight, physical health, and psychosocial functions (227, 228). Sex differences in body fat distribution have also been observed (178, 229), with women showing an increased propensity to gain total body fat, especially subcutaneous abdominal fat, whereas men tend to have more visceral adipose fat (230), which is associated with higher risks of type 2 diabetes, hypertension, dyslipidemia, and cardiovascular disease (231). Most clinical trials do not report sex differences related to health outcomes or treatment responses, but a few existing reports suggest women are less likely to complete treatment, tend to lose less weight than men, have a greater number of unsuccessful attempts to maintain weight loss resulting in the well-known “yoyo” diet phenomenon, and have limited responses to pharmacological treatments (225). Obesity-related studies in humans and rodents have expanded in scope to not only focus on structural and functional brain differences between obese and lean male and females, but also include investigations into the bidirectional signaling associated with the brain-gut microbiome axis (232, 233). In obese individuals, changes in the relative abundance and gut microbial diversity have been linked to changes in metabolism, insulin resistance, inflammation, and fat deposition (234). The importance of the intestinal microbiome to human health has been of interest over the past few decades, with multiple studies now linking the microbiome to energy homeostasis, immune function, and development of obesity and metabolic syndrome (235–237), even though few studies have addressed causality.

Not only does the brain-gut axis demonstrate changes in obese individuals, but evidence also highlights differences in the microbiota based on sex hormones (238). More recently, the effect of sex hormones on the composition of the gut microbiota has been explored, with differences seen in the microbiota between men and women during various stages of human development and maturation (238). These

sexually dimorphic microbiome signatures are likely to contribute to differences in susceptibility to autoimmune and metabolic diseases between the sexes. Studies performed in immunocompromised mouse models have shown delayed onset and lessened severity of type 1 diabetes in female mice who receive male microbiota transplants; testosterone activity and androgen receptor signaling was essential for this protection (239, 240).

These sex-specific differences in the microbial communities persist throughout adult development, with murine models demonstrating the role of testosterone in orchestrating these divergences in host selection of microbial communities (240). In rodents, males exhibit lower microbiome variability relative to females, likely due to the pulsatile nature of estrogens (240). Human studies comparing the microbiome of twins also revealed more divergences in microbial composition in opposite-sex versus same-sex twins (241). When the cecal contents from adult male mice is transferred into female mice, metabolomic profile changes and masculinization of the hormonal profile results, suggesting the gut microbiota’s influence on sex-specific metabolic and behavioral phenotypes (239, 242).

Circulating estrogens in the body are metabolized by the liver and undergo methylation, hydroxylation, and conjugation reactions to produce metabolites that affect host metabolism (243). Certain metabolites are excreted through the bile and are further processed by microbial enzymes in the distal small and large intestine. Certain microbial species secrete beta-glucuronidase, an enzyme that deconjugates biliary estrogen metabolites and allows for its reabsorption into the bloodstream to act on distal sites through binding of estrogen receptors (244). Dysbiosis and decreased microbial diversity result in decreased production of absorbable estrogen metabolites. This mechanism has been implicated in pathologies associated with low circulating estrogens, such as obesity, metabolic syndrome, cardiovascular disease, and cognitive decline in women (245, 246); however, estrogen replacement therapy does not reverse these conditions (247). Growth hormone similarly contributes to sexually dimorphic responses in the above-mentioned diseases (248). In addition, estrogens modulate inflammatory pathways driving disease processes such as nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes (249, 250). More specifically, estrogens regulate adipokines and lipopolysaccharides, which respectively are adipocyte-derived hormones and endotoxins that have been associated with type 2 diabetes (251). Adipokines play a role in metabolic homeostasis as well as in mediating the beneficial and detrimental effects of inflammation (252). The androgen- and estrogen-dependent regulation of adipokines, including leptin, resistin, adiponectin, and visfatin, provides a possible mechanistic link between metabolic disorders (obesity,

atherosclerosis, insulin resistance) and autoimmune dysfunction. The estrogen-microbiome axis can provide a potential avenue for a sex-specific approach to combating metabolic disorders and highlights the bidirectional interaction of estrogens and microbial communities in the pathogenesis of disease processes.

Although the exact signaling mechanisms underlying the communication within the brain-gut-microbiome axis remain incompletely understood, tryptophan metabolites have been implicated as important signaling molecules (253). The most extensively studied tryptophan metabolite is serotonin (5-HT), a molecule with diverse roles in both the gastrointestinal tract (ie, peristalsis, secretion, and absorption) and the central nervous system (ie, mood, pain modulation, behavior, sleep, and ingestive and cognitive functions) (254). Tryptophan also acts as a precursor to the kynurenine (KYN) family of molecules (255). In obesity, the KYN pathway is preferentially activated and may contribute to immune-mediated inflammation, which may drive inflammation-associated changes to the extended reward network described in previous brain studies, particularly changes involving the amygdala and lateral orbitofrontal cortex (256-259). KYN may also modulate signaling within the brain-gut-microbiome axis through downstream neuroactive metabolites, such as kynurenic acid and quinolinic acid, functioning as N-methyl-D-aspartate (NMDA) antagonists and NMDA excitotoxins, respectively (260). Sex differences have been reported in these metabolite products in obese individuals, with lower tryptophan levels but elevated KYN and KYN/tryptophan ratios in women with high BMI compared to men with high BMI (256, 261, 262).

Sex Differences in Stress-Based (Patho) Physiologies

Epidemiological data reveal that the majority of psychiatric disorders occur at different rates in men and women. For example, men are more likely to suffer from attention-deficit/hyperactivity disorder (ADHD), whereas women are more likely to suffer from major depression and posttraumatic stress disorder (PTSD) (219, 263-265). Even when the rates of disorders are similar, their presentations can differ. Schizophrenia, for example, is only slightly more common in men than women, but men develop schizophrenia at an earlier age and present with more negative symptoms, such as social withdrawal and lack of motivation. (224). In the case of bipolar disorder, rates are similar between the sexes, but women more often have more rapid cycling and mixed episodes and they report higher comorbidity with eating disorders and PTSD, whereas men report higher comorbidity with alcoholism (266). Not only does the risk

and presentation of psychiatric disorders vary between men and women, but there are differences in treatment responses. For example, the efficacy of antidepressants differs between the sexes: men respond better to tricyclic antidepressants, whereas women respond better to selective serotonin reuptake inhibitors (267, 268). These findings implicate neurobiological sex differences in contributing to disease. In support of this idea, recent studies using animal models are beginning to uncover molecular processes that can bias males and females toward different pathology. Findings from some of these basic research studies will be highlighted here as examples of how including sex as a biological variable can inform our understanding of the etiology of stress-based disorders, as well as guide the development of better treatments.

While there are sex differences in rodent studies in the structure and the size of certain brain regions that can contribute to sex differences in behavior (211), imaging studies that focused on sex differences in cortical thickness and gyration suggest a role for these brain regions in humans as well. In adolescent girls, cortical thinning in the right temporal regions, the left temporoparietal junction and the left orbitofrontal cortex is faster than in boys (154). In contrast, changes in cortical folding were only found in one cluster of the right prefrontal region, suggesting that the mechanisms underlying changes in cortical thickness and gyration in adolescents are distinct. Sexual dimorphism in the developmental course of the cortical maturation, which coincides with the onset of puberty, might explain sex differences in the age of onset and clinical presentation of many psychiatric disorders (154). Recent evidence has revealed that molecular sex differences in the brain are more widespread than initially thought and such seemingly small-scale differences can have a large impact on physiology and behavior (269). Neurons typically communicate with each other via neurotransmitters and neuropeptides, which are released from a presynaptic neuron and travel across a synapse to bind to receptors on the postsynaptic neuron to exert downstream cellular effects. There are sex differences in production and release of many neurotransmitters and neuropeptides that can result in behavioral changes. In other instances, sex differences in these systems are compensatory, leading to similar behavior endpoints via different mechanisms. For example, both male and female juvenile rats play, but the release of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) into the lateral septum mediates juvenile play only in female rats (270). There are also sex differences in receptors that can influence how these neurochemicals affect their downstream targets. For instance, dopamine 1 (D1) receptors, which belong to the family of G protein-coupled receptors (GPCRs), in the nucleus accumbens, are necessary for social

withdrawal in female but not male California mice (271). The function of GPCRs is often complex and they can induce different downstream effects depending on their conformation and location. Sex differences can occur at each level of receptor function, in some cases altering physiology differently in male vs female rodents. Sex differences in GPCR signaling are particularly important to consider, especially given that GPCRs are the most studied drug target family for a myriad of indications; in fact, 34% of all US Food and Drug Administration (FDA)-approved drugs are targets of GPCRs (272). As an example of the myriad of sex differences that can be mediated by receptors, we will use the corticotropin-releasing factor 1 and 2 (CRF₁ and CRF₂, respectively) receptors that facilitate responses to stress, exhibit sexually dimorphic expression pattern, are modulated by both estrogens and androgens, and have been relatively well characterized in both sexes (273, 274).

Upon perception of stress or perturbation of homeostasis, CRF is synthesized in the paraventricular nucleus and released from the median eminence of the hypothalamus into the pituitary portal circulation, which in turn stimulates the synthesis and secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary into the general circulation. ACTH acts on the adrenal cortex to stimulate the synthesis and release of glucocorticoids and other steroids. This activation of the HPA axis in the classic “flight or fight” response by the CRF system is present in all mammals. The mammalian CRF family comprises 4 agonists, CRF and 3 urocortins (UCN1-3); and 2 known class B GPCRs, CRF₁ and CRF₂. While CRF₁ and CRF₂ share ~68% identity at the amino acid level (275), they perform distinct functions; CRF binding to CRF₁ initiates stress responses by activating the HPA axis, whereas UCN1-3 binding to CRF₂ brings systems back to homeostasis (274). Not surprisingly, perturbations in the components of the CRF family impact several organs and lead to brain-gut disorders, type 2 diabetes, metabolic syndrome, cardiovascular, and reproductive diseases, among others (274). There are sex differences in CRF’s endocrine effects. In female rats, higher levels of CRF mRNA in the paraventricular nucleus are reported that associate with the estrous cycle (276, 277) and are reviewed elsewhere (274). Perhaps as a compensatory response, CRF binding protein, an endogenous protein that sequesters CRF thus preventing its bioavailability, is expressed at higher levels in the pituitary of female compared with male mice (278). In humans, there is evidence for increased CRF receptor sensitivity at the level of the pituitary of women relative to men, because peripherally administered CRF, which acts at the pituitary, increases ACTH to a greater degree in women (279).

During stress, CRF is also released centrally into many brain regions, where its neuromodulatory effects coordinate cognitive and behavioral changes to promote stress coping (280). There are sex differences in the way these brain regions respond to CRF that are largely due to sex differences in CRF receptor signaling (274). For example, there is greater CRF₁ receptor binding in the basolateral amygdala in female rats (281). In contrast, binding of the CRF₂ receptor subtype, which is involved in stress recovery, is greater in the central nucleus of the amygdala in male rats (281). It is unknown precisely how these sex differences affect behavior, but given that the amygdala is critically involved in fear, it is likely that these receptor sex differences differently alter fear processing in males and females. In the brain, CRF₂ is most abundant in the bed nucleus of the stria terminalis, a region that regulates sexual behavior and stress-related functions (282, 283). Promoters in genes for CRF₁ and CRF₂ receptors harbor estrogen and androgen responsive elements and show tissue-specific modulation by sex hormones (284, 285). The sexually dimorphic expression pattern of these receptors at normal physiological states and during stress or disease pathology are summarized in a recent review (274).

Sex differences in CRF₁ receptor signaling have been identified in the noradrenergic-containing nucleus of the locus coeruleus (LC) and these differences have important implications for understanding disease vulnerability (273). The LC-noradrenergic system regulates levels of arousal such that higher levels of norepinephrin are associated with greater levels of arousal (286-289). Stressor exposure causes CRF to be released into the LC, which speeds up LC neuronal firing, increasing norepinephrin release (290, 291). Activation of this system during an acute or moderate stressor is thought to be adaptive, because it is important to be alert during a stressful event. However, if this system is activated inappropriately or persistently it can lead to hyperarousal that contributes to agitation, restlessness, impaired concentration, and sleep disturbance. Hyperarousal is a key feature of PTSD and reported in a subset of depressed patients (292, 293). Similar sex differences in spatiotemporal expression of CRF₂ and its ligands are found in humans with gut disorders, where they could contribute to differences between males and females in vulnerability to brain-gut disorders (127, 294).

There are sex differences in CRF₁ receptor signaling in the LC that increase female sensitivity to CRF. In the LC, CRF receptors primarily couple to Gs to initiate signaling through the cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) signaling pathway (295-297). Sex differences in CRF₁-induced cAMP-PKA signaling are linked to greater coupling of the CRF₁ receptor to Gs in females compared to males (298). This sex difference in

coupling of Gs may indicate that the CRF₁ receptor has a different conformation or binding partner in females vs. males, permitting different proteins to preferentially bind in each sex. Further support for this idea comes from studies demonstrating that, in male rats, acute swim stress increases the binding of a different protein, β -arrestin2, to the CRF₁ receptor, and this effect is not observed in female rats (298). The increased β -arrestin2 in male rats likely contributes to the greater CRF₁ receptor internalization in stressed males (298). When taken together, these findings suggest that CRF₁ receptors preferentially signal through different pathways in males (small GTPases) and females (cAMP-PKA) (299). This difference in signaling could alter physiology and disease risk. In fact, sex differences in CRF₁ receptor signaling in cortex were linked to increased Alzheimer-related pathology, including increased tau phosphorylation and amyloid β signaling in female compared with male mice (300). Few studies investigate sex differences in GPCR signaling, but it is likely that sex differences in GPCRs are also found in receptors other than CRF and that these differences could confer vulnerability and resiliency to many diseases.

In human studies, single nucleotide polymorphisms in the CRF receptor gene (*CRHR2*) are associated with negative emotions in patients with irritable bowel syndrome (IBS) (301). Immune cells secrete CRF₂ in extracellular vesicles that circulate in the plasma and associate negatively with disease severity scores in IBS-diarrhea patients (294). Single nucleotide polymorphisms in *CRHR2* are also associated with lifetime PTSD in women (302) and with type 2 diabetes (303). The prevalence of type 2 diabetes and insulin resistance is greater in men (304). Epidemiological studies have shown that men with high levels of self-reported perceived stress have a 1.4 higher odds ratio of developing type 2 diabetes during a 10-year follow-up period and are at 2-fold higher risk of developing diabetes than women with similar levels of reported stress (305). In agreement with human data, male mice lacking functional stress receptors (*Crhr2*^{-/-}) and haploinsufficient (*Crhr2*^{+/-}) mice have worse glucose and insulin tolerance, microvesicular hepatic steatosis, and dyslipidemia than female *Crhr2*^{-/-} or C57BL/6 male and female mice in a high-fat diet-induced model of diabetes (129). Female *Crhr2*^{-/-} mice had significantly greater brown adipose fat mass on high-fat diet than C57BL/6 female or male mice of either genotype, suggesting greater thermogenic responses that might be protective. However, the mouse study did not address whether steroid hormones contributed to changes in adipose mass or function. Thermogenesis in brown adipose tissue in humans in response to a meal or cold stress suggests that women have greater thermogenic responses

than men and that these responses correlate positively with progesterone levels, but negatively with cortisol levels (306). Thus, analyzing data from both sexes provides insights into sex-specific mechanisms that regulate physiological processes in both sexes.

In colonic tissues of pediatric patients with Crohn's disease, subcellular localization of CRF₂ differs between boys and girls (127). Furthermore, lack of CRF₂ revealed several sex-specific signaling pathways and differential degree of inflammatory responses in male and female mice (127). Treatment with UCN1, a high-affinity agonist for both CRF receptors, rescued *Crhr2*^{-/-} male mice from colitis-induced mortality, whereas UCN1 treatment increased mortality in *Crhr2*^{-/-} female mice (127). Both diabetes and Crohn's disease show sex differences in disease prevalence and outcomes, yet most animal studies use male sex to delineate mechanisms. Analysis of the data by segregating the 2 sexes can reveal significant insights into distinct and shared mechanisms and factors that exist at baseline and during disease. For example, sex differences exist in the etiology of pancreatitis: alcohol and tobacco predominate in men, whereas idiopathic and obstructive etiologies predominate in women (307), yet to date only a few studies have used both sexes to study mechanisms involved in pancreatitis. While both males and females develop pancreatitis in animal models, when administered identical doses of the pancreatic stressor caerulein, C57BL/6 female mice show less severe pancreatitis and histological damage than male mice (128). Lack of CRF₂ rendered female mice more susceptible to caerulein-induced pancreatitis compared with male *Crhr2*^{-/-} mice (128), with both male and female *Crhr2*^{-/-} mice exhibiting similar levels of total histological damage (128). Detailed analysis of components contributing to histopathological damage showed that female C57BL/6J mice have less necrosis, zymogen granules, and vacuolization than male mice with pancreatitis, but they have similar levels of edema and neutrophil infiltration as male mice (128). This data segregation allowed isolation of factors that differentially contribute to histological damage, which otherwise would be lost, if grouped together in this analysis. Taken together, these data support a role for the CRF receptors, product of an autosomal gene and regulated by steroid hormones to bring about sex-specific cellular signaling and function.

Sex Differences in Pharmacotherapy of Stress-Based Diseases

Sex differences in GPCR signaling are also relevant for pharmacology. Biased ligands can shift signaling toward

β -arrestin pathways and away from G-protein-mediated pathways based on how they bind to the GPCR (308). These biased ligands are being designed with the hope of providing more targeted therapies with fewer side effects (308, 309). Understanding sex differences in signaling and how such differences contribute to changes in physiology can inform the development of these biased ligands. For example, a CRF₁ receptor ligand that biases signaling through β -arrestin pathways may be useful for treating hyperarousal symptoms or reducing the progression of Alzheimer disease, especially in women. An idea for such a compound would never have come about if women were excluded from preclinical and clinical studies on CRF₁ receptor function.

The idea of using CRF₁ antagonists to treat depression, PTSD, and irritable bowel syndrome has been around for decades, but these compounds were ineffective in several clinical trials (222, 310). Sex differences in CRF₁ and CRF₂ receptor signaling may also explain the failure of different selective CRF₁ antagonists as treatments for these disorders. While there are likely many reasons for their failure, critical ones could be sex differences in their target, association of CRF receptors with different binding partners in female versus male cells, or heteromerization of CRF receptors (311-313), all of which can result in altered signaling. The consistent efficacy of CRF₁ antagonists in reducing anxiety-like and depressive-like behavior in rodents and nonhuman primates was established in studies primarily conducted in male animals (222, 314-317). In a study in which females were included, local blockade of CRF₁ receptors in the dorsal raphe with an antagonist reduced anxiety in male but not female mice, highlighting sex differences in efficacy (318). Yet these compounds developed primarily in male rodents were tested in clinical trials with participants of both sexes or only in women. Notably the only CRF₁ antagonist study that had success in reducing depressive symptoms, NBI-34041, was conducted only in men (222, 319). The approach of developing compounds in male animal models is not unique to CRF₁ antagonists and has been common practice (222). Collectively, these studies suggest that a failure of certain therapeutics may result from ignoring sex differences in their targets. Sex differences in targets are not well known because most preclinical studies use only male rodents (320, 321). Excluding females in the drug development stage particularly impacts women's health. Indeed, it is likely that some compounds deemed ineffective in male rodents would work in females, yet such compounds never would have a chance to make it to market, because of testing exclusively in male subjects. Moreover, the fact that most

drugs are designed using males also likely contributes to the higher rates of adverse drug reactions in women compared to men (322).

Including both sexes in mechanistic studies is critical for developing drugs that work efficaciously in both sexes (see Box 4). Latent sex differences can also impact drug development: a compound targeting a mechanism in men may not work in women. As the field moves forward, we may find that sex-specific therapeutics based on understanding latent sex differences are required to truly improve patient outcomes. In sum, there are observable sex differences in behavior that extend beyond reproductive function. Molecular sex differences in several organs, such as the gut and the central nervous system, play a key role in driving these functional and behavioral differences. Moreover, even when function and behavior are consistent between the sexes, the underlying processes can differ. Thus, including both sexes in preclinical molecular studies guiding drug development is key for improving the health of men and women.

Section IV

Sex Differences in the Cardiovascular-Renal System

Cardiovascular disease (CVD) is the major cause of premature death in both sexes worldwide, although women generally develop CVD 10 years later than men (328). In 2016, ~18 million people died from CVD, representing ~30% of all deaths worldwide (329). There are marked sex differences in CVD and renal disease. For example, women are protected from heart disease during the reproductive years but are more likely to die in the first year following a cardiovascular event than males (330). Most heart conditions, including myocardial infarction, Takotsubo syndrome, and cardiac arrhythmia, exhibit sex differences in symptoms and severity (331). Chronic kidney disease (CKD) is more prevalent in women but, once established, progresses more rapidly in men (332). However, this female advantage is lost after menopause. These sex differences in cardiovascular and renal disease have long been overlooked and underappreciated. The clinical presentation, the response to pharmacotherapies, standard care practices, and the underlying pathophysiological mechanisms differ in women compared to men. Furthermore, lack of understanding of sex differences in mechanisms underpinning cardiovascular and renal disease has led to poorer outcomes in women than in men. A major problem is that mechanistic preclinical studies in animal models have largely been conducted in males (333). Yet, it has become increasingly clear that sex differences

Box 4. Sex differences in pharmacokinetics and pharmacodynamics of drugs

Thalidomide, a sedative that was prescribed to many pregnant women to relieve pregnancy-associated nausea, was first sold in Germany (without a prescription) in 1957; it had been tested in animals and in men, but not in women. It was soon noted to cause multiple birth defects, most notably phocomelia (arrested limb development) and postnatal deaths. Fortunately, it was never approved in the United States, but thousands of children were affected around the world. In 1962, the US Congress passed the Kefauver-Harris Drug Amendments Act requiring manufacturers to prove a drug is both safe and effective (323). Consequently, the US Food and Drug Administration (FDA) recommended against drug testing on women, particularly those of child-bearing age, until the early 1990s. To date, most treatment guidelines are based on results from clinical trials conducted on middle-aged men. Dosage, pharmacokinetics, and pharmacodynamics data for women (and children) are lacking for most drugs. Activities of cytochrome P450 (CYP) enzymes show significant sex differences in drug metabolism in Phase I clinical trials (324). Gastric enzymes involved in oxidative degradation such as alcohol and aldehyde dehydrogenases are significantly more active in men than in women resulting in higher bioavailability of ethanol in women versus men. In Phase II trials, glucuronidating enzymes and some efflux transporters have been shown to be more active in men than in women. Together with estrogens and androgen that alter transmembrane transporters, these processes contribute to efficacy of metabolism in both Phase I and II. Drugs used for treatment of cardiovascular disease, such as angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor blockers, diuretics, the aldosterone blocker eplerenone, antiplatelet agents, and oral antithrombotic medications, all show sex differences in efficacy and safety (325, 326). Over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen are more effective in men than women; there is more liver toxicity with acetaminophen use in women, whereas opioids and benzodiazepine work better in women. While some sex differences in metabolic clearance for statins and beta-blockers are known for these frequently prescribed drugs, dosing and adverse event monitoring in routine clinical practice is inadequate. Alosetron, a serotonin receptor 3 antagonist, is approved for treatment of severe irritable bowel syndrome–diarrhea symptoms in women, as it is largely ineffective in men (327). These findings emphasize that women and men take divergent routes (molecular mechanisms and signaling pathways) to reach the same destination (normal function or diseased state), with paths often intersecting. In the era of personalized medicine, there is no one-size-fits-all therapy, and considering sex-specific outcomes in pharmacokinetics and pharmacodynamics of drugs as well as clinical guidelines is warranted to ensure efficacy and safety of medications.

are apparent in all endocrine systems, which are modified by sex chromosomes and sex hormones, with temporal actions across the lifespan.

Blood Pressure Links Cardiovascular and Renal Diseases

Cardiovascular and renal diseases are linked by the relationship of each to arterial pressure (Fig. 5). The cardiovascular system determines arterial pressure, with the heart generating cardiac output and the blood vessels determining total peripheral resistance. The kidneys contribute by regulating extracellular and intravascular fluid volume, and hence blood volume, and venous return. It is established that CVD leads to chronic kidney disease (CKD) and that CKD leads to the development of CVD. For example, following a myocardial infarct, cardiac output declines and arterial pressure falls causing the kidney to vasoconstrict and retain extracellular fluid, with the effect to increase venous return and normalize cardiac output. However, this has the unwanted effect of placing further stress on the failing heart. Conversely, kidney failure causes fluid retention and hypertension (334). Thus, cardiovascular and kidney function are intertwined, as are the endocrine systems that regulate organ function; including the renin-angiotensin-aldosterone system

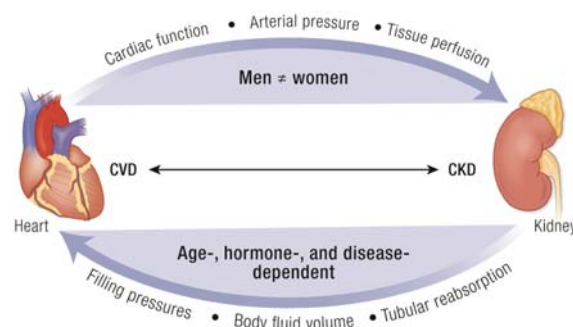


Figure 5. Heart and kidney functions are linked. Sex differences exist in many aspects of heart and kidney function at baseline and in CVD and CKD, as shown. Both organs feed-forward and influence each other's function. Genes, hormones, and age are some known factors that modulate this relationship in a sex-specific manner. Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease.

(RAAS), the endothelin system, atrial natriuretic peptides, vasopressin, and glucocorticoid and mineralocorticoid hormones. There is an increasing recognition that there are fundamental sex differences in each of these systems. For example, aldosterone contributes to obesity-induced CVD with a greater impact in females than males (335). However, further research is required to fully elucidate the sex differences present in each endocrine system and how these impact disease development and progression.

Sex Differences in Arterial Pressure and Hypertension

Hypertension is a major risk factor for cardiovascular and renal disease. Over the lifespan there are age- and sex-related differences in arterial pressure. The majority of the data are derived from cross-sectional studies, but a few powerful studies have tracked arterial pressure over decades within a population (332, 336-339). Arterial pressure increases in both men and women with age, although the slope of the relationship is different between men and women. Sex differences in arterial pressure emerge during adolescence and are maintained throughout adulthood until women reach menopause (336, 337, 339). Arterial pressure is ~5 to 10 mmHg greater in men than age-matched women during the reproductive years (340-342). Postmenopause arterial pressure rises steeply in women regardless of race, ethnicity, or country of origin (340-342). One of the most striking characteristics of hypertension is that the prevalence and severity is lower in premenopausal women than in age-matched men. The prevalence of hypertension is ~10% in young premenopausal women, ~50% in postmenopausal women and by the age of 75 years almost ~80% of women are hypertensive (342-344).

Nonhuman mammalian species also display sex differences in arterial pressure. Arterial pressure in adult females is lower in normotensive dogs, sheep, rabbits, rats, and mice as compared with adult males (338, 345). Furthermore, in rodents, rabbits, and sheep, females of reproductive age are protected against the development of hypertension, such that arterial pressure increases significantly less in females than in males, in settings of disease (338). Thus, sex differences are present in the pathophysiology of cardiovascular and renal diseases. Yet, the mechanisms underlying the sexual dimorphism of arterial pressure in men and women as they age are poorly understood. However, extensive evidence indicates that sex hormones likely contribute to the regulation of arterial pressure through their actions on endocrine systems.

Sex Differences in Endocrine Control of Arterial Pressure and Kidney Function

There are subtle differences in most endocrine actions between men and women. It is not the maximal response of each system but rather the slope of the response that is altered. In this manner, a system responds maximally in a hemodynamic crisis (eg, hemorrhage) but in a sex-specific manner to lesser challenges. For example, a greater dose of the vasoconstrictor angiotensin II is required to increase arterial pressure in female than male mice (346). Consistent with this finding, the same dose of angiotensin II caused a

greater reduction in renal blood flow in men than women, with the suggestion that this was an angiotensin type 2 receptor (AT₂R) mediated effect (347). In rodents, females of reproductive age have a greater AT₂R to angiotensin type 1 receptor (AT₁R) ratio than males, which contributes to the reduced pressor response to angiotensin II (348). This has been indirectly demonstrated in women, in studies examining forearm vascular resistance responses to AT₂R blockade (349). The AT₂R also mediates a leftward shift in the pressure natriuresis-diuresis relationship, an effect that is greater in female than male mice (350). In women, indirect evidence also indicates a more pronounced role for the AT₂R in the regulation of renal blood flow responses to angiotensin II (347). This is linked to differential expression of components of the RAAS in males and females, which have been demonstrated in most mammalian species, including humans (351). In the context of the above example, estrogen interacts with the glucocorticoid response element on the X-linked *AGTR2* gene, to increase AT₂R expression in females (352). In addition, there are sex differences in human aminopeptidase A, aminopeptidase N, and angiotensin-converting enzyme 2 levels, responsible for generation of the angiotensin peptide fragments, angiotensin III, and angiotensin-(1-7), which have a high affinity for the vasodilatory AT₂R and Mas receptors, respectively (353-356). Lastly, there are marked and important sex differences in the production and function of aldosterone, although this has only recently been started to be examined (335). Thus, in females the RAAS is balanced toward the protective depressor RAAS arm, which at the lower physiological range may prevent arterial pressure increasing to the same extent as in males. However, this delicate balance may be lost in women after menopause and in the situation of metabolic syndrome.

Other vasoconstrictor systems also have sexually dimorphic actions. Endothelin-1 causes vasoconstriction via the endothelin type A receptor (ET_AR), and vasodilation and sodium excretion via the ET_BR. Testosterone increases ET_AR and estrogen increases ET_BR expression, which contributes to the differential control of arterial blood pressure and renal function between the sexes (357). Vasopressin, with important roles in circulatory and water homeostasis, is affected by age and sex. Urinary concentrating ability declines with age, but more steeply in women. Young men produce more concentrated urine than women, in part due to higher plasma arginine vasopressin levels and greater vasopressin type 2 receptor expression in the collecting ducts of the kidney in males (358, 359). Renal vasopressin type 2 receptor expression declines with age in association with a reduction in maximal urine concentrating ability (358, 359). Interestingly, aldosterone signaling via mineralocorticoid receptors is associated with increased CVD risk and is

enhanced in obese women (another example of how the RAAS is differentially modulated in females), which has been linked to leptin-induced endothelial dysfunction (360, 361). Moreover, evidence in rodents indicates that sodium reabsorption along the length of the renal tubule is sexually dimorphic, with reabsorption shifted to the later segments in females compared to males. This was associated with greater sodium epithelial channel expression, under the control of aldosterone, in the collecting duct, which could also contribute to the increased cardiovascular and renal risk associated with aldosterone in females (362). Finally, oxytocin, relaxin, and prolactin, which are traditionally known for their roles in pregnancy, have differential cardiovascular and renal actions in nonpregnant female and male rodents (348, 363, 364). Thus, evidence points to sex differences in endocrine control of extracellular fluid homeostasis and vascular function, which likely contribute to age- and sex-related disparities in renal and cardiovascular disease risk. Further studies are warranted to understand this complex issue more fully. In particular, it is important to take into account the subtle effects within the physiological range that counterbalance function of each hormonal system, rather than examine the impact of pharmacological doses which can mask sex differences in responses.

Cardioprotective Mechanisms in Women Sustain a Healthy Pregnancy

The cardioprotective mechanisms that predominate in women during the reproductive years enable the extensive hemodynamic adaptations required to meet the metabolic demands of the developing fetus and a successful pregnancy. During a normotensive pregnancy, blood volume increases and cardiac output increase by ~30% to 50%, but arterial pressure declines due to marked peripheral vasodilatation (365, 366). The associated renal vasodilation accommodates an increase in glomerular filtration rate to process the additional blood volume, but an increase in vasopressin type 2 receptor expression enables increased tubule reabsorption of sodium and water. However, in women with preeclampsia, a pregnancy-induced form of hypertension, these cardiovascular adaptations are perturbed. Accumulating evidence now indicates that women with a history of pregnancy-associated hypertension have a 2- to 5-fold increased risk of CVD in later life (367). Understanding the mechanisms underpinning this dysregulation of vascular function in pregnancy-related hypertension may lead to the identification of new therapeutic targets for the treatment of cardiovascular disease in both sexes. For example, relaxin, which is known best for its role in pregnancy but is also produced in males, plays

roles in the regulation of renal function, blood pressure, and tissue fibrosis (363). Thus, it is a mistake to assign hormonal systems a specific role as most have wide-ranging tissue-specific pleiotropic effects.

Sex Hormones and Sex Chromosome Complement in CVD

Sex hormones contribute to sexual dimorphism in endocrine control of the cardiovascular system, with evidence suggesting that there is a “sweet spot” for both testosterone and estradiol, as unusually high or low levels of either promote disease (368–370). This has been the cause of apparent discrepancies in the literature. In particular, this remains a problem in animal studies in which the dose of estrogen used to study the impact of estrogen replacement in aged or gonadectomized models varies widely (~1000-fold), as does the route or length of administration; none of which accurately reflect the cyclic pattern of in vivo production. This lack of rigor into investigation of the effects of sex hormones in preclinical models likely contributes to the controversy that surrounds hormone replacement therapy for the prevention of CVD risk. Despite extensive evidence that hormone replacement therapy is cardioprotective, the negative results of the Women’s Health Initiative Trial effectively halted the use of hormone replacement therapy (371). Certainly, high-dose estrogen can increase blood pressure and cardiovascular risk in women (372). However, continued investigation supports the use of hormone replacement therapy in subsets of women, and further work in this area is required (373). In contrast, in men with low testosterone, beneficial cardiovascular effects are seen with testosterone replacement (374). In women with polycystic ovary syndrome, high testosterone levels are associated with elevated blood pressure (374). Dose-ranging studies are required to delineate these effects.

The sex chromosomes may have a direct impact on sex differences in the physiology and pathophysiology of the cardiovascular system and cardiovascular risk, independent of sex hormones. Human sex chromosome aneuploidies, such as Turner and Klinefelter syndromes, suggest that sex chromosome abnormalities can carry an increased risk of CVD. Women with Turner syndrome have around a 3-fold greater mortality and reduced life expectancy relative to the general population (375–377). CVD is a leading cause of increased mortality in Turner syndrome (375–377). Congenital cardiac anomalies, hypertension, coarctation of the aorta, diabetes, ischemic heart disease, and stroke are commonly associated with this condition (378). Similarly, men with Klinefelter syndrome have a high cardiovascular risk profile (379, 380), and an increased risk of

mortality from cardiovascular disease (381, 382). However, observations from studies in individuals with sex chromosome aneuploidies are complicated by confounding factors, including abnormal gonadal sex hormone levels associated with gonadal failure. Thus, it is very difficult to distinguish between hormonal versus genetic mechanisms and cardiovascular risk in these human conditions.

Experimental approaches, such as the FCG mouse model discussed in “Section I,” and Box 3 can discriminate between hormonal and sex chromosome effects in cardiovascular disease (115). Beyond genes on the sex chromosomes, there are sex differences in autosomal gene expression, which can be both organ or cell specific (383). In the kidney and the heart, hundreds of rat and human genes are regulated differently between the sexes (384–386). This disparate expression is triggered by sex hormones in ~30% of cases, with the other 70% linked to sex chromosome and microRNA dimorphisms (384, 385). For example, sex differences have been reported in the expression of nitric oxide synthase, tyrosine hydroxylase, and sodium channels in the rodent heart and kidney (332). However, few studies to date have compared gene expression and the effect on the proteome between the human sexes, and further studies are required.

Sex Differences in Pharmacotherapy for Cardiovascular and Renal Disease

Men and women respond to disease differently: kidney diseases progress faster in men than women, kidney transplants from women to men tend to fail more frequently than the reverse, and the effects of diabetes on the kidney differ between the sexes (387–392). Furthermore, symptoms and mechanisms of heart failure differ between the sexes (393). This suggests that sex-specific treatments for CKD and CVD could be required. There is currently little evidence to suggest that men and women respond differently to current treatments for hypertension (394). In large part, this is because clinical trials have lacked statistical power to take this into account. It will be difficult to achieve such an outcome for drugs that have already received FDA approval. However, some treatments are more frequently prescribed, without any basis in evidence (395). There are also marked differences in pharmacokinetics and pharmacodynamics (see Box 4), leading to more frequent adverse drug reactions in women, related to differences in drug clearance and breakdown (396). Therefore, sex should be taken in account for new treatments seeking approval in the future. When women are considered, important and unexpected sex differences are observed in almost every aspect of cardiovascular and renal function in health and

disease. Further research is required to fully understand these differences, and in turn to guide the development of sex-specific treatment guidelines for CVD and CKD.

Section V

Challenges for the Future of Sex Differences Research—Areas Requiring Special Attention

Sex differences exist in anatomy, behavior, and physiology across the animal taxa. By extension, because of these innate differences, sex differences exist at molecular and cellular levels in mechanisms that underlie these processes. Despite concerted efforts by the Office of Research on Women's Health and the Organization for the Study of Sex Differences in educating researchers about the distinction between sex versus gender, the indiscriminate use of the word “gender” continues to pervade scientific literature. The sex of established cultured cell lines is another issue; in addition to aneuploidy, chromosomal numbers change as cells are passaged and are dependent upon the tissue of origin (397, 398), but this aspect is beyond the scope of this Statement. Not surprisingly, sex differences are seen in etiology, prevalence, and outcomes in a myriad of human diseases that range from psychological and autoimmune to gastrointestinal, cardiovascular, renal, and reproductive; SARS-CoV-2 causes more severe COVID-19 disease in men than in women despite similar infection rates (399–401). Besides genetic makeup (predisposition), extraneous factors, such as the socioeconomic, demographics, education level, profession, age, and the environment, greatly influence an individual's health; COVID-19 disease outcomes especially highlight the contribution of these extraneous factors in health disparities. Factors such as the endocrine-disruptive chemicals can disproportionately affect one sex over the other; regardless, whether favorable or adverse effects are present in one or both sexes, the effects would impact trans and cisgender persons, and hence these sex-specific effects should not be overlooked or underestimated (402). Some human studies addressing sex differences take these factors into account, whereas others are more selective. Many studies of disease pathways are sensitive to levels of gonadal steroid hormones, which contribute to sex differences. In human studies, unless gender information is explicitly collected or available, the study deals with biological sex, not gender. Use of sex and gender interchangeably deemphasizes the importance of studying gender as an independent variable.

In animals or experimental models of human diseases, effects of estrogens have been investigated more often than effects of progestins and androgens, which should

be corrected. Paradoxically, female sex is often excluded from experimental design on the basis that: (i) the estrus cycle will interfere with data interpretation; (ii) mechanisms that operate in the male sex will operate in the female sex and thus only need to be confirmed in females; (iii) metabolic demands are similar between the sexes; (iv) the X chromosome in males and females is subject to similar regulation; and (v) autosomal genes will be subject to equal variance between the sexes. The same studies often ignore the diurnal cycling nature of testosterone in males; testosterone levels in male rodents can show more day-to-day variability than estrogen and progesterone levels in females. Other steroid hormones, such as glucocorticoids, that show circadian rhythm and whose levels differ between the sexes also influence gene expression and function. In rodents but not primates, sex differences in secretion of growth hormone result in sexually dimorphic hepatic metabolism of drugs and xenobiotics (403). In rodents, endocrine disruption can have transgenerational effects on male and female reproductive systems (404). Since changes in hormone levels and gene expression are dynamic, can be localized, and are spatiotemporally distinct, no one study design or condition can be used as a gold standard. Animal housing and handling conditions can also create sex differences, and thus any experimental design and data interpretation should take these variables into account. If sex-segregated data does not differ for the aspects under study, then data can be pooled from the 2 sexes and reported accordingly.

Studies in animal models have just begun to uncover unequal effects of the sex chromosomes in XX vs XY cells, so we expect further discoveries about such effects in the future. Once genes that cause sex differences are discovered in animals, the findings generate new hypotheses and rationalize human studies to determine whether the same gene also creates sex differences in humans. That question can be studied by the methods of human genetics, relating genetic variation to disease incidence and outcome. Without the animal studies, however, it is difficult to understand detailed molecular mechanisms. It is also important to remember that no single rodent or animal model can capture the complexity of any human disease, but each model provides valuable insights into one or another major aspect of disease. If different etiologies of a given disease share mechanisms, then mimicking the precise conditions that initiate human disease may not be critical.

The study of sex chromosome effects is in its infancy and has focused on proving that sex chromosomes play a role and finding the genes responsible for the effects. So far there has been little effort to understand how these factors interact with steroid hormones to cause sex differences. If

both types of factors cause differences in disease incidence, are they affecting the same or different downstream pathways? Do their effects converge, or do they independently affect different mechanisms that each influence a complex disease? Do male-biased factors (hormones, Y-chromosome genes) act synergistically to induce a male-specific state, or do they counteract each other to reduce the difference between males and females (123, 405)? Are the diverse sex-biasing factors changing in their effects across the lifespan, leading to changes in the type or amount of sex difference at different ages?

When studying sex differences in animal models of human diseases, it is important to first understand and elucidate differences at baseline in gonadally intact animals. As pointed out earlier, steroidogenic enzymes are also present in nongonadal tissues, especially the brain, thus it is not entirely possible to eliminate effects of sex steroids from all tissues. Moreover, tamoxifen-inducible *Cre* recombinase used to routinely perform lineage tracing and gene inactivation studies in mice has its own problems (406, 407) that are largely ignored and can further confound sex-specific data analysis; tamoxifen antagonizes actions of estrogen receptor- β and inhibits expression of over 70 genes (408), but the contribution of these tamoxifen-regulated genes on study results and outcomes is never accounted for and requires careful consideration. Before mechanisms behind sex differences in physiology and disease can be elucidated, a fundamental understanding of sex differences that exist at baseline, is needed.

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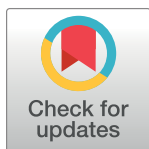
RESEARCH ARTICLE

Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK

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Abstract

Background

In adolescents with severe and persistent gender dysphoria (GD), gonadotropin releasing hormone analogues (GnRHa) are used from early/middle puberty with the aim of delaying irreversible and unwanted pubertal body changes. Evidence of outcomes of pubertal suppression in GD is limited.

Methods

We undertook an uncontrolled prospective observational study of GnRHa as monotherapy in 44 12–15 year olds with persistent and severe GD. Prespecified analyses were limited to key outcomes: bone mineral content (BMC) and bone mineral density (BMD); Child Behaviour Checklist (CBCL) total t-score; Youth Self-Report (YSR) total t-score; CBCL and YSR self-harm indices; at 12, 24 and 36 months. Semistructured interviews were conducted on GnRHa.

Results

44 patients had data at 12 months follow-up, 24 at 24 months and 14 at 36 months. All had normal karyotype and endocrinology consistent with birth-registered sex. All achieved suppression of gonadotropins by 6 months. At the end of the study one ceased GnRHa and 43 (98%) elected to start cross-sex hormones.

There was no change from baseline in spine BMD at 12 months nor in hip BMD at 24 and 36 months, but at 24 months lumbar spine BMC and BMD were higher than at baseline (BMC +6.0 (95% CI: 4.0, 7.9); BMD +0.05 (0.03, 0.07)). There were no changes from baseline to 12 or 24 months in CBCL or YSR total t-scores or for CBCL or YSR self-harm indices, nor for CBCL total t-score or self-harm index at 36 months. Most participants reported

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positive or a mixture of positive and negative life changes on GnRHa. Anticipated adverse events were common.

Conclusions

Overall patient experience of changes on GnRHa treatment was positive. We identified no changes in psychological function. Changes in BMD were consistent with suppression of growth. Larger and longer-term prospective studies using a range of designs are needed to more fully quantify the benefits and harms of pubertal suppression in GD.

Introduction

Gender dysphoria (GD) describes the experience of incongruence between an individual's experienced gender and the sex they were assigned at birth. GD [1] in children and young people, also known as Gender Incongruence [2] and previously known as Gender Identity Disorder (GID), is associated with considerable distress or impairment in social, school or other important areas of functioning [3,4]. Interventions include psychosocial support, therapy and medical or surgical interventions to align the body with the identified gender [3,5]. Terminology in this field can be challenging [6]. Here we use birth-registered sex to refer to the sex assigned at birth by clinicians based upon external genitalia [6]. Gender identity refers to a young person's personal sense of their gender. We use the terms 'continuation' and 'discontinuation' to refer to GD across childhood and adolescence.

GD in adolescence is highly likely to continue into adult life where gender dysphoria persists after the onset of puberty [3]. Those with earlier onset or more intense GD and those in whom the development of secondary sexual characteristics in puberty is associated with increasing gender dysphoria or psychological distress are more likely to have persistent GD [3,7]. In adolescents with severe and persistent GD, international [8] and national [9–11] guidelines recommend the use of treatments to suppress the rise in sex hormones (oestradiol or testosterone) in young people during puberty. Gonadotropin releasing hormone analogues (GnRHa) are synthetic peptides that work by stimulating gonadotropin release in a tonic fashion which desensitises the gonadotropin receptors, resulting in reversible suppression of sex hormone production.

In GD, GnRHa can be used from the early/middle stages of puberty with the aim of delaying irreversible and unwanted pubertal body changes and giving young people the opportunity to explore their gender identity during a period when puberty is not advancing [3]. This period also allows clinicians more time to assess the stability of young people's gender identity [6]. Despite this treatment being given in mid-puberty it is also called early puberty suppression, where 'early' refers to earlier than the historic practice of suppression after completion of puberty.

Pubertal suppression is currently practised in the majority of international centres across Europe, the Americas and Australasia, as evidenced by a recently published survey of 25 international centres by the European Society of Paediatric Endocrinology (ESPE) [12]. Pubertal suppression with GnRHa as monotherapy is a time-limited strategy, due to the potential for side effects with long-term use. In the UK, for those commencing under age 15 years, use of GnRHa alone ceases after 16 years when young people face a decision to return to the sex hormones produced by their body or begin cross-sex hormones [5]. There are limited data on the outcomes of pubertal suppression in the treatment of young people with GD [3,13]. A recent

systematic review included data on the physical and mental health outcomes of pubertal suppression using GnRHa in over 500 young people [4]. Longer-term follow-up data on pubertal suppression in GD are limited to individuals from four cohorts [14–19].

In 2011 a study was begun to evaluate the proximal outcomes of mid-pubertal suppression using GnRHa in young people with persistent GD (see <http://gids.nhs.uk/our-early-intervention-study>). Use in the UK began after mid-pubertal suppression had been incorporated into international guidelines [20] and had become available in the USA [21,22], the Netherlands [15], Australia [23] and a number of European countries. The Gender Identity Development Service (GIDS) at the Tavistock and Portman NHS Foundation Trust, London, is a national service for children and young people with GD, drawing from England, Wales and Ireland. Mid-pubertal suppression was offered by the GIDS from 2011 initially only within an ethically approved uncontrolled observational research study with prospective data collection, where all participants received GnRHa. We anticipated that we would recruit 10–15 young people per year for 3 years and follow them up to the end of monotherapy with GnRHa. At the time, a randomised controlled study was not considered feasible due to very small numbers and inability to retain participants in the control arm, as the control treatment would have resulted in progression into near complete puberty and an increasing number of UK families were accessing mid-pubertal suppression internationally. Allocation blinding was also not considered feasible in young people using a product requiring monthly injections.

Here we describe the short-term outcomes of 44 young people with GD from this research cohort, recruited aged 12–15 years and followed to the end of GnRHa monotherapy after age 16 years. This paper describes their medical, psychological and social outcomes during the GnRHa treatment pathway up to the point of decisions about whether or not to undertake further physical treatment. The aims of the study as defined at inception in 2011 were:

1. To evaluate the benefits and risks for physical and mental health and wellbeing of mid-pubertal suppression in adolescents with GD
2. To add to the evidence base regarding the efficacy of GnRHa treatment for young people with GD
3. To evaluate continuation and discontinuation of GD and the continued wish for gender reassignment within this group.

Methods

We undertook an uncontrolled prospective observational study of GnRHa monotherapy in a highly selected group of young people with persistent and severe GD.

Participants

The cohort consisted of 44 sequentially eligible young people, aged 12 to 15 years, who were recruited between April 2011 and April 2014 and who commenced GnRHa treatment between June 2011 and April 2015. They were all recruited from patients referred to the GIDS.

Eligibility criteria were chosen to match those used for a Netherlands cohort [24], namely that the young person:

- A. is aged 12–15 years
- B. Psychological criteria
 1. has been seen by the GIDS for at least 6 months and attended at least 4 interviews for assessment and therapeutic exploration of their gender identity development.

2. psychological stability sufficient to withstand the stresses of medical treatment for GID.
3. fulfils the following criteria relating to GID:
 - a. Throughout childhood (defined as over 5 years) the adolescent has demonstrated an intense pattern of cross-gendered behaviours and cross-gender identity.
 - b. The adolescent has gender dysphoria that is significantly increased with the onset of puberty. Following assessment the clinician(s) working with the young person deem that there is a high likelihood of the young person experiencing severe psychological distress consequent on experiencing full pubertal development before pubertal suppression is implemented.
4. The young person and their parents/guardians are actively requesting pubertal suppression.
5. is able to give informed consent.

C. Physical/medical criteria

1. is in established puberty:
 - For birth-registered males Tanner (genital and pubic hair (PH)) stage 3 and above.
 - For birth-registered females Tanner (breast and PH) stage 2 and above.

The rationale for the sex difference was that the pubertal growth spurt which early intervention aims to avoid occurs typically two years earlier in females (Tanner stage 2–3) than in males (Tanner stage 3–4), thus earlier intervention is required in females.
 2. has normal endocrine function and karyotype consistent with birth registered sex.
- Note that the presence of mildly elevated androgens in birth registered females consistent with polycystic ovarian syndrome is not an exclusion criterion.
- Exclusion criteria:
1. Inability to participate with full investigatory protocol e.g. needle phobia, failure to attend for tests and scans.
 2. Body mass index (BMI) <2nd centile for age and birth-registered sex [20].
 3. Serious psychiatric conditions (e.g. psychosis, bipolar condition, anorexia nervosa, severe body-dysmorphic disorder unrelated to GD).
 4. Inability to give informed consent according to the Fraser/Gillick guidelines.
 5. Low spine or hip bone mineral density (BMD) on DXA scan: more than 2 SD below expected BMD for age and birth-registered sex. In exceptional circumstances a low BMD was acceptable if:
 - i. it was felt to be clinically appropriate by the treating clinicians, who felt that on the balance of risks, pubertal suppression was justified despite the later risk of osteoporosis
 - ii. the young person and parents understood the risks of GnRHa treatment for bone density (i.e. potential risks of later osteoporosis)
 - iii. The young person and parents consented to more frequent monitoring of BMD (repeat DXA scans 6 months after starting GnRHa and yearly thereafter while on GnRHa) despite the small DXA radiation dose

- iv. The young person and parents consented to stopping treatment if raw BMD fell whilst on GnRHa.

The treatment

The treatment under study was suppression of puberty using the GnRHa *triptorelin* together with psychosocial support and therapy, from study entry until the end of the GnRHa monotherapy pathway at age 16 years or older. GnRHa monotherapy ceased when young people either started cross-sex hormones (and continued on GnRHa) or stopped GnRHa. Treatment duration was therefore from 1 to 4 or 5 years depending on age at study entry. Consenting young people were given triptorelin 3.75mg by intramuscular injection every 28 days during the treatment period. Two participants who found monthly injections difficult were moved to a ten-weekly preparation of 11.25mg of triptorelin. The aim of treatment was to suppress gonadotropins and sex hormones to near pre-pubertal levels [13]. Continued regular attendance for psychological support and therapy throughout the study was a precondition of GnRHa prescription. In addition local psychological services provided support for co-occurring difficulties for participants as required.

Procedures and pathway

All young people and families attending the GIDS during the study period were provided with an information leaflet about research underway within the unit. Those wishing to find out more about the study discussed it with their GIDS clinicians and those deemed likely to be eligible were given detailed written study information. Those wanting to participate were invited to a medical clinic at UCLH for an initial discussion. At the first medical clinic, young people and families were seen by a senior paediatric endocrinology clinician together with a senior GIDS clinician, who discussed with the family the then current state of knowledge and rationale for treatment, eligibility criteria and potential risks and benefits of participation. Risks included the anticipated side-effects of GnRHa treatment including symptoms resulting from the withdrawal of sex steroids (headaches, hot flushes), fatigue, loss of libido and low mood, the potential that treatment could influence the continuation of their GD and the potential for unknown risks. It was emphasised that young people needed to continue with both regular medical and psychosocial follow-up during the study and that treatment would cease if they did not comply with the treatment or monitoring requirements. A full medical history was elicited and the clinicians also reviewed a summary of the psychological history and assessment from the GIDS. In this visit information sheets were re-provided if families had lost them or forgotten details of the study. If young people and families remained interested in participation, medical investigations were organised and families were invited for a repeat discussion and a formal evaluation of eligibility at a second medical clinic visit approximately 3 months later. Families were asked to think about the issues raised in the meeting and to discuss with their GIDS clinicians if necessary, in order to discuss further at the second visit.

At the second medical clinic visit, the same clinicians repeated the discussion of risks and benefits and explored understanding with the young person and family. A chaperoned medical examination was undertaken including pubertal assessment and the results of medical investigations were reviewed. Endocrine and GIDS clinicians jointly reviewed eligibility and offered participation in the study to those deemed eligible.

The implications of treatment for fertility were discussed at the first and second medical visits and all young people were urged to consider storing gametes before starting GnRHa. Access to storage depended on regional availability within the NHS. Note that counselling on fertility

continued across the study, and clinicians periodically checked with young people who had decided against storage whether they wished to revisit their decision.

Informed consent was obtained in writing from both the young person and a parent or carer holding parental responsibility. The ability of the young person and parents to give informed consent was assessed jointly by the senior adolescent endocrine and GIDS clinicians, informed by written notes from the GIDS team. The consent forms were read with the young person and the parent by the clinicians to be sure they fully understood the information on the forms before signing.

48 young people and families attended the medical clinics for discussion of participation in the trial, of whom 44 wished to participate. Eight young people (7 birth assigned males) were not eligible for participation at the second medical visit as they were not yet sufficiently advanced in puberty. They were followed up every 3–6 months and entered the study subsequently when sufficiently advanced in puberty (median waiting time 7 months).

The date of signing the consent form was taken as the start of study treatment, although it frequently took one to three months for GnRHa treatment to start due to administrative requirements. Participants were followed up in the endocrine clinic, 3–6 monthly in the first 18 months and 12-monthly thereafter, till the end of the treatment pathway, defined as the date on or after the 16th birthday when a decision was made to either cease GnRHa or start cross-sex hormones. The final participant completed the pathway in February 2019.

Outcomes

The following data were collected:

A. Baseline explanatory variables

1. Sex and gender: Young people were classified by their sex assigned at birth (birth-registered sex) and self-identified gender.
2. Ethnicity: Ethnicity was obtained from clinic records. For analysis, ethnicity was grouped as white, South Asian, black or mixed.
3. Puberty: Pubertal status at baseline was classified using information on genital/breast and pubic hair Tanner stages as appropriate. This was summarized into a single pubertal stage, with the breast/genital stage taking precedence if there was discrepancy between breast/genital and public hair stage.
4. Clinical data: These consisted of a) identification of normal phenotype on physical examination for birth-registered sex; b) venepuncture assessment of endocrinology (gonadotropins, prolactin, oestrogen or testosterone, adrenal androgens, thyroid function; and a short synacthen test in birth-registered females only), karyotype, full blood count, renal and liver function, calcium and vitamin D; and c) imaging including wrist bone age and (in birth-registered females only) pelvic ultrasound scan. Medical assessment at baseline and follow-up was consistent with Endocrine Society guidelines [8,20].

B. Study outcomes

Study outcomes concerned domains including response to treatment, bone health, safety indicators and adverse events, psychological function; participant experience and satisfaction; and decisions regarding treatment following GnRHa. Outcome data were collected at routine clinic visits to GIDS or medical clinics at UCLH and timings therefore varied. For the purposes of these analyses, data for each participant were assigned to baseline (before treatment) and to the closest of the following outcome periods: 12, 24, 36 and 48 months on treatment. For safety and response to pubertal suppression outcomes, data were also examined at 6 months.

1. Response to pubertal suppression

Gonadotropins (LH, FSH), testosterone (in birth-registered males) and oestrogen (birth-registered females) were measured after venepuncture. Height, weight and blood pressure were recorded by trained clinic staff. BMI z-score for age and birth-registered sex was calculated [25]. Menarcheal status and presence/absence of menstrual periods was obtained by report from birth-registered females.

2. Bone health

Bone mineral content (BMC) and bone mineral density (BMD) in the lumbar (L1 to L4) spine and hip (total hip) were measured by dual energy X-ray absorptiometry (DEXA) scans using a Hologic Discovery QDR series model 010–1549 (Hologic Inc, Bedford, MA, USA). BMD z-scores for age and birth-registered sex appropriate to this machine were calculated [26]. BMD z-scores for spine and hip were further adjusted for height (height-adjusted z-scores) using published formulae [27].

3. Safety indicators and adverse events

Blood samples were collected by venepuncture for liver and renal function, full blood count, calcium and vitamin D, prolactin, adrenal androgens and thyroid function. Participants were routinely questioned about adverse events at medical clinic visits, including anticipated events such as headaches, hot flushes or fatigue plus any other unanticipated events.

4. Psychological function

Psychological outcomes included a clinical outcome routinely collected after GIDS appointments and a range of outcomes assessed using questionnaires. A standardised set of psychological questionnaires used in the GIDS clinic was completed at the time young people were deemed potentially eligible and referred to the medical clinic. Questionnaires were completed at home by the young person and parent between GIDS clinical meetings, and a research assistant followed up families to ensure their completion. Questionnaires were repeated approximately every 12 months on treatment.

i. General psychological functioning

The Child Behaviour Checklist (CBCL) (parent report) and Youth Self Report (YSR) (self-report) are general measures of psychological functioning and part of the Achenbach System of Empirically Based Assessment (ASEBA; www.aseba.org). The CBCL consists of 113 questions and is validated for children aged 6–18 years in international population samples [28]. The YSR consists of 112 questions and is validated in international populations of young people aged 11–18 years [29]. Questions in both are scored on a three-point Likert scale (0 = absent, 1 = occurs sometimes, 2 = occurs often), with the time frame for item responses being the past six months. Scoring for both instruments provides a total problems score, an internalizing problems score (items which assess anxious/depressed, withdrawn-depressed, and somatic complaints) and an externalizing score (focusing on rule-breaking and aggressive behaviours). Each questionnaire was scored with Assessment Data Manager Software using ASEBA standard norms and t-scores were generated based on reference data for birth-registered sex and broad age-ranges (here 12–18 years). Higher scores indicate greater morbidity. To account for normative change within our age-range, we used international reference data [29] to transform YSR raw scores into z-scores for year of age. As reference data from the UK were not available, reference data from both Australia and the Netherlands were used.

ii. Self-harm index

Self-harm actions and thoughts were assessed through two questions in each of the CBCL (parent report) and YSR (self-report): Item 18 (I deliberately try to hurt or kill myself) and Item 91 (I think about killing myself). Possible responses for each question were 0 = not true, 1 = somewhat or sometimes true, or 2 = very true or often true. We followed previous studies in calculating a self-harm index score to avoid multiple statistical comparisons across

correlated categorical-response variables. The index was calculated as the sum of the two items in each scale to create an index from 0 to 4 for each of the CBCL and YSR [30–32], a higher score indicating greater self-harm thoughts and behaviour.

iii. Health related quality of life (HRQoL)

This was assessed through separate young person and parent Kidscreen-52 questionnaires, each consisting of 52 items which assess HRQoL across ten dimensions: physical well-being; psychological well-being; moods and emotions; self-perception; autonomy; relations with parents and home life; social support and peers; school environment; social acceptance (bullying); and financial resources. All items use five-point Likert-style scales to assess either the frequency (never-seldom-sometimes-often-always) of certain behaviours/feelings or the intensity of an attitude (not at all-slightly-moderately-very-extremely). The measure was developed for young people aged 8–18 years, with the recall period of one week. The questionnaires provide scores in the form of continuous t-scores for the ten subscales derived from a multinational European sample [33]. Lower scores indicate lower HRQoL, i.e. greater morbidity.

iv. Body image

The Body Image Scale (BIS) is a self-report measure of 30 items used to assess body image satisfaction or dissatisfaction validated for age 12+. The instrument considers 30 body features which the respondent is asked to rate in terms of satisfaction on a five-point scale (1 = very satisfied, 2 = satisfied, 3 = neutral, 4 = dissatisfied, and 5 = very dissatisfied). The BIS provides a total score in the form of a continuous score for the total scale as well as for three subscales assessing primary sexual characteristics, secondary sexual characteristics and ‘neutral’ characteristics (i.e. non-sexual characteristics, e.g. nose) [34]. Higher scores represent higher degrees of body dissatisfaction.

v. Gender dysphoria

The Utrecht Gender Dysphoria Scale (UGDS) is a self-report measure used to assess the intensity of GD validated for age 12+. It comprises of 12 statements with agreement on a five-point scale (1 = agree completely, 2 = agree somewhat, 3 = neutral, 4 = disagree somewhat, and 5 = disagree completely). There are separate versions for birth-registered males and females. Items are summed to give a single total score, with higher scores indicating greater GD.

vi. Clinical outcomes

The Children’s Global Assessment Scale (CGAS) is a rating of functioning in children and young people aged 6–17 years, extensively used as a routine clinical measure in child and adolescent mental health services in the UK. Treating clinicians assign young people a single score between 1 and 100, based on a clinician’s assessment of a range of aspects related to a child’s psychological and social functioning, with the time period being the previous month. Higher scores indicate better functioning, with categories ranging from ‘extremely impaired’ (1–10) to ‘doing very well’ (91–100) [35].

5. Participant experience and satisfaction with GnRHa

Young people were invited to participate in semi-structured qualitative interviews at 6–15 months and 15–24 months after starting GnRHa. Interviews were conducted in person or by telephone with a research assistant. If young people were unavailable, questions were posted to be completed and returned. The interview consisted of 12 questions related to changes young people had experienced in ten domains since starting on GnRHa: life overall, memory, focus, sense of direction, mood, energy levels, relationships with friends, relationships with family, gender role and sexuality. For each domain, young people were asked first about the general direction of change in that domain (whether changes were positive, neutral, negative or mixed positive and negative) and then asked for examples of changes experienced and why they assigned the chosen change rating. At the end of the interview two further questions were asked about change in any other experiences (i.e. allowing open ended responses) and whether

young people wished to continue on GnRHa treatment. Note there was no interview conducted before young people started GnRHa. Interviews were recorded in contemporaneous written notes by the researcher. The questionnaire is provided in the [S1 Appendix](#).

6. Further treatment decisions

Decisions made at the end of the GnRHa pathway were recorded in terms of which if any further treatment for GD young people chose.

Note that other measures of gender dysphoria (Gender Identity Interview; Recalled Childhood Gender Identity Scale) were specified in our original protocol, however they were discontinued during the study as: a) they were historical instruments with poor construct validity and the binary references to male and female roles were challenging for some participants; and b) repeated questioning about gender dysphoria resulted in some distress to respondents. Our protocol had originally included the ASEBA Teacher Report Form (TRF), however we were unable to obtain data from teachers so this outcome was dropped. The Social Responsiveness Scale (SRS) was a baseline only assessment of autistic traits; these data will be analysed in the future.

Analysis plan

Analyses were conducted according to the Statistical Analysis and Dissemination Plan, lodged with the ethics committee that approved the study before the analysis started (see [S2 Appendix: Statistical Analysis Plan](#)). The analysis plan was designed to report data on all outcomes but to minimise the likelihood of chance findings due to the large number of outcomes and small sample size. Sample sizes necessarily varied across follow-up as young people were recruited at different ages (12–15 years) but left the study soon after their 16th birthday. All 44 participants had data at 12 months follow-up. As participants necessarily left the study soon after their 16th birthday, numbers reduced after 12 months follow-up as participants could no longer remain in the study. Note this does not represent drop-out. There were 24 left at 24 months, 14 at 36 months and 4 at 48 months. In view of this, outcome reporting was restricted to change from baseline to 12, 24 and 36 months. We made no attempt to account for missing data due to the small sample size and the likelihood of the data missing not at random.

We restricted analyses to primarily descriptive statistics, with formal statistical testing of change across the study restricted to six pre-specified outcomes, i.e.:

1. Overall psychological functioning
 - a. parent report: CBCL total t-score
 - b. young person self-report: YSR total t-score
2. Self-harm index
 - a. parent report: CBCL self-harm index
 - b. young person self-report: YSR self-harm index
3. Bone health
 - a. BMD and BMC for lumbar spine
 - b. BMD and BMC for hip

Assessment of change was through paired t-tests for normally distributed data and the Wilcoxon matched-pairs sign-rank test for non-normal data. The number of formal statistical tests conducted in the study was 16; with overall significance at $p = 0.05$ and a Bonferroni correction, the appropriate threshold for statistical significance is about $p = 0.003$.

In our results and conclusions we refer to change in outcomes only for those that were formally tested. Reporting for other continuous outcomes was restricted to mean and 95% confidence intervals (95%CI) or median and interquartile range (IQR). For categorical outcomes, simple proportions were reported. We reported laboratory tests as normal or abnormal based upon laboratory reference data for age, with the exception of gonadotropins. We did not report data where the sample size was less than 8.

Analysis of potential predictors of outcome was confined a priori to two factors, birth-registered sex and pubertal stage at baseline. Three pre-specified continuous outcomes were examined at 12 months, namely:

1. BMD for lumbar spine
2. YSR total t-score
3. CGAS score

Associations were examined using linear regression of follow-up score on baseline score, adding each baseline factor separately to the model and considering the interaction of predictor with baseline score. All analyses were conducted using Stata 16 (Statacorp, College Station TX).

Responses to the semi-structured interview questionnaires were analysed simply for the thematic content in terms of the direction and amount of change that young people experienced in each domain. This involved coding responses about experiences since starting GnRHa into categories; i.e. either positive/improving, negative/deteriorating, both positive and negative, no change or not known. The question on change in sexuality was coded as yes change, no change or not known. Wishes to continue with GnRHa were coded as yes, no or don't know.

To compare our findings with the literature, we drew upon recent reviews [3,4,6,13] and updated a recent review [4] from 1 June 2017 to 31 December 2019 using the same search terms in Medline (see [S1 Appendix](#)).

Ethics

Ethical approval for the study was obtained from the National Research Ethics Service (NRES: reference 10/H0713/79) in February 2011. Study consent allowed the use of routinely collected clinical data (medical and psychological) as part of clinical treatment for the study. Study procedures including consent were reviewed by the UK Health Research Authority.

Data sharing. These are highly sensitive data from a small group of vulnerable young people treated in a single service and the risk of identification and disclosure is high. Research ethics permissions at the time the study was undertaken did not include permission to share data. After discussions with the Health Research Authority, UK, an anonymised dataset modified to remove sensitive data and minimise disclosure risk of personal information has been deposited with the UK Data Service.

Results

Participants received psychosocial assessment and support within the GIDS before entering the study for a median of 2.0 years (IQR 1.4 to 3.2; range 0.7 to 6.6). The median time between first medical assessment at UCLH and starting treatment was 3.9 months (IQR 3.0 to 8.4; range 1.6 to 25.7). Median time in the study was 31 months (IQR 20 to 42, range 12 to 59).

Baseline characteristics of the participants by birth-registered sex are shown in [Table 1](#). Median age at consent was 13.6 years (IQR 12.8 to 14.6, range 12.0 to 15.3). A total of 25 (57%) were birth-registered as male and 19 (43%) as female. At study entry, birth-registered males

Table 1. Participant characteristics at baseline.

		Total sample	Birth-registered sex	
		n = 44	male n = 25	female n = 19
Age at consent (years)	Median (IQR)	13.6 (12.8, 14.6)	13.4 (12.7, 14.1)	13.9 (13.5, 14.7)
Ethnic group n (%)	white	39 (89)	24 (96)	15 (79)
	South Asian	1 (2)	1 (4)	0
	black	2 (5)	0	2 (11)
	Mixed ethnicity	2 (5)	0	2 (11)
Pubertal status n (%)	Stage 2	0	0	0
	Stage 3	19 (43)	17 (68)	2 (10)
	Stage 4	16 (36)	5 (20)	11 (58)
	Stage 5	9 (21)	3 (12)	6 (32)
Menarcheal status n (%)	Premenarcheal	-	-	4 (21)
	Post-menarcheal	-	-	15 (79)
Time in study (months)	Median (IQR)	31 (20, 42)	37 (24, 43)	29 (17, 36)
Age at end of pathway (years)	Median (IQR)	16.1 (16.0, 16.4)	16.1 (16.0, 16.5)	16.1 (16.0, 16.3)

At baseline, all participants had normal endocrinology, karyotype, imaging and clinical phenotype on physical examination for birth-registered sex and normal full blood count and liver and renal function. No participants had evidence of disorders of sexual differentiation. Eight participants (18%) had vitamin D insufficiency at baseline and were given vitamin D supplements.

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were predominantly in stage 3 puberty (68%) whilst birth-registered females were predominantly in stages 4 (58%) or 5 (32%) with 79% (15/19) post-menarcheal. 89% of participants were of white ethnicity. Birth-registered females were on average 6 months older than birth-registered males at study entry.

Response to treatment

All participants achieved adequate suppression of gonadotropins and sex hormones by 6 months (mean LH 0.5IU/L; mean FSH 1.4IU/L) and maintained it throughout the study (see Table 2). Liver function, basic haematology and biochemistry were normal in all participants at 3–6 months. All post-menarcheal birth-registered females reported amenorrhoea in the 3 months after starting GnRHa treatment and remained so throughout treatment. No participants reported progression in pubertal development. Height and weight were normal at baseline. Height growth continued through the study but more slowly than expected for age, thus

Table 2. Growth and gonadotropin levels at baseline, 12, 24 and 36 months.

Growth		Baseline		12 months		24 months		36 months	
		n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)
Height	z-score	44	0.4 (0.1, 0.7)	44	0.2 (-0.1, 0.4)	24	0.0 (-0.4, 0.4)	14	0.0 (-0.5, 0.5)
Weight	z-score	44	0.8 (0.4, 1.3)	44	0.8 (0.3, 1.3)	24	0.6 (-0.1, 1.3)	14	1.0 (0.1, 1.9)
BMI	z-score	44	0.7 (0.2, 1.1)	44	0.7 (0.2, 1.2)	24	0.6 (-0.1, 1.3)	14	1.1 (0.3, 1.9)
Gonadotropins									
LH	IU/L	42*	4.2 (2.8, 5.6)	44	0.60 (0.42, 0.68)	17	0.40 (0.22, 0.60)	7	0.30 (0.14, 0.46)
FSH	IU/L	42*	3.9 (3.2, 4.5)	44	1.3 (1.0, 1.7)	17	1.0 (0.6, 1.5)	7	1.4 (0.7, 2.2)

*In two participants data recorded as normal at baseline were not available.

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height z-score fell over time (Table 2). Weight and BMI z-scores were stable from baseline to 24 months but increased at 36 months.

Three participants had brief periods off GnRHa prior to their 16th birthday. In one, treatment was withdrawn by clinicians due to non-attendance at clinics and restarted 4 months later. Another requested a period off GnRHa to think further about treatment in view of other things happening in their life; they restarted 4 months later. A third, birth-registered male, stopped GnRHa for 9 months to attempt to store sperm, contrary to their earlier decision not to, and restarted afterwards.

Median age at the end of the GnRHa pathway was 16.1 years (Table 1). A quarter of participants made their decision more than six months later, either because they wished to delay due to school exams or other events or because clinicians felt they were not yet ready to make the decision. One young person decided to stop GnRHa and not start cross-sex hormones, due to continued uncertainty and some concerns about side-effects of cross-sex hormones. The remaining 43 (98%) elected to start cross-sex hormones.

Bone mineral density. BMD was available on 44 participants at baseline, 43 at 12 months, 24 at 24 months and 12 at 36 months (Table 3). Numbers were lower for hip than for spine as some hip scans were not done for technical reasons. The table shows mean values at baseline and 12, 24 and 36 months, along with mean baseline values corresponding to the paired samples at each time point. There was no change from baseline in spine or hip at 12 months nor in hip at 24 and 36 months, but at 24 months lumbar spine BMC and BMD were higher than at baseline, as was lumbar BMC at 36 months. Lumbar and hip BMD age-adjusted z-scores were in the normal range at baseline but point-estimates fell at 12 and 24 months but not at 36 months. Point-estimates for height-adjusted z-scores for lumbar and hip BMD also fell at 12 and 24 months but not at 36 months.

Psychological outcomes. For the standardised questionnaires, baseline assessments were conducted at a median of 0.5 (IQR 0.4, 0.8) years before starting treatment, and were available for all 44 participants by self-report and 43 by parental report. Data on the CBCL, YSR, Kidscreen-52, BIS and CGAS were normally distributed whilst those for UGDS and the CBCL and YSR self-harm indices were skewed.

The first psychological follow-up was at a median of 13 (IQR 12, 14) months after start of treatment, with ASEBA data available for 41 participants (parent and self-report). ASEBA data at 24 months (median 25 (21, 28)) were available on 20 young people by parent report and 15 by self-report, and at 36 months (median 36 (29, 39)) on 11 by parent report and 6 by self-report.

Formal testing was undertaken only for key ASEBA outcomes (Table 4). For the CBCL total t-scores, there was no change from baseline to 12, 24 or 36 months. Similarly for the YSR total t-score, there was no change from baseline to 12 or 24 months; YSR data at 36 months (n = 6) were not analysed. There were no significant changes in parent-report CBCL self-harm index scores from baseline to 12, 24 or 36 months, nor for self-report YSR self-harm index scores.

Other psychological outcomes are described in Table 5. Point-estimates of scores on the Kidscreen-52, BIS, UGDS and CGAS showed little change over time.”

The pre-specified outcomes of BMD at lumbar spine, YSR total t-score and CGAS score at 12 months, adjusted separately for birth-registered sex and baseline pubertal status, along with the baseline level of the outcome, are shown in Table 6. None of the outcomes were associated with birth-registered sex or pubertal status, and there were no important interactions.

Participant experience, satisfaction and side effects. 41 participants completed interviews at 6–15 months (median 9) and 29 at 15–24 months (median 21); 3 missed both. Fig 1 shows proportions with positive or negative changes for life overall, mood and friendships, with summary data for all questions shown in S1 Appendix (S1 and S2 Tables).

Table 3. Bone mineral density outcomes at baseline, 12, 24 and 36 months.

		12 months							24 months				
		Baseline		Baseline for those followed up		Follow-up	Change	p	Baseline for those followed up		Follow-up	Change	p
		n	Mean (95% CI)	n	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)		n	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
Lumbar	BMC	44	39.5 (35.9, 43.1)	42	39.6 (35.8, 43.4)	41.2 (38.2, 44.2)	1.6 (0.2, 3.1)	0.03	24	34.1 (30.3, 37.9)	40.1 (36.7, 43.5)	6.0 (4.0, 7.9)	<0.0001
	BMD	44	0.76 (0.71, 0.80)	43	0.76 (0.71, 0.80)	0.77 (0.72, 0.81)	0.01 (-0.00, 0.03)	0.17	24	0.68 (0.63, 0.74)	0.73 (0.68, 0.78)	0.05 (0.03, 0.07)	0.0001
Hip	BMC	43	25.2 (23.2, 27.1)	39	25.5 (23.4, 27.6)	26.1 (24.4, 27.9)	0.7 (-0.2, 1.5)	0.13	22	23.9 (21.2, 26.6)	26.3 (24.1, 28.6)	2.4 (0.7, 4.1)	0.008
	BMD	43	0.80 (0.75, 0.86)	39	0.81 (0.75, 0.87)	0.82 (0.78, 0.86)	0.01 (-0.02, 0.05)	0.6	22	0.76 (0.68, 0.85)	0.79 (0.74, 0.84)	0.03 (-0.04, 0.10)	0.4
BMD z-scores	Spine	44	-0.3 (-0.7, 0.0)	43	-0.3 (-0.7, 0.1)	-1.0 (-1.3, -0.7)			24	-0.5 (-1.1, 0.0)	-1.5 (-2.1, -0.8)		
	HAZ spine	44	-0.5 (-0.8, -0.1)	43	-0.4 (-0.8, -0.1)	-1.0 (-1.3, -0.6)			24	-0.7 (-1.2, -0.1)	-1.3 (-1.9, -0.7)		
	Hip	43	-0.5 (-0.9, -0.1)	39	-0.5 (-0.9, -0.1)	-1.0 (-1.3, -0.6)			21	-0.5 (-1.1, 0.1)	-1.4 (-2.0, -0.9)		
	HAZ hip	43	-0.7 (-1.0, -0.3)	39	-0.6 (-1.0, -0.2)	-0.9 (-1.3, -0.5)			21	-0.5 (-1.1, 0.1)	-1.2 (-1.7, -0.6)		
36 months													
				Baseline for those followed up		Follow-up	Change	p					
				n	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)						
Lumbar	BMC			12	37.05 (31.0, 43.1)	42.4 (37.4, 47.4)	5.3 (2.8, 7.8)	0.0007					
	BMD			12	0.72 (0.65, 0.80)	0.76 (0.70, 0.82)	0.03 (.00, 0.07)	0.05					
Hip	BMC			12	26.1 (22.1, 30.0)	26.8 (21.2, 32.3)	0.7 (-3.8, 5.2)	0.7					
	BMD			12	(0.82, 0.73, 0.91)	0.81 (0.74, 0.88)	-0.009 (-0.05, 0.03)	0.6					
BMD z-scores	Spine			12	-0.2 (-1.0, 0.6)	-1.5 (-2.2, -0.8)							
	HAZ spine			12	-0.4 (-1.2, 0.3)	-1.3 (-2.2, -0.5)							
	Hip			12	-0.3 (-1.3, 0.6)	-1.1 (-1.8, -0.5)							
	HAZ hip			12	-0.5 (-1.5, 0.5)	-1.0 (-1.8, -0.2)							

BMD: bone mineral density; BMC bone mineral content; HAZ height adjusted z-score.

BMD z-scores were not formally tested—see [Methods](#).

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Most participants reported positive or a mix of positive-negative changes in their life at both time points. At 6–15 months 46% reported only positive changes, including feeling happier, relieved, less facial hair or stopping periods. A further 37% reported both positive and negative changes such as feeling happier but also experiencing hot flushes and headaches. In addition 12% reported overall negative changes namely hot flushes, tiredness, and feeling more emotional, while 5% reported no change. At 15–24 months, 55% reported solely positive changes such as feeling happier, no longer experiencing side effects and feeling more

Table 4. ASEBA outcomes at baseline, 12, 24 and 36 months.

		12 months							24 months				
		Baseline		Baseline for those followed up	Follow-up	Change	p		Baseline for those followed up	Follow-up	Change	p	
		n	mean (95% CI)	n	mean (95% CI)	mean (95% CI)	mean (95% CI)		n	mean (95% CI)	mean (95% CI)	mean (95% CI)	
Parent report CBCL	Total problems t-score	43	61.6(58.4, 64.7)	41	61.5(58.2, 64.7)	61.8(58.4, 65.1)	0.3(-2.0, 2.6)	0.8	20	61.2(56.5, 65.8)	60.2(54.6, 65.8)	-1.0(-4.0, 2.1)	0.5
	Externalising problems t-score	43	55.8(52.4, 59.3)	41	55.7(52.1, 59.3)	55.4(51.8, 59.0)			20	55.4(49.9, 60.9)	55.2(48.9, 61.5)		
	Internalising problems t-score	43	62.1(58.7, 65.5)	41	61.8(58.3, 65.3)	62.9(59.5, 66.3)			20	60.4(55.7, 65.1)	60.1(54.6, 65.6)		
Self-report YSR	Total problems t-score	44	57.9(55.0, 60.8)	41	57.6(54.5, 60.6)	58.4(54.6, 62.2)	0.8(-3.1, 4.8)	0.7	15	55.1(50.9, 59.2)	56.5(50.6, 62.5)	1.5(-3.4, 6.3)	0.5
	Total problems z-score (ref: Netherlands)	44	1.01(0.67, 1.36)	41	0.97(0.62, 1.33)	0.99(0.55, 1.42)			15	0.66(0.17,1.15)	0.65(-0.05, 1.36)		
	Total problems z-score (ref: Australia)	44	0.72(0.37, 1.06)	41	0.68(0.32, 1.03)	0.68(0.24, 1.12)			15	0.39(-0.11,0.89)	0.37(-0.32, 1.07)		
	Externalising problems t-score	44	52.3(49.2, 55.5)	41	52.3(49.2, 55.4)	52.5(48.7, 56.3)			15	53.1(48.5, 57.6)	52.3(45.3, 59.4)		
	Internalising problems t-score	44	58.0(54.9, 61.2)	41	57.7(54.3, 61.0)	60.1(55.9, 64.3)			15	53.9(49.9, 58.0)	55.9(50.8, 61.1)		
Self-harm scores													
Parent report CBCL	Median (IQR)	43	0(0, 1)	40	0(0, 1)	0(0, 1)		0.3	20	0(0, 1)	0(0, 1)		>0.9
Self-report YSR	Median (IQR)	43	0(0, 1)	39	0(0, 1)	0(0, 2)		0.4	15	0(0, 0)	0(0, 0)		0.3
				36 months									
					Baseline for those followed up	Follow-up	Change	p					
				n	mean (95% CI)	mean (95% CI)	mean (95% CI)						
Parent report CBCL	Total problems t-score			11	62.4(55.1, 69.6)	61.1(52.3, 69.9)	-1.3(-6.6, 4.0)	0.6					
	Externalising problems t-score			11	56.8(48.0, 65.6)	56.2(48.3, 64.1)							
	Internalising problems t-score			11	60.4(53.5, 67.2)	62.5(53.6, 71.5)							
Self-harm scores													
Parent report CBCL	Median (IQR)			11	0(0, 1)	0(0, 1)		0.8					

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comfortable with puberty suspended. A further 17% reported both positive and negative changes including less body hair but continued growth in height, or having clearer skin but also experiencing more hunger, weight gain and tiredness. 17% reported largely negative changes such as mood swings, tiredness and hot flushes whilst 10% reported no change.

Reports of change in mood were mixed. At 6–15 months, the majority reported mood to be improved (49%), mixed changes (such as both feeling happier but experiencing some mood swings; 15%) or no change (7%), however 24% reported negative changes in mood such as

Table 5. Other psychological outcomes at baseline, 12, 24 and 36 months.

		Baseline		12 months		24 months		36 months	
		n	mean (95% CI)	n	mean (95% CI)	n	mean (95% CI)	n	mean (95% CI)
Kidscreen-52 HRQOL									
Parent report CBCL t-scores	Physical wellbeing	42	44.9(41.4, 48.5)	36	40.4(37.5, 43.3)	14	40.5(36.8, 44.2)		
	Psychological Wellbeing	41	39.8(36.7, 42.8)	36	39.0(35.4, 42.6)	14	42.4(36.9, 48)		
	Moods and Emotions	41	40.6(37.6, 43.6)	36	41.2(37.3, 45.1)	14	42.5(36.3, 48.7)		
	Self-perception	42	34.6(32.6, 36.5)	36	34.8(32.0, 37.5)	14	34.8(31.3, 38.2)		
	Autonomy	42	46.2(43.2, 49.2)	36	48.2(45.0, 51.4)	14	46.7(41, 52.4)		
	Parent relations and home life	42	48.1(44.5, 51.6)	35	46.7(42.9, 50.5)	14	49.5(44.1, 54.9)		
	Social support and peers	39	48.0(44.7, 51.4)	36	51.9(48.4, 55.3)	13	51.4(45.6, 57.2)		
	School environment	42	38.2(35.0, 41.4)	35	39.4(35.3, 43.4)	13	43.7(36, 51.3)		
	Social acceptance	39	44.7(40.7, 48.7)	32	42.3(38.1, 46.4)	13	43.5(35.9, 51.2)		
	Financial resources	42	37.9(33.9, 41.9)	36	35.8(31.5, 40.2)	14	36.3(26.4, 46.3)		
Self-report t-scores	Physical wellbeing	42	45.1(41.8, 48.5)	36	41.5(38.0, 45.0)	13	43.9(38.9, 48.9)		
	Psychological Wellbeing	42	43.0(39.6, 46.4)	36	41.1(37.0, 45.2)	14	51(45.8, 56.2)		
	Moods and Emotions	42	46.3(42.7, 49.9)	36	43.9(40.4, 47.3)	14	50.1(45.5, 54.7)		
	Self-perception	42	38.8(36.7, 40.9)	36	37.9(35.1, 40.6)	14	43.1(39.9, 46.2)		
	Autonomy	42	46.6(43.6, 49.6)	36	46.7(42.9, 50.5)	13	51.9(47.4, 56.4)		
	Parent relations and home life	42	49.7(46.2, 53.2)	36	48.7(45.2, 52.3)	14	58.4(53.3, 63.5)		
	Social support and peers	37	45.6(42.5, 48.7)	35	48.1(44.6, 51.6)	14	49.7(44.3,55.1)		
	School environment	41	45.9(42.3, 49.4)	36	44.7(39.7, 49.7)	14	49(43.6, 54.3)		
	Social acceptance	41	47.4(43.5, 51.3)	33	45.5(40.9, 50.1)	13	53.6(46.3, 60.8)		
	Financial resources	42	42.2(38.1, 46.3)	34	43.2(38.2, 48.1)	14	46.3(39.1, 53.5)		
Body image scale	Overall score	42	3.1(2.8, 3.3)	40	3.2(3.0, 3.4)	16	3(2.7, 3.2)	8	3.1(2.4, 3.7)
	Primary characteristics score	42	4.5(4.2, 4.7)	39	4.3(4.2, 4.5)	16	4.5(4.3, 4.7)	8	4.2(3.9, 4.5)
	Secondary characteristics score	41	2.9(2.6, 3.1)	40	3(2.8, 3.3)	16	2.9(2.5, 3.2)	8	2.9(2, 3.8)
	Neutral characteristics score	42	2.5(2.203, 2.707)	40	2.7(2.5, 3.0)	-	-		
Utrecht Gender dysphoria score	Median (IQR)	41	4.8(4.6, 5.0)	40	4.7(4.6, 5.0)	18	4.7(4.3, 5.0)		
Clinical outcome									
CGAS global score	Mean (95% CI)	42	62.9(59.6, 66.2)	35	64.1(59.9, 68.3)	18	65.7(59.6, 71.8)	12	66.0(58.1, 73.9)

Note: Change in outcomes in this Table were not formally tested.

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Table 6. Associations between birth-registered sex and baseline pubertal status and outcomes at 12 months.

		Outcomes at 12 months adjusted for baseline								
		BMD at lumbar spine			YSR total t-score			GCAS score		
		n	Coefficient (95% CI)	p	n	Coefficient (95% CI)	p	n	Coefficient (95% CI)	p
Birth-registered sex										
Main effect (baseline value of outcome)		43	0.86 (0.75, 0.97)	<0.0001	41	0.43 (0.05, 0.82)	0.03	33	0.74 (0.42, 1.06)	<0.0001
Birth-registered sex	Male (ref)		0			0			0	
	Female		-0.02 (-0.05, 0.01)	0.2		2.1 (-5.2, 9.4)	0.6		-3.2 (-10.0, 3.5)	0.3
Pubertal status										
Main effect (baseline value of outcome)		43	0.85 (0.72, 0.97)	<0.0001	41	0.43 (0.01, 0.84)	0.04	33	0.69 (0.37, 1.00)	<0.0001
Pubertal stage at baseline	3		0.008 (-0.03, 0.04)	0.7		0.2 (-8.3, 8.7)	0.9		1.6 (-5.5, 8.8)	0.6
	4 (ref)		0			0			0	
	5		-0.009 (-0.05, 0.03)	0.7		0.4 (-9.9, 10.8)	0.9		-7.9 (-17.6, 1.8)	0.11

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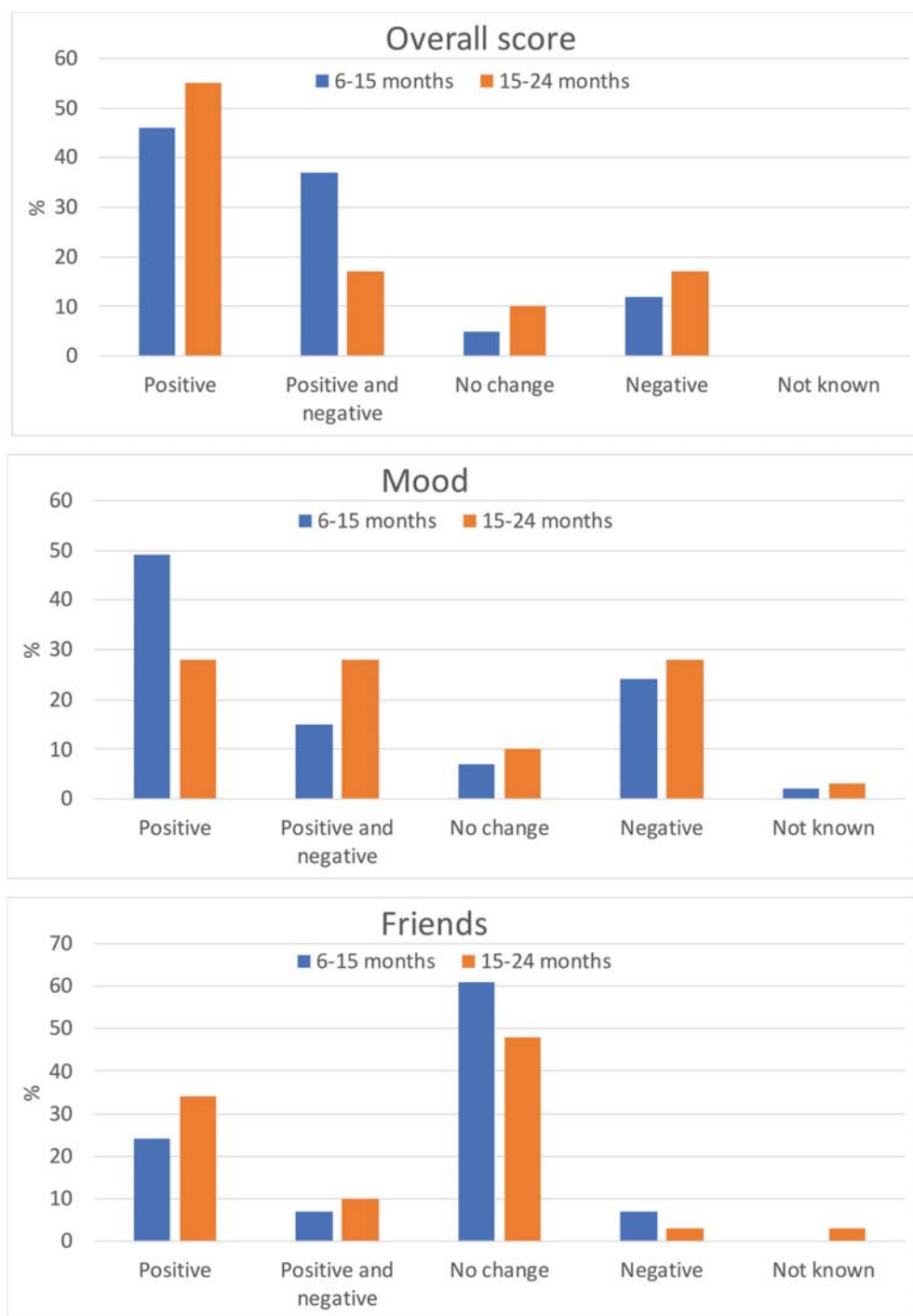


Fig 1. Ratings of change in life overall, mood and friendships at 6–15 months (n = 41) and 15–24 months (n = 29).

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experiencing more mood swings or feeling low. Findings at 15–24 months were similar. The most common negative change was reduced energy levels, reported by 29% at 6–15m and 38% at 15–24m.

Young people's reports of change in family and peer relationships were predominantly positive or neutral at both time points. Positive changes included feeling closer to the family,

Table 7. Adverse events reported across the study.

Participants	0–6m	7–12m	13–24m	25+m
	n = 44	n = 44	n = 36	n = 24
	n (%)	n (%)	n (%)	n (%)
Mild headaches or hot flushes	11 (25%)	10 (23%)	8 (22%)	4 (17%)
Moderate or severe headaches and hot flushes	2 (5%)	4 (9%)	1 (3%)	0
Fatigue—mild	2 (5%)	3 (7%)	3 (8%)	1 (4%)
Fatigue—moderate or severe	0	0	0	0
Mood swings	1 (2%)	0	0	0
Weight gain	1 (2%)	0	1 (3%)	0
Sleep problems	1 (2%)	0	1 (3%)	0
Other events	0	0	0	0
Total events recorded*	18	17	14	5

* individuals may have more than 1 event.

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feeling more accepted and having fewer arguments. Those reporting both positive and negative change reported feeling closer to some family members but not others. At 6–15 months, negative family changes were largely from family members not accepting their trans status or having more arguments. But by 15–24 months only one young person reported this. Improved relationships with peers related to feeling more sociable or confident and widening their circle of friends; negative changes related to bullying or disagreements at school. Again, at 15–24 months only one young person reported negative change, related to feelings of not trusting friends.

At 6–15 months, changes in gender role were reported by 66% as positive, including feeling more feminine/masculine, living in their preferred gender identity in more (or all) areas of life and feeling more secure in their gender identity, with no negative change reported. At 15–24 months, most reported no change although 41% reported positive changes including experimenting more with physical appearance and changing their details on legal documents.

All young people affirmed at each interview that they wished to continue with GnRHa treatment. Note that this was also the case when asked routinely at medical clinics (excepting those who briefly ceased GnRHa as noted above).

Adverse events. Adverse events are shown in Table 7. All adverse events were minor and anticipated, i.e. they were previously described in study participant information and/or noted in the triptorelin medication package inserts. Anticipated adverse events were common in the first two years, particularly mild headaches or hot flushes which were reported in 25% at 0–6m, 23% at 7–12m and 22% at 13–24m. Moderate or severe headaches and/or hot flushes were uncommon. Birth-registered females with distressing headaches or hot flushes were offered ‘add-back’ oestrogen therapy, and two accepted treatment briefly with very small doses of oestradiol, which was effective in reducing symptoms. Mild fatigue was reported by 5–8% over the first two years and no participants reported moderate or severe fatigue. Sleep problems, mood swings and weight gain were reported by very small numbers and in each case symptoms were mild. Adverse events were less common after 12 months of treatment.

Discussion

We report the short and medium-term outcomes of a prospective cohort of 44 young people with persistent and severe GD treated with GnRHa resulting in pubertal suppression from mid-puberty for 1–4 years. Young people were considered for recruitment after lengthy

assessment, spending an average of 2 years and up to 6 years within the GIDS psychological service before being referred to the endocrine clinic for assessment to enter the study. Medical assessment found no endocrine abnormalities at baseline. GnRHa treatment started in the majority of participants in later stages of puberty, with 57% in puberty stages 4 and 5 and 79% of birth-registered females being post-menarcheal. After starting GnRHa all quickly achieved and maintained suppression of pubertal hormones and none experienced pubertal progression. At the end of the study, 43 (98%) chose to start cross-sex hormones whilst one young person chose to stop GnRHa and continue with puberty consistent with their birth-registered sex.

As anticipated, pubertal suppression reduced growth that was dependent on puberty hormones, i.e. height and BMD. Height growth continued for those not yet at final height, but more slowly than for their peers so height z-score fell. Similarly for bone strength, BMD and BMC increased in the lumbar spine indicating greater bone strength, but more slowly than in peers so BMD z-score fell. These anticipated changes had been discussed with all participants before recruitment to the study. Young people experienced little change in mean weight or BMI z-score in the first two years. The rise in weight and BMI z-score at 36 months may represent a trend towards greater adiposity in those on GnRHa for a prolonged period, or reflect a higher baseline in this group.

Information on side-effects was available through routine reporting in medical clinics and in the participant experience interviews. Anticipated side effects of treatment were common, particularly mild symptoms directly related to suppression of sex hormones. Severe symptoms were uncommon. Fatigue or low energy was reported rarely in medical clinic assessments but frequently at interview (38% at 15–24m). The relationship of symptoms such as headaches, fatigue and sleep disturbance to GnRHa treatment is unclear as they are all very common in early adolescence [36,37], although a conservative perspective would regard them as side-effects of treatment.

Young people experienced little change in psychological functioning across the study. We found no differences between baseline and later outcomes for overall psychological distress as rated by parents and young people, nor for self-harm. Outcomes that were not formally tested also showed little change.

Participant experience of treatment as reported in interviews was positive for the majority, particularly relating to feeling happier, feeling more comfortable, better relationships with family and peers and positive changes in gender role. Smaller numbers reported having mixed positive and negative changes. A minority (12% at 6–15 months and 17% at 15–24 months) reported only negative changes, which were largely related to anticipated side effects. None wanted to stop treatment due to side effects or negative changes. We are not aware of comparative patient experience data from other cohorts.

The median age at consent in our study was very similar to that in the earliest published outcome study of mid-pubertal suppression using GnRHa treatment in Dutch young people (13.6 years) [24]. Similarly to this Dutch cohort, all but one of our participants elected to start cross-sex hormones after completing the GnRHa pathway. However they spent an average of 31 months on GnRHa compared with 23 months in the Dutch cohort [24]. In our study, the successful suppression of puberty and cessation of menses with GnRHa, the impact on height growth [4,16,38] and BMD [4,16] and the normality of liver and renal function through treatment were each consistent with previous reports [4,16].

Our findings that BMD increased over time in the lumbar spine but more slowly than in same age peers, resulting in a fall in z-score, are similar to others [4,14,39,40]. The fall in height-adjusted BMD z-score was consistent with but larger than the fall in height z-score. We found that birth-registered sex and pubertal status at baseline were not associated with later BMD. There is evidence that accretion of bone mass resumes and that BMD increases with the

start of cross-sex hormone therapy [4,14,39,41]. Future research needs to examine longer-term change in BMD in young people treated with mid-pubertal suppression.

We reported a range of adverse events previously described to be associated with pubertal suppression [42], with the exception of mild sleep disturbance although this is a known association with triptorelin use. As anticipated, the withdrawal of sex hormones produces symptoms such as headaches and lack of energy, although in the great majority (11 of 13 at 0–6 months; 10 of 14 at 7–12 months; 8 of 9 at 13–24 months) the symptoms were minor. Symptoms diminished over time as has previously been noted [4], and no young people chose to cease treatment due to the side-effects.

Our finding that 1 participant ceased pubertal suppression and did not commence cross-sex hormones is somewhat similar to the experience of one US cohort and a second Dutch cohort; Kuper et al. described that 2 of approximately 57 young people aged 10–15 years who commenced pubertal suppression treatment stopped this treatment without commencing cross-sex hormones [17]. Brik et al. reported that in a cohort of 137 young people who began GnRHa between 10 and 18 years and were followed until eligible to commence cross-sex hormones, 5 (3.6%) ceased treatment and did not later commence cross-sex hormones [19].

Three longitudinal studies from the Netherlands and the USA have examined psychological function over time in cohorts of young people treated with GnRHa and then cross-sex hormones [17,18,24], although the two US cohorts were of limited size. Our study adopted the same psychological outcome measures as the Dutch cohort, to facilitate comparison [24]. Mean baseline YSR scores in our cohort were similar to those previously reported in 141 young people aged 12–18 years from the London GIDS [43], and baseline CBCL and YSR scores were close to those at baseline from the original Dutch cohort [24]. A number of other studies have shown that young people with GD have higher scores on the CBCL or YSR than same-age population peers, and that they are similar to young people referred to clinical services for a range of mental health problems [44–46]. Population-based studies in America support higher baseline levels of mental health problems amongst young people with GD, with the prevalence of self-harm notably higher than for male or female peers [47,48]. Young people in our study had baseline YSR scores 0.7–1.0 SD higher than norms for age in comparable countries [29,46].

We found no evidence of change in psychological function with GnRHa treatment as indicated by parent report (CBCL) or self-report (YSR) of overall problems, internalising or externalising problems or self-harm. This is in contrast to the Dutch study which reported improved psychological function across total problems, externalising and internalising scores for both CBCL and YSR and small improvements in CGAS [24]. It also contrasts with a previous study from the UK GIDS of change in psychological function with GnRHa treatment in 101 older adolescents with GD (beginning > 15.5 years) which reported moderate improvements in CGAS score over 12 months of GnRHa treatment [49]. CGAS scores in this previous study increased from 61 to 67 with GnRHa treatment, similar to those (63 at baseline, 66 at 24 months) in our study. Follow-up of the Kuper et al. cohort found non-significant changes in depression and anxiety scores in those ($n = 25$) who had only pubertal suppression treatment, although improvements were seen in the whole sample combining these with those receiving cross-sex hormones [17]. A second US cohort reported that in 23 young people who had received pubertal suppression (using GnRHa or anti-androgens in birth-registered males and either GnRHa or medroxyprogesterone in birth-registered females), there was a reduction in depression scores in birth-registered males but not females.

A recent large US survey found that those who received pubertal suppression in early or mid adolescence had lower odds of lifetime suicidal ideation when studied in adulthood compared with those who did not, regardless of whether they later received cross-sex hormones

and after adjustment for a range of confounding factors [50]. This implies an enduring benefit of pubertal suppression on psychological function, however the cross-sectional design and retrospective exposure classification means the findings require replication. Data are also available from other conditions in which GnRHa is used to suppress puberty during adolescence. A trial of GnRHa suppression of puberty during early adolescence in young people born small-for-gestational-age (SGA) who were also treated with human growth hormone (GH) reported that those treated with GnRHa had similar cognitive and psychological function in adult life to those treated only with GH [51].

The differences between our findings and the previous GIDS study re change in psychological function may relate simply to sample size. But why our findings differ from those of the Dutch study is unclear. They may relate to the timing of assessments; we assessed young people multiple times whereas in the Dutch study the second assessment was shortly before starting cross-sex hormone treatment. Alternatively, there may have been baseline differences in the two cohorts. Whilst some aspects of psychological function were similar, as noted above, the baseline CGAS scores were notably higher in the Dutch group (indicating better function). A previous international comparison study has found that young people aged 12–18 years with GD from the UK have higher scores indicating greater problems on the CBCL and YSR than those from the Netherlands, Belgium and Switzerland [52].

Psychological distress and self-harm are known to increase across early adolescence. Normative data show rising YSR total problems scores with age from age 11 to 16 years in non-clinical samples from a range of countries [29]. Self-harm rates in the general population in the UK and elsewhere increase markedly with age from early to mid-adolescence, being very low in 10 year olds and peaking around age 16–17 years [53–56]. Our finding that psychological function and self-harm did not change significantly during the study is consistent with two main alternative explanations. The first is that there was no change, and that GnRHa treatment brought no measurable benefit nor harm to psychological function in these young people with GD. This is consonant with the action of GnRHa, which only stops further pubertal development and does not change the body to be more congruent with a young person's gender identity. The second possibility is that the lack of change in an outcome that normally worsens in early adolescence may reflect a beneficial change in trajectory for that outcome, i.e. that GnRHa treatment reduced this normative worsening of problems. In the absence of a control group, we cannot distinguish between these possibilities. We aimed to use normative reference data to examine this issue. However age- and gender-standardised t-scores for ASEBA and other outcomes cannot answer this question as they cover a very broad age range (e.g. 12–18 years). We had anticipated that z-scores on the YSR available by calendar year for two comparable countries (Netherlands; Australia) might be informative however confidence intervals were too wide to draw reliable inferences.

Gender dysphoria and body image changed little across the study. This is consistent with some previous reports [24] and was anticipated, given that GnRHa does not change the body in the desired direction, but only temporarily prevents further masculinization or feminization. Other studies suggest that changes in body image or satisfaction in GD are largely confined to gender affirming treatments such as cross-sex hormones or surgery [57]. We found that birth-registered sex and baseline pubertal status were not associated with later psychological functioning on GnRHa, consistent with previous reports [24,49].

These data correct reports from a recent letter by Biggs [58] which used preliminary data from our study which were uncleaned and incomplete data used for internal reporting. In addition there were many statistical comparisons which inflated the risk of type 1 error. Our statistical analysis plan restricted testing all outcomes for differences by sex due to the type 1

error risk. Contrary to Biggs's letter, we found no evidence of reductions over time in any psychological outcomes, and no material differences by sex.

Strengths and limitations

Our study provides comprehensive data on this cohort during follow-up, with an anonymised dataset containing standardised scores deposited to allow other researchers to replicate our findings where data-sharing allows. The study size and uncontrolled design were key limitations. The small sample size limited our ability to identify small changes in outcomes. This was an uncontrolled observational study and thus cannot infer causality. Further, many of the outcomes studied here, including psychological function, self-harm and BMD, undergo normative changes by age and developmental stage during puberty that could confound any observed effect of GnRHa treatment in an uncontrolled study. The analysis plan aimed to take these issues into account as far as possible, however this particularly limits the potential for the study to show benefits or harms from treatment. However, some conclusions can be drawn. It is unlikely that the reported adverse events such as headaches do not relate directly to GnRHa treatment. Equally, given that there were no changes in psychological function and differences in point estimates were minimal for nearly all outcomes, it is unlikely that the treatment resulted in psychological harm. Observational studies are important sources of data on harms of treatment [59–61].

Our data are subject to a number of other limitations. This was an unfunded study undertaken within a clinical service and we were dependent on the clinical service for data collection. There were varying sample sizes for differing tests as some participants did not attend certain investigations and some follow-up medical tests were processed locally to patients; these data are reported as normal or otherwise. Missing items on psychological questionnaires resulted in some unusable data. Some young people found repeated completion of questionnaires about gender issues intrusive and refused to complete them at later follow-ups, as has been reported in other studies [62]. This questionnaire fatigue also affected parent responses. Scoring of psychological questionnaire data was rechecked at the completion of the study however this was not possible in very small numbers of participants in whom only scale scores rather than individual item data were preserved during data migration in hospital clinical information systems. In sensitivity analyses, repeat analysis of ASEBA psychological outcomes restricted to those with rescored data showed highly similar findings to the full sample (see S3 Table in [S1 Appendix](#)).

A more detailed qualitative evaluation of participant experience was not possible due to lack of interviewer time, and reporting of interview data was restricted to perceptions of positive or negative change and the giving of examples.

Implications and conclusions

Treatment of young people with persistent and severe GD aged 12–15 years with GnRHa was efficacious in suppressing pubertal progression. Anticipated effects of withdrawal of sex hormones on symptoms were common and there were no unexpected adverse events. BMD increased with treatment in the lumbar spine and was stable at the hip, and BMD z-score fell consistent with delay of puberty. Overall participant experience of changes on GnRHa treatment was positive. We identified no changes in psychological function, quality of life or degree of gender dysphoria.

The great majority of this cohort went on to start cross-sex hormones, as was hypothesized given the severity and continuation of their GD. However one young person did not, providing some evidence that development of gender identity continues on GnRHa treatment and

confirming the importance of continuing supportive psychological therapy to allow further exploration of gender identity and a range of future pathways whilst on GnRHa.

This cohort will be followed up longer term to examine physical and mental health outcomes into early adulthood. However larger and longer-term prospective studies using a range of designs are needed to more fully quantify the harms and benefits of pubertal suppression in GD and better understand factors influencing outcomes [3]. These are beginning to be funded in a number of countries [63].(<https://logicstudy.uk>) Given that pubertal suppression may be both a treatment in its own right and also an intermediate step in a longer treatment pathway, it is essential for such studies to examine benefits and harms across the longer pathway including pubertal suppression and initiation of cross-sex hormones.

Supporting information

S1 Appendix.

(DOCX)

S2 Appendix. Statistical analysis plan.

(DOCX)

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RESEARCH ARTICLE

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Engaged or excluded: LGBTQ youth's participation in school sports and their relationship to psychological well-being

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Abstract

Sports participation has been shown to positively affect youth well-being. However, research has also shown that sports environments can be unsafe for lesbian, gay, bisexual, transgender, and queer (LGBTQ) youth. Using data from a large study on school-related experiences of LGBTQ secondary students who reported on their extracurricular activities in school, ($N = 15,813$), this study examined LGBTQ youth's participation in school sports, the effects of participation on well-being and school belonging, and whether any such benefits of participation varied by transgender status and gender binary identity. Over a quarter of LGBTQ respondents in our study had participated in school sports, and being transgender and being nonbinary were related to a lower likelihood of sports participation. Transgender males and transgender nonbinary youth had the lowest likelihood of sports participation. In general, LGBTQ youth who participated in sports had increased well-being and greater school belonging. However, in regard to self-esteem, transgender nonbinary youth appeared to have greater benefit from participating in sports than did their transgender male and transgender female peers. Considering these results, schools have a responsibility to ensure that school sports are safe and welcoming for LGBTQ youth.

KEYWORDS

LGBTQ youth, psychological well-being, sexual minority youth, sports, transgender youth

1 | INTRODUCTION

Participation in sports has been shown to have positive effects on youth's development, including physical development (Biddle & Asare, 2011; Snyder et al., 2010), social skills (Bailey, 2006; Eime et al., 2013; Holt et al., 2017; Snyder et al., 2010), and psychological well-being. Specifically, psychological benefits of sports include improved emotion regulation (Eime et al., 2013; Hansen et al., 2003), decreased hopelessness and suicidality (Taliaferro et al., 2009, 2011), fewer depressive symptoms (Boone & Leadbeater, 2006; Eime et al., 2013), and higher self-esteem (Adachi & Willoughby, 2014; Bailey, 2006; Eime et al., 2013; Slutzky & Simpkins, 2009). Additionally, research has found that sports participation is related to greater feelings of school belonging and pro-school behaviors (Bailey, 2006; Eime et al., 2013; Toomey & Russell, 2012).

Sexual minority youth are more likely to experience mental health issues, such as depression, than their heterosexual peers, and also report more suicidal ideation and suicide attempts (Baams, 2018; Kann et al., 2018). Transgender and gender-nonconforming youth are particularly vulnerable, and experience even poorer mental health than their cisgender LGBTQ (lesbian, gay, bisexual, transgender, and queer) and non-LGBTQ peers (Luk et al., 2018; The Trevor Project, 2019). This poor mental health is not inherent to holding an LGBTQ identity, but is instead caused by experiences of victimization and marginalization because of one's sexual orientation and gender identity (Mustanski et al., 2016; Toomey et al., 2010). LGBTQ youth regularly experience hostile school climates and face discrimination and victimization in their schools, which in turn contributes to poorer mental health and well-being (Kosciw et al., 2018). Considering the benefits associated with sports participation in general populations of youth, sports may provide a protective environment and a promising venue for positive mental health and well-being development for LGBTQ youth.

Despite all of the recorded benefits, some research has also found negative effects of sports participation, including social exclusion and feelings of unsafety (Cunningham & Pickett, 2017; Eime et al., 2013). These results are important to note when considering the specific school experiences of LGBTQ youth who regularly experience hostile school climates (Kosciw et al., 2018). In a national survey, one quarter (24.7%) of LGBTQ youth reported avoiding athletics fields or facilities at school because they felt unsafe, and 11.3% reported that they were prevented or discouraged from playing sports by school staff or coaches because of their LGBTQ identity (Kosciw et al., 2018). Additionally, students largely felt uncomfortable talking to athletic coaches and physical education teachers about LGBTQ topics (Kosciw et al., 2018).

Other research has documented the heterosexism and homophobia that often pervade sports environments, suggesting that sports participation may not be safe or beneficial for LGBTQ youth and instead may expose them to additional bullying, harassment, and social exclusion (Anderson, 2011; Greenspan et al., 2017; Hargie et al., 2015; Toomey & Russell, 2012). National and international research on lesbian, gay, bisexual, and queer (LGBQ) adults finds heterosexism, homophobia, and anti-LGBTQ prejudice present in sports (Cunningham & Melton, 2011), and almost one in four adults reported the belief that youth sports are not a safe space for lesbian, gay, and bisexual (LGB) people (Denison & Kitchen, 2015).

Homophobic attitudes are also pervasive among young athletes. LGBTQ youth experience harassment and ignorance from youth on their team and on the teams they play against, and from adults such as coaches (Gill et al., 2010; Hargie et al., 2015; Morrow & Gill, 2003). Homophobia in sports is not just reported by LGBTQ youth, but also by their non-LGBTQ peers and adults in school (Morrow & Gill, 2003). Although some research suggests that attitudes toward LGBTQ people in sports are improving, and that LGBTQ youth are more accepted by their teammates than they previously have been, sports still remain an institution that is not entirely inclusive for LGBTQ youth (Anderson, 2011).

LGBTQ youth may choose not to engage in sports participation if these environments are unsafe and unwelcoming spaces due to their sexual orientation or gender identity. Decision-making with regard to participating in sports among youth is related not only to interest in athletics, but also to social contextual factors such as peer and adult encouragement (Chriqui et al., 2013; Gordon-Larsen et al., 2000; Slater et al., 2012). LGBTQ youth may

fear threats to their safety in such social contexts if peers and adults involved in sports are perceived as unsupportive. In fact, research has shown that sexual minority youth participate in sports at lower rates than their heterosexual peers (Denison & Kitchen, 2015; Doull et al., 2016; Jones et al., 2017; Kulick et al., 2019; Mereish & Poteat, 2015). A national survey of U.S. secondary school students showed that non-LGBTQ youth were more than twice as likely to participate in sports at school as were LGBTQ youth, with 40.2% of non-LGBTQ youth participating in interscholastic sports versus 19.2% of LGBTQ youth (Greytak et al., 2016). Calzo et al. (2014) found that physical activity decreased with age among all youth, but that sexual minority youth had lower levels of participation at all time points, and that sexual minority youth were less likely to participate in sports compared to their heterosexual peers. Similarly, Doull et al. (2016) found in a population of Canadian youth that sexual minority teens in general were less likely to participate in sports than heterosexual teens, and that sports participation decreased as all youth got older. Some research has examined the effects of sexual minority youth participation in sports and found that these youth hear more anti-LGBTQ remarks, feel less safe (Kulick et al., 2019), and have poorer attitudes about their own athletic abilities than their heterosexual peers (Calzo et al., 2014). If sports are unsafe and hostile for LGBTQ youth, the benefits of participation typically seen in the general youth population may not translate to this population, or worse, participation may have negative effects on development.

It is important to recognize that LGBTQ youth are not a monolith and may have varying experiences in sports participation. Although the results are mixed, research suggests that gender plays a role in sports participation. Toomey and Russell (2012) found that heterosexual boys were more likely than heterosexual girls and all sexual minority youth to participate in sports, and further, sexual minority girls were less likely to participate than heterosexual girls and sexual minority boys. Calzo et al. (2014) also found that females overall, regardless of sexual orientation, were less physically active than males, and that sexual minority girls participated in sports at lower rates than heterosexual girls. In another study, sexual minority males were less likely to participate in sports than heterosexual males, but participation varied by sexual minority orientation identity among females. While bisexual females were less likely to participate in sports than heterosexual girls, there was no difference in participation between lesbian and heterosexual girls (Doull et al., 2016). However, other research has found no difference in physical activity between sexual minority and heterosexual girls (Rosario et al., 2014).

Considering these gender differences among cisgender students, it is important to examine the role that gender nonconformity (i.e., how strictly girls or boys adhere to traditional stereotypes of femininity or masculinity, respectively) might play in sports participation. Interestingly, Calzo et al. (2014) found that childhood gender nonconformity accounted for sexual orientation differences in physical activity among boys, but not for girls. It is possible that gender nonconformity among girls is more accepted in the context of sports than it is among boys, as sports are a space in which masculinity is celebrated and valued (Anderson, 2011; Gill et al., 2010). However, this might also lead sexual minority girls who are not out about their sexual orientation to avoid sports participation, given engagement in activities that are traditionally viewed as masculine may lead others to perceive them as not heterosexual (Anderson, 2011; Calzo et al., 2014; Gill et al., 2010; Sartore & Cunningham, 2009). This valuation of masculinity and stereotypically masculine traits may also make sports a particularly unsafe space for sexual minority males (Rosario et al., 2014; Toomey & Russell, 2012). For example, Gill et al. (2010) found that in both school and physical activity spaces, homophobic bullying was more tolerated for males than for females.

The vast majority of research exploring sports participation among LGBTQ youth only examines sexual orientation differences, and very little research specifically examine the experiences of transgender and nonbinary youth. Because of the highly gendered nature of sports environments, it is likely that sports environments are more hostile for these youth than for their cisgender LGBQ peers. Research with transgender adults has found that sports are not safe and welcoming, and that the discrimination and gendered norms inherent in sports result in transgender adults forming negative feelings about sports and about themselves, which in turn leads to low levels of sports participation (Hargie et al., 2015; Symons et al., 2017). Generally, transgender adults involved in sports have negative experiences, report difficulty navigating sports contexts, and face verbal harassment from other athletes (Carroll et al., 2012; Krane et al., 2012; Lucas-Carr & Krane, 2012; Travers & Deri, 2010), and a lack of

welcoming and affirming sports environments prevents transgender individuals from participating (Jones et al., 2017). However, in a recent study of youth in Michigan, there were no differences in rates of participation in sports among transgender and cisgender youth, but transgender students reported feeling less safe while playing sports than did their cisgender peers (Kulick et al., 2019). Among college students, Cunningham and Pickett (2017) found that prejudice toward transgender individuals in sports was higher than prejudice toward sexual minority individuals, and although this prejudice decreased over time, this change was less pronounced than the change in attitudes toward sexual minority athletes.

Just as it is in adult sports, gender segregation is deeply imbedded into youth sports. School sports teams are almost always separated along the gender binary, which poses problems for nonbinary students who do not identify on the gender binary as either male or female, and for transgender students who identify with the binary gender opposite of their assigned sex at birth. Transgender students may face coaches and teachers who do not affirm their gender identity or encounter school policies that prevent them from playing on a team that aligns with their gender identity. Few schools have policies in place to help improve the sports climate for transgender youth. GLSEN's 2017 School Climate Survey found that only 4.8% of transgender and gender-nonconforming youth reported having a policy at school that allows transgender youth to participate in the sports team that aligns with their gender, and only 5.2% reported having a policy that allowed them to use the locker room that matches their gender identity (Kosciw et al., 2018). Even when policies are in place in schools, Cunningham and Pickett (2017) found that the lack of a welcoming environment prevented transgender youth from participating.

In addition to team assignments being dictated by sex, facilities integral to sports participation, such as locker rooms, are also separated by sex, which reinforces the gender binary and creates intimidating spaces for transgender individuals (Hargie et al., 2015; Kulick et al., 2019; Wernick et al., 2017). Many transgender and gender-nonconforming youth avoid sports-related areas in school because they are unsafe spaces. In a national sample of LGBTQ youth, 60.0% of transgender males, 48.4% of transgender females, 45.6% of transgender nonbinary youth, and 44.3% of nonbinary youth who did not also identify as transgender avoided locker rooms (Kosciw et al., 2018). It is critical that locker rooms are made to be safe spaces for transgender youth, as some research has found that students who felt safer in locker rooms were not only more likely to participate in sports, but to also feel safe while doing so (Kulick et al., 2019). Unsafe spaces in sports may lead to lower levels of sports participation in transgender and nonbinary youth, and the unwelcoming climate found in sports might prevent transgender and nonbinary youth from benefitting from the positive effects associated with sports participation.

2 | OBJECTIVES AND RESEARCH QUESTIONS

The preponderance of literature shows the benefits of sports involvement for youth, as discussed. However, research has also shown that for LGBTQ students, physical education classes and school athletic facilities are often seen as the most unsafe spaces at school and are commonly avoided for that reason (Kosciw et al., 2018). Further, LGBTQ students often feel the least comfortable discussing LGBTQ issues with coaches or physical education (PE) teachers at school (Kosciw et al., 2018). Thus, it is important to examine whether school sports participation for cisgender, transgender, and nonbinary LGBTQ students has the same benefits to well-being as has been shown for students in general.

The literature on sports participation has also shown that girls and boys participate in sports at different rates (Calzo et al., 2014; Toomey & Russell, 2012). However, the vast majority of the literature has not examined experiences beyond the experiences of cisgender boys and girls. Thus, it is important to understand whether there are differences in sports involvement across diverse gender identities among LGBTQ students and whether there are differential benefits of sports participation by gender. Transgender students in particular face more hostile school climates and experience poorer mental health and well-being than their cisgender peers. Further, gendered spaces in school, such as locker rooms and athletic teams in secondary schools are primarily gendered,

which may inhibit transgender and gender nonbinary students from participation and may hinder the typical benefits of actual participation. For these reasons, this article examines both gender differences in school sports participation as well as gender differences in the possible benefits of sports participation to well-being. Further, it is important for us to consider separately transgender status (i.e., whether one is transgender, cisgender, or nonbinary) and identification on the gender binary (i.e., regardless of transgender status, whether one identifies as male, female, or nonbinary), as well as the intersection of the two.

The three research questions are:

1. Does sports participation vary between cisgender and transgender youth (transgender status) and additionally between male, female, and nonbinary youth (gender binary identity)?
2. Are there positive effects on mental health and well-being for LGBTQ youth who participate in school sports?
3. Are there differences in the benefits of participation by transgender status (transgender or cisgender) and by gender binary identity (male, female, or nonbinary)?

We hypothesized that transgender students and nonbinary students (i.e., students who do not identify on the gender binary) would be less likely to participate in sports, and would have less benefit to well-being from their participation relative to cisgender students and male and female students, respectively. Given that among transgender students, male-identified students typically have more negative experiences in school (Kosciw et al., 2018; Toomey et al., 2018), we would further hypothesize that transgender males would evidence the least participation in sports and have less benefit from participation, whereas we hypothesize that the opposite would be true for cisgender males.

3 | METHODS

3.1 | Sampling

Data came from a large study on the school-related experiences of LGBTQ secondary school students. To obtain a more representative sample of LGBTQ youth, we used multiple recruitment methods. Notices and announcements of the survey, which were available online, were sent through a national LGBTQ education organization's email and chapter networks as well as through national, regional, and local organizations that provide services to or advocate on behalf of LGBTQ youth. To ensure representation of transgender youth, youth of color, and youth in rural communities, special outreach efforts were made to notify groups and organizations that work predominantly with these populations about the survey. Contacting participants only through LGBTQ youth-serving groups and organizations would have limited our ability to reach LGBTQ students who were not connected to LGBTQ communities in some way. Thus, to broaden our reach to LGBTQ students who may not have had such connections, we conducted targeted advertising on social media sites. Notices about the survey were shown to users between 13 and 18 years of age who gave some indication on their profile that they were lesbian, gay, bisexual, transgender, or queer.

Data collection occurred through an online survey between April and August 2017. Participants were provided a written informed consent/assent briefing on the first page of the survey containing information about the nature of the study, and youth indicated whether they agreed or declined to participate in the survey before proceeding. Youth were excluded from the study if they were not in a K–12 school at some point during the 2016–2017 school year, were not in school in the United States, or identified as heterosexual (except for those who were also transgender). Given the nature of the survey method and to protect the anonymity of the respondents, documentation of written informed consent/assent and parental consent were waived by the institution's Research Ethics Review Committee. Given that many LGBTQ youth in the sample may not be out to their parents or peers,

requiring such documentation would have potentially exposed them to increased risk of harm or deter them from participating in the study.

The final sample, after listwise deletion, consisted of a total of 15,813 students between the ages of 13 and 20 ($M = 15.7$ years) from all 50 states and the District of Columbia. We excluded participants with a pattern of incomplete and illogical responses, and we also asked respondents to verify their age at two different time points during the survey. We also excluded participants who said that they did not have any sports extracurricular activities at their school (4.2%), as well as those participants who did not answer the question about sports involvement (4.7%). About two-thirds of the sample (68.1%) was White, more than half cisgender (56.7%), and more than two-thirds identified as gay or lesbian (41.3%). Respondents were somewhat more highly represented from the South relative to the Northeast. Respondents were 15.7 years old on average. Over one quarter (28.4%) had participated in sports-related extracurricular activities at school, and 92.1% had participated in other non-sports extracurricular activities at schools, including Gender and Sexuality Alliances (GSAs). Descriptive statistics for variables used in the analysis are shown in Tables 1 and 2.

3.2 | Measures

3.2.1 | Demographic and school characteristics

Participants self-reported their gender, age, state, and locale of their school. Gender was assessed with two items. First, respondents identified their sex and/or gender identity by selecting from a list of identity terms: cisgender (defined for respondents as “your gender identity is the same as your sex assigned at birth”), transgender, genderqueer, intersex, or some other way (with the ability to write in a response). Second, respondents identified their gender binary identity by selecting male, female, nonbinary (defined for respondents as “do not identify as male or female”), or another gender (with the ability to write in a response). Students’ answers to these two items allowed for the creation of six gender identity groups: (1) transgender male (identified as transgender and male), (2) transgender female (identified as transgender and female), (3) transgender nonbinary (identified as transgender and nonbinary or genderqueer), (4) cisgender male (identified as cisgender and male), (5) cisgender female (identified as cisgender and female), and (6) nonbinary not transgender (did not identify as cisgender or transgender and identified as nonbinary and/or genderqueer). Region was created by coding the U.S. state in which respondents indicated the location of their school (Northeast, South, Midwest, West). School locale was assessed by a single item asking whether their school was in an urban, suburban, or small town/rural area.

3.2.2 | Outness

Three items assessed outness among participants: outness to other students, outness to school staff, and outness to parents or guardians. Two items measured the degree to which students were out: “Which of the following best describes how ‘out’ you are to [other students/to teachers and other school staff] at your school about your being gay, lesbian, bisexual, transgender, questioning or queer?” (0 = *out to none*; 1 = *out to only a few*; 2 = *out to most*; 3 = *out to all*). A single dichotomous item measured whether students were out to none or any parent or guardian.

3.2.3 | School extracurricular activities

Participation in school extracurricular activities was assessed with a 13-item measure listing types of after-school activities, including intramural sports and extramural sports, and whether respondents had participated, had been

TABLE 1 Sample demographic characteristics

N = 16,711	%	N
Gender identity		
Cisgender male ^a	18.7	2958
Cisgender female	38.0	6007
Transgender male	18.8	2980
Transgender female	1.7	276
Transgender nonbinary	5.4	857
Nonbinary, not transgender	17.3	2735
Sexual orientation		
Gay or lesbian	41.3	6530
Bisexual	27.7	4374
Pansexual	20.3	3205
Other sexual orientation	10.8	1704
Race or ethnicity		
White	68.1	10,772
African American or Black	3.2	505
Hispanic or Latinx	15.1	2389
Asian or Pacific Islander	3.0	469
Native American	0.7	113
Arab or Middle Eastern	1.2	190
Multiracial	8.7	1375
School type		
Public	90.7	14,340
Religious-affiliated	4.1	646
Other private or independent (not religious-affiliated)	5.2	827
Region		
Northeast	18.6	2948
South	33.2	5256
Midwest	23.4	3697
West	24.7	3912
Locale		
Suburban	44.8	7083
Urban	23.6	3736
Rural	31.6	4994

(Continues)

TABLE 1 (Continued)

N = 16,711	%	N
Outness to peers		
None	5.7	903
A few	39.4	6226
Most	31.6	4994
All	23.3	3690
Outness to school staff		
None	38.8	6141
A few	32.5	5142
Most	14.0	2214
All	14.6	2316
Outness to parent or guardian		
None	36.9	5835
One or more	63.1	9978
Average age = 15.7 years (<i>SD</i> 1.4)		

^aAll cisgender students in the sample identified as lesbian, gay, bisexual, queer, pansexual, or another nonheterosexual identity.

a leader, or the school did not have the activity available. To create an indicator of any extracurricular activity, a dichotomous variable was computed such that any participation in any of the activities was coded as 1 and no participation in any was coded as 0. To create an indicator of sports participation, any participation in either intramural or extramural sports was coded as 1 and no participation in either was coded as 0.

3.3 | Psychosocial indicators

Three key psychosocial indicators were examined: self-esteem, depression, and psychological attachment to school (school belonging). Self-esteem was measured using the 10-item Rosenberg Self-Esteem Scale (RSE; Rosenberg, 1989).

TABLE 2 Descriptives of independent and dependent variables

	M	(SD)
Self-esteem	2.27	(0.67)
Depression	29.81	(14.31)
Psychological attachment to school	2.52	(0.61)
	%	N
Participation in school sports	28.4	4686
Participation in other school extracurricular activities	92.1	14,603

RSE items ask respondents how much they agree with statements regarding their global self-worth using a 4-point Likert scale (1 = *strongly disagree*; 4 = *strongly agree*). This measure has demonstrated considerable reliability and validity among general adolescent samples in several studies (Demo, 1985; Hagborg, 1996), and for our LGBTQ adolescent sample, the scale also had high internal reliability (Cronbach's $\alpha = 0.92$). Mean total scores, with higher scores indicating more positive self-esteem, were computed. Depression was measured using the 20-item Likert-type Center for Epidemiological Studies Depression scale (CES-D; Eaton et al., 2004). Scale items were summed (range 0–60), with higher scores indicating greater depressive symptoms; the scale demonstrated high internal reliability (Cronbach's $\alpha = 0.94$). School belonging was assessed using the 18-item Likert-type scale Psychological Sense of School Membership developed for use with adolescents (Goodenow & Grady, 1993). Mean total scores, whereby higher scores indicated greater school belonging, were computed, and the scale evidenced high internal reliability in this sample (Cronbach's $\alpha = 0.93$).

3.4 | Analysis

To assess the likelihood of school sports participation among LGBTQ students vis-à-vis demographic and school characteristics, we performed a hierarchical logistic regression analysis. In the first step, demographic and school characteristics were entered as controls: grade level, outness to peers, outness to school staff, outness to parents, school type (public [reference group], religious, nonreligious private), region (Northeast [reference group], South, Midwest, West), race/ethnicity (White [reference group], Black/African American, Hispanic or Latinx, Asian American Pacific Islander, Arab/Middle Eastern, multiracial), and locale (suburban [reference group], urban, rural). In the second step, gender was entered: transgender male, transgender female, transgender nonbinary, cisgender male [reference group], cisgender female, and nonbinary not transgender.

To assess the relationship between school sports involvement and gender on depression, self-esteem, and school belonging, we conducted a series of three-way analyses of covariance (ANCOVAs), with school sports involvement, transgender status, and gender binary identity as independent variables controlling for demographic and school characteristics.

4 | RESULTS

4.1 | Predictors of school sports participation

Table 3 shows regression coefficients, Wald statistics, odds ratios, and 95% confidence intervals for odds ratios of the independent variables predicting sports participation at school from the final model. The set of covariates was entered in the first step of the model, and were statistically significant, $\chi^2(20) = 449.88$, $p < 0.001$. Participation in other extracurricular activities had the strongest relationship with sports participation. With regard to school characteristics, students in the Midwest were more likely to participate in sports than those in the Northeast, students in rural schools were more likely to participate in sports than those in suburban schools, and students in public school were less likely to participate in sports than those in religious and other private schools. With regard to personal characteristics other than gender, age, being out to school staff, and being out to parents were also associated with a lower likelihood of sports participation. Although outness to adults was a significant contributing factor to sports participation, outness to peers was not. In the second step, transgender status and gender binary identity were added in the model and were also significantly predictive of sports involvement, $\chi^2(3) = 200.77$, $p < 0.001$. Being transgender and being nonbinary were related to a lower likelihood of sports participation. The interaction of transgender status by gender

TABLE 3 Logistic regression statistics of school sports participation on gender with demographic covariates

	<i>B</i>	<i>SE</i>	Wald	Sig.	Odds ratio	95% C.I.
Extracurricular participation	1.07	0.09	149.78	<0.01	2.91	2.45–3.45
Region (ref. Northeast)			12.08	<0.01		
South	−0.03	0.05	0.22	0.64	0.98	0.88–1.08
Midwest	0.13	0.06	5.87	0.02	1.14	1.03–1.27
West	0.00	0.06	0.00	0.96	1.00	0.90–1.12
Locale (ref. urban)			10.61	<0.01		
Suburban	−0.01	0.05	0.03	0.87	0.99	0.91–1.09
Small town or rural	0.12	0.05	5.98	0.01	1.13	1.02–1.24
Outness to peers	0.04	0.03	2.13	0.14	1.04	0.99–1.11
Outness to school staff	−0.05	0.03	4.43	0.04	0.95	0.90–1.00
Outness to parent/guardian	−0.17	0.04	18.79	<0.01	0.84	0.78–0.91
School type (ref. public)			103.00	<0.01		
Religious	0.58	0.08	48.28	<0.01	1.79	1.52–2.12
Other private school	0.59	0.08	60.86	<0.01	1.81	1.56–2.09
Age	−0.07	0.01	28.83	<0.01	0.93	0.91–0.96
Race/ethnicity (ref. White)			26.39	<0.01		
Black/African American	0.23	0.10	5.47	0.02	1.26	1.04–1.53
Asian/Native Hawaiian/Pacific Islander	0.35	0.10	12.11	<0.01	1.42	1.17–1.73
Native American	0.30	0.20	2.20	0.14	1.35	0.91–2.02
Hispanic/Latinx	0.10	0.05	3.48	0.06	1.10	1.00–1.22
Arabic/Middle Eastern	−0.11	0.17	0.43	0.51	0.90	0.64–1.25
Multiracial	0.18	0.06	8.51	<0.01	1.20	1.06–1.36
Transgender	−0.73	0.06	141.07	<0.01	0.48	0.43–0.54
Gender binary identity (ref. male)			69.40	<0.01		
Female	−0.14	0.05	8.00	<0.01	0.87	0.79–0.96
Nonbinary	−0.48	0.06	65.48	<0.01	0.62	0.55–0.70
Transgender × Gender binary identity			20.58	<0.01		
Transgender × Female	0.38	0.16	5.84	0.02	1.46	1.07–1.99
Transgender × Nonbinary	0.48	0.11	18.17	<0.01	1.62	1.30–2.02

binary identity in the third step was also significant, $\chi^2(2) = 20.17$, $p < 0.001$. Transgender males and transgender nonbinary respondents had the lowest likelihood of sports participation (OR = 0.48 for both) relative to the cisgender male reference group, followed by transgender females (OR = 0.61), nonbinary not transgender students (OR = 0.62), and cisgender females (OR = 0.87).

4.2 | Benefits of sports participation and gender differences

Table 4 shows the results of the analyses of covariance (ANCOVA) and Table 5 shows estimated marginal means across the gender groups for each of the independent variables. For all three dependent variables, the main effects of sports participation, transgender status, and gender binary identity were significant. Sports participation was related to higher levels of self-esteem, lower levels of depression, and greater school belonging. Transgender status, however, was related to lower self-esteem, greater depression, and lower school belonging. A pairwise comparison for the three categories of gender binary identity indicated that students who identify as nonbinary were lower on self-esteem and school belonging and higher on depression than both students who identify as male and students who identify as female. As compared to male-identified students, female-identified students were marginally lower on self-esteem and marginally higher on depression ($p < 0.10$), and the two groups did not differ on school belonging.

For all three dependent variables, the Transgender $\times$ Gender Binary interaction was significant, indicating significant differences in well-being across the resulting six groups. On all three dependent variables, transgender males had the most negative outcomes (i.e., lower self-esteem and school belonging, and higher depression). Transgender females, transgender nonbinary participants, and nonbinary not transgender participants did not differ from one another. Cisgender males had the most positive outcomes compared to all other groups (i.e., higher self-esteem and school belonging, and lower depression), and cisgender females had more positive outcomes than all others except cisgender males.

Neither the Transgender $\times$ Sports nor the Gender Binary $\times$ Sports interactions were significant. However, there was a significant three-way Transgender $\times$ Gender Binary $\times$ Sports interaction for self-esteem only. Among students who did not identify as transgender, we saw only the main effect of sports and of gender binary identity. Among transgender students, however, transgender students who identify as nonbinary appeared to have greater benefit with regard to self-esteem from school sports participation than their transgender male and female peers.

TABLE 4 Analysis of covariance (ANCOVA) results for gender and school sports participation on psychosocial indicators for LGBTQ youth

	Self-esteem			Depression			School belonging		
	df	F	η_p^2	df	F	η_p^2	df	F	η_p^2
Sports involvement	1, 15783	40.65*	0.003	1, 15783	20.60*	0.001	1, 15783	88.73*	0.006
Transgender status	1, 15783	196.90*	0.012	1, 15783	219.06*	0.014	1, 15783	247.81*	0.015
Gender binary identity	2, 15783	53.65*	0.007	2, 15783	64.95*	0.008	2, 15783	40.30*	0.005
Transgender $\times$ Gender Binary	2, 15783	197.79*	0.024	2, 15783	172.18*	0.021	2, 15783	124.29	0.016
Transgender $\times$ Sports	1, 15783	0.18	0.000	1, 15783	0.35	0.000	1, 15783	1.27	0.000
Gender Binary $\times$ Sports	2, 15783	0.27	0.000	2, 15783	0.27	0.000	2, 15783	0.01	0.000
Transgender $\times$ Gender Binary $\times$ Sports	2, 15783	4.56**	0.001	2, 15783	1.37	0.000	2, 15783	1.36	0.000

Note: Covariates not included above: age, region, school type, outness to peers, outness to staff, outness to parents, race, and other non-sports extracurricular school participation.

* $p < 0.001$.

** $p < 0.05$.

** $p < 0.01$.

TABLE 5 Estimated marginal means for psychosocial dependent variables by gender and school sports involvement^a

	Self-esteem		Depression		School belonging	
	No sports involvement	Sports involvement	No sports involvement	Sports involvement	No sports involvement	Sports involvement
Transgender male	1.95	2.04	36.43	34.75	2.20	2.36
Transgender female	2.14	2.23	33.27	31.98	2.32	2.48
Transgender nonbinary	2.04	2.25	34.70	31.46	2.28	2.49
Cisgender male	2.56	2.71	23.49	21.45	2.70	2.86
Cisgender female	2.31	2.43	28.18	26.64	2.58	2.73
Nonbinary not transgender	2.09	2.16	34.03	32.84	2.36	2.46

^aAdjusted for covariates: age, region, school type, outness to peers, outness to staff, outness to parents, race, and other non-sports extracurricular school participation.

5 | DISCUSSION

The current study expands upon the existing literature on school sports involvement and its potential benefits by examining the experiences of LGBTQ youth, including predictors and effects of sports participation. This study also illuminates important differences within the LGBTQ youth population with regard to school sports. Previous research has shown that LGBTQ students are much less likely to be involved in school sports than their LGBTQ peers (Greytak et al., 2016; Kulick et al., 2019; Mereish & Poteat, 2015), which may be because athletic spaces, including PE classes, are seen as unsafe (Kosciw et al., 2018). Nevertheless, over a quarter of LGBTQ respondents in our study had participated in school sports. The largest predictor of sports participation among LGBTQ students was participating in other extracurricular activities. Thus, for LGBTQ youth, participation on a school sports team provides added benefit that they might gain from other extracurricular involvement. LGBTQ youth experience hostile school climates, and often feel unsafe in their schools (Kosciw et al., 2018). Thus, it is necessary to find and establish positive school experiences and contexts for LGBTQ youth. Given our finding that among LGBTQ youth, sports participation was related to greater well-being, it is critical that schools make sports a more safe and welcoming space for LGBTQ youth.

As this study only examines the well-being effects of participation in school sports and not of all extracurricular activity participation, future research should further examine the well-being effects of other school activities, such as clubs and service groups, for LGBTQ youth. As we found that the largest predictor of participating in sports was being involved in another extracurricular activity, it is important to consider the interaction of sports participation with other extracurricular participation. It is also important to consider how participation with the school community in general may lead to a greater sense of school belonging, and in turn, result in improved mental health.

Educators, education leaders, and school practitioners must also be mindful of those youth who are not at all connected to school activities, who may be the most disenfranchised. Our findings show that LGBTQ students in the Midwest and in small towns or rural areas are more likely to be involved in school sports. Although these geographical differences may likely reflect sports involvement for the general population of youth, it is important to note that these areas correspond to places where LGBTQ students often experience greater victimization and have fewer positive LGBTQ supports in school (Kosciw et al., 2018). Thus, these youth may be more likely to experience victimization in sports than students in other regions and areas because they participate more in sports, and also report more negative experiences in school spaces, including in athletic spaces. Special attention must be

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paid to ensure that school athletics, just as with the whole school environment, are safe and affirming environments for these youth who live in areas and regions in which they are exposed to more hostile school climate and victimization.

The degree to which LGBTQ youth were out about their LGBTQ identity and to whom they were out was a significant factor in sports participation. Whereas being out to peers was not related to sports participation, being out to school staff and to parents were both associated with a lower likelihood of sports participation. With regard to school staff, it may be that LGBTQ students may feel less at risk for exclusion from school activities, including sports, if they are not open about their identities with staff. Both school staff and parents have some control over youth's access to sports. School staff, including coaches and administrators, are able to create and enforce policies and practices that prevent LGBTQ youth from participating in sports (Kosciw et al., 2018). Parents may control youth's access to sports by not giving permission to participate in sports. In contrast, peers might have more influence over the climate of the team and the relationships and experiences youth experience in their sports participation.

There may also be different motivations by gender for youth not being out to their parents. As already discussed, sexual minority boys who are not out might participate in sports because it allows them to demonstrate masculinity (Anderson, 2011; Gill et al., 2010), which could lead to others, including parents, to perceive them as heterosexual. For sexual minority girls, however, not being out may be related to their fears that they could lose access to sports. Because girls in sports are often perceived as masculine and as lesbians (Anderson, 2011; Gill et al., 2010; Sartore & Cunningham, 2009), girls may remain closeted to their parents so that they can continue to play sports. Perhaps being out to parents about being LGBQ may lead parents to prevent their daughters from engaging in sports because it is perceived as a space for LGBQ girls. Future research is needed to explore this finding about outness and sports, and the possible differences in motivation by gender.

As hypothesized, transgender students were far less likely to participate in school sports than their cisgender sexual minority peers. Transgender nonbinary students, along with transgender males, were least likely to participate, followed by nonbinary students who did not identify as transgender and transgender females. Cisgender students were most likely to participate. In general, most secondary schools of our participants would have had binary-gendered (i.e., "boys" or "girls") teams. Thus, it is not surprising that cisgender students in our study were most involved in sports—their sex or gender of record would permit them to participate in the sport corresponding with their identity. Further, given trends in the United States regarding athletic opportunities among youth in general (Centers for Disease Control and Prevention, 2017; Veliz et al., 2019), it is also not surprising that among cisgender LGBTQ students, male students are more likely to be involved in school sports than female students. Lower participation among transgender students may likely be related to how sports teams are gendered in most U.S. secondary schools. Transgender students in our study may not have been allowed to play on the team that corresponds with their gender identity, and were thus forced to make a choice between playing on a team that does not correspond to their gender identity or not participating in school sports. However, it is puzzling that among transgender students, those identifying as male were less likely to participate in sports than those identifying as female, as both groups would likely face the same barriers to participation. Previous research has shown that transgender female students were less likely to be out about their transgender identity at school compared to transgender male students, and in general, transgender males often experience the most difficult experiences with regard to school climate (Kosciw et al., 2018). Such factors may, in part, explain the differences among the transgender students in our sample.

Our findings on gender and psychosocial indicators were consistent with our hypotheses: transgender students overall had worse indicators than cisgender LGBQ students (i.e., lower self-esteem and school belonging, and higher depression), and female and nonbinary students who did not also identify as transgender had worse indicators than males. However, we found that the main effects and the interaction of transgender status and gender binary identity indicated that transgender males had the lowest levels of self-esteem and school belonging and the highest levels of depression. These findings are consistent with prior literature that has shown greater risk

behaviors overall for transgender youth (Johns et al., 2019), but also the greatest mental health risk for transgender males (Toomey et al., 2018). In addition, research has shown that LGBTQ students commonly encounter hostile school climates, and among these students, transgender students and transgender males in particular report the harshest experiences (Kosciw et al., 2018). These findings together indicate an alarming need for attention to improving school experiences for these students.

Research on extracurricular involvement among secondary students very often does not include indicators of sexual orientation, and inclusion of non-cisgender identities is rare. Given that LGBTQ students generally report more negative school experiences than their non-LGBTQ peers, and that sports are perceived as unsafe for LGBTQ people, one might expect LGBTQ youth to experience few benefits from participation in sports, in contrast with the benefits typically experienced by non-LGBTQ youth or the general population of youth. Nevertheless, we found that in general, LGBTQ youth had increased well-being and greater school belonging when they participated in school sports. Given the preponderance of LGBTQ students who experience discrimination and victimization at school, it would be important for further research to examine whether these benefits hold true under varying conditions of school climate. Relatedly, it would be important to examine the role of other school supports in schools, such as inclusive sports policies, and in particular policies that allow transgender youth to play on the team that best aligns with their gender identity. Future research should examine the effects of such policies on transgender youth's participation in sports and the effects of that participation.

As mentioned previously, LGBTQ youth do not feel comfortable talking to coaches and physical education teachers about LGBTQ topics (Kosciw et al., 2018), which could make sports an unwelcoming space for LGBTQ athletes. The role of educators and administrators who are supportive of LGBTQ students in general, particularly those who are involved in sports, should be examined in future research.

By and large, the results of the two-way and three-way interactions involving sports with transgender status and gender binary identification were not significant, largely indicating that there are mainly effects by gender and by sports on the psychosocial indicators for LGBTQ youth. However, the three-way interaction with the two gender variables and sports participation was significant for self-esteem, indicating that transgender nonbinary students may benefit more from sports participation than their transgender peers. Thus, even though transgender nonbinary students were among those who were least likely to participate, they had greater benefits to their own personal regard when they did. Again, we do not know the type of sports in which the respondents in our study participated, nor do we know whether the sport team was gendered and, if so, the gender of the team on which they played. It may be that these students are not as negatively affected by the gender restrictions often seen with sports teams because they do not identify with the gender binary. Whereas a transgender male or female student may not be allowed to be on a team that corresponds with their gender identity, nonbinary students may have less of a strong preference or connection to either a boys' team or girls' team. Thus, the interaction effect may not reflect a much greater benefit for self-esteem from sports participation, but rather an effect that is not as hindered by any gender restrictions of team assignment. Further research is indicated that considers the type of sports and the gender of team in which transgender and nonbinary students participate and how these may influence the benefits of sports participation at school.

6 | LIMITATIONS

This study expands upon the current research on LGBTQ youth and on the benefits of school sports participation by using a national sample of LGBTQ secondary school students that includes cisgender youth, transgender youth, and youth who identify outside the gender binary. However, there are limits to the generalizability of the findings. The survey was specifically intended for youth who identify as lesbian, gay, bisexual, transgender, or queer. Thus, we cannot make determinations from our data about the experiences of youth who might be engaging in same-sex sexual activity or experiencing same-sex attractions but who do not identify themselves as lesbian, gay, or bisexual,

or about the experiences of youth whose gender identity or gender expression is outside of traditional cultural norms but do not identify as transgender. The data may not reflect the experiences of these youth, who may also be more isolated and without the same access to resources as the LGBTQ-identified youth in the survey.

Furthermore, although the data collection methods resulted in a fairly representative sample of LGBTQ youth (i.e., representation from all 50 states and the District of Columbia), it is important to note that our sample was representative only of youth who identified as LGBTQ and who were able to find out about the survey in some way, either through a connection to LGBTQ or youth-serving organizations that publicized the survey, or through social media. We conducted targeted advertising on the social networking sites Facebook and Instagram to broaden our reach and obtain a more representative sample. Advertising on these sites allowed LGBTQ students who did not necessarily have any formal connection to the LGBTQ community to participate in the survey. However, the social networking advertisements for the survey were sent only to youth who gave some indication that they were LGBTQ on their profiles or visited pages that include LGBTQ content. LGBTQ youth who were not comfortable identifying as LGBTQ in this manner or viewing pages with LGBTQ content would not have received the advertisement about the survey. Thus, LGBTQ youth who are perhaps the most isolated, without a formal connection to the LGBTQ community or without access to online resources and supports, may be under-represented in the survey sample.

Although there are no national population parameters regarding LGBTQ youth, we believe that the methods used for our survey resulted in a nationally representative sample of LGBTQ students who identify as lesbian, gay, bisexual, transgender, or queer (or another nonheterosexual sexual orientation and/or non-cisgender gender identity) and who were able to find out about the survey in some way, either through a connection to LGBTQ or youth-serving organizations that publicized the survey, or through social media. However, our sample does include a disproportionate number of transgender males compared to transgender females. It is important to note that our sample only includes students who had been in school during the 2016–2017 school year, and it is possible that transgender girls drop out of school at higher rates than do transgender boys, thereby leading to fewer transgender girls eligible to take our survey. It is also possible that transgender boys come out earlier than do transgender girls, which would lead to higher numbers of transgender male secondary school students.

Other demographic characteristics, such as race, might play a role in students' sports participation and well-being. Compared to data from the Center for Disease Control's Youth Risk Behavior Survey (YRBS), the percentage of LGBQ African American/Black students in our sample was lower, and the percentage of LGBQ Hispanic/Latinx students in our sample was somewhat higher. As the YRBS does not require an item assessing gender identity beyond male or female, this comparison only includes LGBQ youth and serves as a rough estimate of the larger LGBTQ youth population. In addition to striving to have samples that are wholly representative of all races and ethnicities, future research should further explore the role that race plays in sports participation among LGBTQ youth. Although the current study did not examine race/ethnicity by transgender status or by gender binary identity, we did find that Asian or Pacific Islander, Black/African American, and multiracial LGBTQ youth were more likely to participate in school sports than their white peers, and these findings should be further explored.

As previously mentioned, we only asked respondents whether they had participated in school sports and did not ask those who participated questions about their experiences. Thus, especially for understanding the experiences of transgender and nonbinary students, it would have been useful to know the type of sports and the type of team on which they played. Additionally, we combined students who played intramural and interscholastic sports into one group of students who participated in sports, in part, due to a small number of students participating in intramural sports at school. Interscholastic sports are typically more formal, more competitive, and involve adult coaches, while intramural sports are generally more relaxed and recreational, and students lead the teams themselves. It is possible that LGBTQ students' experiences with sports may differ by these two different sports contexts. Future research is needed to understand more thoroughly the experiences of LGBTQ youth in school sports and its possible benefits.

7 | CONCLUSION AND RECOMMENDATIONS

The current study is one of the few that examines school sports participation for LGBTQ youth, and specifically examines the effects of participation. LGBTQ youth may be less likely to participate in school sports relative to available statistics on the general population of youth, and our study demonstrates that transgender and nonbinary youth are even less likely than their LGBQ cisgender peers. Yet LGBTQ youth appear to benefit from participation in school sports, evidenced by higher self-esteem and school belonging and lower depression. Schools have a responsibility to provide an equitable school experience for all their students. Educators and administrators must assess whether LGBTQ students have the same access to extracurricular activities, including sports, as other students, and whether schools employ discriminatory policies and practices that hinder access.

Providing professional development for school athletic coaches and physical education teachers on how to create more welcoming sports environments for LGBTQ students may result in more LGBTQ students having access to the benefits of sports participation, as well as enhancing the beneficial effects for those students who already participate. This professional development must teach educators and coaches general LGBTQ competencies. This professional development should specifically include training on intervention in anti-LGBTQ name-calling and harassment, which LGBTQ athletes are likely to hear on their field, and which responsible coaches must interrupt. In addition, training should include the unique experiences and needs of transgender and nonbinary athletes, and best practices on how to support these youth. Finally, professional development about creating safe athletic environments for LGBTQ youth should address the importance of inclusive school policies.

In recent years, there has been much public and political discourse around policies about transgender youth in sports. Many states attempted to pass bills denying transgender youth the right to access the locker room that aligns with their gender (ACLU, 2020). Although most were unsuccessful, courts, including the Supreme Court, have decided that discrimination based on transgender identity is discrimination based on sex, and is prohibited by civil rights law (Liptak, 2020). However, these contentious conversations persist in schools across the country. Recently, attempts to prevent transgender and nonbinary youth from accessing locker rooms and bathrooms have moved to barring them from playing sports on the team that aligns with their gender. Alabama, Arkansas, Georgia, Idaho, Indiana, Iowa, Kentucky, Louisiana, Nebraska, New Mexico, and Texas have policies set by their state's high school athletic association that are discriminatory toward transgender student athletes (TransAthlete, n.d.). Some of these policies require students to play on the team that matches their sex assigned at birth. Others only allow students to play sports on the team that aligns with their gender identity after undergoing gender-affirming medical care (i.e., hormone treatment or affirming surgeries). In contrast, 16 states have policies that protect the rights of transgender student athletes, allowing them to participate in sports without any restrictions. However, these policies are under attack. For example, in Connecticut, a group of cisgender female athletes filed a lawsuit that argued that the Connecticut policy allowing transgender students to participate in sports put cisgender girls at a disadvantage (Maxouris, 2020). The U.S. Department of Education, in a letter from the Office of Civil Rights, agreed with these students, arguing that Connecticut's transgender affirming policy violated cisgender girls' civil rights (Associated Press, 2020).

It is imperative that schools enact and implement policies and practices to ensure that transgender and nonbinary students have equal access to school sports and facilities. Educators, especially coaches, should be informed on their state and local policies about transgender athletes. Although multiple states have policies that affirm transgender students, results from a national survey found that only 4.8% of transgender and gender-nonconforming youth reported that their school had, or that they were aware of, a policy that allows transgender students to play on the team that aligns with their gender. Only 5.2% of transgender and gender-nonconforming youth reported that their school had, or that they were aware of, a policy that allowed transgender and nonbinary students to use the locker room that aligns with their gender (Kosciw et al., 2018), illustrating that many transgender youth who live in states with supportive policies are not aware of them. In addition to learning and understanding their schools' policies, coaches must be responsible for informing transgender athletes of their

rights and the policies that protect them. In schools without policies or protections, coaches and administration should work together to create an inclusive policy for transgender athletes. According to GLSEN, such inclusive policies state that students have “a right to participate in athletics in a manner consistent with their gender identity,” and have “the right to access the same facilities as their teammates” (GLSEN, 2019). Coaches and administrators in states with supportive policies should be well educated about what the policy entails, and ensure that it is being implemented in their school.

Discriminatory policies not only affect the students in the states in which they exist. The conversations around them have garnered national attention, and the negative public reaction by many may cause transgender athletes across the country to avoid sports because they feel unwelcome and unsafe in athletic spaces. Conversely, inclusive and affirming policies can signal to transgender students that they are welcome and wanted on their schools' sports teams.

Given the psychosocial benefits of sports inclusion for these youth, school mental health practitioners can play an important role as advocates with school administration, as a resource for their colleagues in working with this population of youth, and in helping LGBTQ students to navigate encounters with discrimination at school, whether it be inside or outside the classroom (Glisen et al., 2019). When working with LGBTQ students who are involved in school sports, school mental health practitioners should also be mindful of, assess, and address any possible discriminatory experiences that these students may have when involved in these activities. In general, school mental health practitioners should explore with this population their experiences with and access to everyday school life activities, both curricular and extracurricular. Given that psychological attachment to school is important as it relates to educational success, it is important for these school professionals to work at the individual- and school-level to address any inequities in access.

Sports are an important context for positive school experiences for LGBTQ youth, who regularly experience hostile school climate. The current study finds that sports provide benefits to LGBTQ youth's well-being and school belonging. However, it is crucial to recognize the role that transgender status and gender binary status play in this relationship. Schools must ensure that sports environments are welcoming and safe for all students, including LGBTQ students, especially those who identify as transgender and nonbinary.

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NEW RESEARCH

Mental Health and Self-Worth in Socially Transitioned Transgender Youth



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Objective: Social transitions are increasingly common for transgender children. A social transition involves a child presenting to other people as a member of the “opposite” gender in all contexts (e.g., wearing clothes and using pronouns of that gender). Little is known about the well-being of socially transitioned transgender children. This study examined self-reported depression, anxiety, and self-worth in socially transitioned transgender children compared with 2 control groups: age- and gender-matched controls and siblings of transgender children.

Method: As part of a longitudinal study (TransYouth Project), children (9–14 years old) and their parents completed measurements of depression and anxiety ($n = 63$ transgender children, $n = 63$ controls, $n = 38$ siblings). Children (6–14 years old; $n = 116$ transgender children, $n = 122$ controls, $n = 72$ siblings) also reported on their self-worth. Mental health and self-worth were compared across groups.

Results: Transgender children reported depression and self-worth that did not differ from their matched-control

or sibling peers ($p = .311$), and they reported marginally higher anxiety ($p = .076$). Compared with national averages, transgender children showed typical rates of depression ($p = .290$) and marginally higher rates of anxiety ($p = .096$). Parents similarly reported that their transgender children experienced more anxiety than children in the control groups ($p = .002$) and rated their transgender children as having equivalent levels of depression ($p = .728$).

Conclusion: These findings are in striking contrast to previous work with gender-nonconforming children who had not socially transitioned, which found very high rates of depression and anxiety. These findings lessen concerns from previous work that parents of socially transitioned children could be systematically underreporting mental health problems.

Key words: transgender children, gender nonconformity, social transitions, mental health, self-worth

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An increasing number of parents of transgender children, or children who identify as the gender “opposite” their natal sex (e.g., natal male children who assert they are girls and natal female children who assert they are boys), have allowed their children to “socially transition.” A social transition is a nonmedical decision to allow a child to change his or her first name, pronouns, hairstyle, and clothing to live everyday life as one’s asserted gender.¹ In most cases, these children have asserted their gender identity as different from their natal sex for months or years, during which they often express dissatisfaction and/or disgust with their anatomy, which in extreme cases can trigger threats or attempts at self-harm.^{2–5} Parent decisions to allow transgender children to socially transition have received significant media attention,^{6–8} with many lay and scientific skeptics asserting concern for the wellbeing of these children in the short and long term.^{9–13} In contrast, one small qualitative study described the intervention, from the perspective of parents, as having

been transformative for their children by alleviating mental health problems and improving the child’s wellbeing almost immediately.¹⁴ Despite considerable debate on these early childhood social transitions, remarkably little empirical evidence on this issue has appeared in the scientific record.

To date, there have been no reports on socially transitioned transgender children’s views of their own wellbeing. Self-reports of transgender people’s mental health have been limited to older teens and adults and indicate dramatically increased rates of anxiety and depression^{15–18} and alarming rates of suicidality.^{19–23} Some estimates have suggested that as many as 41% of transgender adults have attempted suicide in their lifetime.²²

Although self-report data on the mental health of socially transitioned transgender children are absent in the literature, a recent study examined parent-reported mental health in these children.²⁴ Parents reported that socially transitioned transgender children had normative levels of depression and marginally increased levels of anxiety compared with national norms. Compared with their siblings and age- and gender-matched controls, no significant increases in anxiety and depression were observed. These findings were notable because previous work with gender-nonconforming children who had *not* socially transitioned reported drastically increased rates of anxiety and depression, with more than 50% of older children falling in the clinical range of internalizing symptoms.^{25–27}



This article is discussed in an editorial by Mr. Jack L. Turban on page 101.



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Importantly, there are several potential issues with relying on parent reports of internalizing symptoms. Even in children who are “gender typical,” parents often underreport internalizing symptoms, possibly because they are unaware of these internal experiences.²⁸⁻³¹ The tendency to underreport internalizing symptoms is especially likely for parents of socially transitioned transgender children because these parents could be motivated (intentionally or not) to report low rates of psychopathology, even if children are experiencing difficulties. This might occur because parents want to justify their decision to socially transition their child. Research in social psychology has long suggested that people show confirmation biases,³² that is, seeking out information that supports their existing beliefs. In this way, parents might see what they expect to see, even if a child is struggling. For these reasons, examining children’s perceptions of their own mental health is especially crucial.

In addition to assessing anxiety and depression, this study assessed self-worth. Previous work has suggested that self-worth is an important predictor of future mental health outcomes in typically developing children and adolescents,³³⁻³⁶ and self-worth measurements can be used reliably with children at young ages.³⁷

Therefore, the present work assessed socially transitioned transgender children’s self-worth (6–14 years old) and mental health (anxiety and depression, 9–14 years old) compared with a group of age-matched controls and a group of siblings of transgender children. In addition, children’s reports of their own anxiety and depression were compared with parents’ reports of the same children’s anxiety and depression (on the same day). The latter allowed us to assess whether parents tend to underreport mental health problems in their socially transitioned transgender children.

METHOD

Participants

Participants were enrolled at the time of the study in the TransYouth Project (TYP), a national, longitudinal study of socially transitioned transgender children. Families of socially transitioned transgender children were recruited into the broader TYP study through word of mouth, national and local support groups, summer camps, and online forums for families of transgender and gender-nonconforming youth. Transgender children came from 23 US states and 1 Canadian province: 22% from the Pacific Northwest, 18% from California, 6% from the Mountain states, 7% from the Southwest, 21% from the Midwest, 11% from the South, 6% from the Mid-Atlantic region, and 9% from the Northeast. Of the families of transgender children, 52% identified themselves as living in a suburban area, 25% as living in an urban area, 17% as living in a small town, 3% as living in a rural area, and the remaining 3% listed multiple categories.

To be included as a transgender participant in the present study, children needed to identify as the gender opposite their natal sex in everyday life, to have socially transitioned by using the pronoun associated with their asserted gender in all contexts,¹ and be enrolled in the study from March 2015 to February 2016 (when the present measurements were included). The TYP also

includes 2 control groups: siblings of transgender children and age- and gender-matched controls. The siblings were recruited through the same methods as the transgender group and the matched controls were recruited through a university database of families interested in participating in child development research. More details about these groups are presented in Supplement 1 (available online).

The present analytic sample included 63 transgender children, 63 age-matched controls, and 38 siblings 9 to 14 years old who completed the depression and anxiety measurements. Their parents also reported on the child’s depression and anxiety symptoms. The analytic sample for the self-worth measurement included 116 transgender children, 122 control children, and 72 siblings 6 to 14 years old, inclusive of most children who completed the mental health measurements. Demographics for these groups are presented in Table 1, and detailed inclusion information is available in Supplement 1, available online.

Procedure

Whenever possible, parents and children completed the measurements in separate rooms or far enough apart in the same room to be out of earshot. For children no older than 11 years, the researcher read the questions out loud, and the children could answer out loud or point to their response on a scale with response options. Parents and children at least 12 years old completed written versions of the measurements privately, with a researcher nearby to answer questions if needed. All procedures and recruitment were approved by our institutional review board.

Measurements

Internalizing Psychopathology. Children reported on anxiety ($\alpha = 0.858$) and depression ($\alpha = 0.859$) symptoms using the pediatric short form of the National Institutes of Health’s Patient Reported Outcomes Measurement Information System (PROMIS) scale,³⁸ and parents completed the proxy versions of the anxiety (parent 1, $\alpha = 0.935$; parent 2, $\alpha = 0.912$) and depression (parent 1, $\alpha = 0.880$; parent 2, $\alpha = 0.892$) PROMIS scales.³⁹ Each scale consists of items such as “I felt unhappy” or “I felt worried,” and participants indicated how often they (or their child) felt that way during the past 7 days, selecting from the options “never,” “almost never,” “sometimes,” “often,” or “almost always,” which were converted to a Likert-type scale. Participants’ scores across items were summed and then converted to a standardized *T* score. *T* scores are normed such that a score of 50 represents the national average for children, with 10 points representing a standard deviation and a score of at least 63 indicating clinically significant anxiety or depression (top 10% of all children).

All child-reported data in this study are new and unpublished. However, for comparison, we also included parent-reported mental health, which in some cases, for some participants, was previously published. Specifically, anxiety and depression scores reported by parents of 21 transgender participants, 16 siblings, and 18 control participants were reported in a previous article²⁴ (although for 10 transgender children, 7 controls, and 7 siblings, the present report involves analysis from a more recent visit). All other parent reports are new and unpublished.

Of the 63 transgender children who filled out anxiety and depression measurements in the present work, 36 children had 2 parents who completed assessments and the remaining 27 children had 1 parent who completed the assessments. Of the 38 siblings who filled out anxiety and depression measurements, 25 children had 2 parents who completed assessments and 13 children had 1 parent who

TABLE 1 Sociodemographic Characteristics of Participants Completing (A) Mental Health Measurements and (B) Self-Worth Measurement

	Participants Completing Mental Health Measurements			Difference Among Groups
	Transgender (n = 63)	Controls (n = 63)	Siblings (n = 38)	
Gender ^a				$\chi^2 = 0.10, p = .952^d$
Boys	33	33	21	
Girls	30	30	17	
Race or ethnicity ^b				$\chi^2 = 0.73, p = .693$
White, non-Hispanic	37	41	25	
Black	1	0	1	
Hispanic	8	3	6	
Asian	4	2	1	
Multiracial/other	13	17	5	
Age (y), mean (SD)	10.8 (1.3)	10.9 (1.4)	10.6 (1.2)	$F_{2,161} = 0.53, p = .590$
Annual family income, % ^c				$F_{2,161} = .640, p = .529^e$
<\$25,000	0	0	1	
\$25,001–\$50,000	4	9	5	
\$50,001–\$75,000	14	4	5	
\$75,001–\$125,000	23	20	13	
>\$125,000	22	30	14	
	Participants Completing Self-Worth Measurement			Difference Among Groups
	Transgender (n = 116)	Controls (n = 122)	Siblings (n = 72)	
Gender ^a				$\chi^2 = 4.95, p = .084$
Boys	48	49	40	
Girls	68	73	32	
Race or ethnicity ^b				$\chi^2 = 0.12, p = .943$
White, non-Hispanic	75	79	45	
Black	1	0	0	
Hispanic	14	8	12	
Asian	6	4	3	
Multiracial or other	20	31	12	
Age (y), mean (SD)	9.3 (2.0)	9.2 (2.0)	9.1 (1.8)	$F_{2,307} = 0.18, p = .840$
Annual family income, % ^c				$F_{2,307} = 3.14, p = .045^e$
<\$25,000	3	1	4	
\$25,001–\$50,000	9	10	9	
\$50,001–\$75,000	22	11	10	
\$75,001–\$125,000	42	44	22	
>\$125,000	40	56	27	

Note: SD = standard deviation.

^aGender for transgender participants refers to asserted gender, not sex.

^bRace difference was assessed as percentage of white versus non-white in χ^2 analyses owing to small numbers of each non-white group.

^cFor comparison across groups, income was converted to a scale of 1 to 5.

^dTransgender and control participants were matched for gender. When samples are unequal, it was because fewer transgender participants completed the task because of experimenter error (failing to provide the measurement) or participants' requests to stop participation.

^eAlthough there was a significant difference in mean income, no single group comparison was significant as indicated by Tukey post hoc tests (control versus transgender, $p = .146$; control versus siblings, $p = .058$; transgender versus controls, $p = .793$).

completed the assessments. Only 1 parent was present for participation with the control children, and therefore only 1 parent completed an assessment. For consistency with past work,²⁴ when children had 2 parent reporters, the responses of the 2 parents was averaged (in general, the 2 parents' responses were associated: depression, $r = 0.508, p < .001, n = 61$; anxiety, $r = 0.470, p < .001, n = 61$). Analyses for single-parent reporters for all participants are reported in Supplement 1, available online; the conclusions are identical.

Self-Worth. Self-worth scores were reported using the Global Self-Worth Subscale from the Harter Self-Perception Profile for Children.⁴⁰ In this subscale, children were presented with a description of 2 kinds of children (e.g. "some kids like the kind of person they are BUT other kids wish they were different") and were asked to select which kind of child they are most like. Once the children made a selection, they were asked whether this was "sort of true" or "really true." Responses were recoded to a scale from 1 to 4,

such that scores of 1 indicated the lowest self-worth and 4 indicated the highest. Scores were computed by averaging the 6 items ($\alpha = 0.671$). This measurement was administered to children 6 to 14 years old in the present work.

RESULTS

Internalizing Symptoms

We found no differences in self-reported depressive symptoms across the 3 groups (Table 2 lists the means; $F_{2,161} = 1.18$, $p = .311$). Similarly, we found no significant, albeit marginal, difference in self-reported anxiety symptoms across the 3 study groups ($F_{2,161} = 2.62$, $p = .076$). Post hoc Tukey tests showed that controls did not differ from the transgender group ($p = .160$) or sibling group ($p = .110$) and that siblings and transgender participants did not differ ($p = .905$). We also tested whether any of these groups differed significantly from the national average (50) on either measurement. For depressive symptoms, the transgender group ($t_{62} = 1.07$, $p = .290$) and the sibling group ($t_{37} = 1.63$, $p = .112$) did not differ from national averages, whereas the matched-control group showed lower than average depressive symptoms ($t_{62} = 3.54$, $p = .001$). For anxiety, the transgender group ($t_{62} = 1.69$, $p = .096$), the control group ($t_{62} = 0.99$, $p = .328$), and the sibling group ($t_{37} = 1.67$, $p = .104$) did not differ from national averages. Rates of children in the clinical range for depression and anxiety (T scores ≥ 63 , which represent the approximately top 10% of scores nationally) in each participant group are listed in Table 2. Further analyses of these values can be found in Supplement 1, available online.

Parents also reported no differences among groups on depressive symptoms ($F_{2,161} = 0.32$, $p = .728$) but did report significant differences on anxiety symptoms ($F_{2,161} = 6.22$, $p = .002$; Table 3 lists the means). Post hoc Tukey tests indicated that parents reported higher rates of anxiety in transgender participants than in controls ($p = .002$) and marginally more than in siblings ($p = .073$), although siblings and matched controls did not differ from one another ($p = .718$). We compared these values with the expected national average ($T = 50$) and found no differences from national averages on depression for any group (transgender,

TABLE 2 Self-Report Anxiety and Depression Mean (Standard Deviation) T Scores and Percentage of Children in the Clinical Range by Participant Group

	Transgender	Controls	Siblings
All participants, n	63	63	38
Depression	48.7 (9.4)	46.4 (8.0)	47.9 (7.9)
In clinical range, %	6	2	3
Anxiety	52.0 (9.6)	49.0 (7.7)	52.8 (10.5)
In clinical range, %	13	3	16
Participants with family income <\$75,000, n	18	13	11
Depression child report	46.7 (9.3)	47.3 (10.8)	45.2 (6.3)
In clinical range, %	0	8	0
Anxiety child report	59.5 (7.5)	48.5 (10.5)	51.6 (10.8)
In clinical range, %	6	15	9

TABLE 3 Parent Report Anxiety and Depression Mean (Standard Deviation) T Scores and Percentage of Children in the Clinical Range by Participant Group

	Transgender	Controls	Siblings
All participants, n	63	63	38
Depression	50.2 (8.8)	49.4 (7.8)	48.9 (7.1)
In clinical range, %	6	3	0
Anxiety	54.9 (9.0)	49.6 (8.6)	51.0 (8.2)
In clinical range, %	22	5	8
Participants with family income <\$75,000, n	18	13	11
Depression	53.4 (8.6)	50.8 (11.1)	48.0 (6.9)
In clinical range, %	5	8	0
Anxiety	56.2 (8.4)	50.0 (6.8)	50.6 (7.1)
In clinical range, %	21	0	9

$t_{62} = 0.14$, $p = .886$; control, $t_{62} = 0.63$, $p = .530$; siblings, $t_{37} = 0.96$, $p = .345$). However, parents reported higher than average anxiety for the transgender group ($t_{62} = 4.32$, $p < .001$). Parents reported results that did not differ from national averages for the control group ($t_{62} = 0.37$, $p = .714$) or sibling group ($t_{37} = 0.74$, $p = .463$). Rates of children in the clinical range for depression and anxiety (T scores ≥ 63) in each participant group as defined by parent reporters are listed in Table 3. Further analyses of these scores can be found in Supplement 1, available online.

Counter to the hypothesis that parents of socially transitioned transgender children are underreporting anxiety and depression, parents of transgender children reported greater anxiety in their children than the children reported ($t_{62} = 2.11$, $p = .039$), and they did not differ from children's self-reports on depression ($t_{62} = 0.97$, $p = .338$).

Sensitivity Analysis

Because previous work has pointed out that the TYP has a particularly high-income skew,⁴¹ we also computed mean anxiety and depression for the subset of children coming from homes with household incomes no higher than \$75,000. These means and percentages of participants in the clinical range are listed in Tables 2 and 3.

In addition, the present sample included some children who were on hormone blockers, some children who were on cross-sex hormones, and some children who were on neither intervention. Table 4 lists the mean anxiety and depression scores for children in each of these groups as reported by the children and their parents. None of the differences among these groups approached significance ($p > .500$ for all comparisons).

Self-Worth

The age range and sample size were considerably larger for self-worth, allowing us to examine not only differences between conditions but also differences by age group. Therefore, we ran a condition (transgender, control, sibling) by age (6–8, 9–11, 12–14 years old) group between-participants analysis of variance. We found no significant effect of condition ($F_{2,300} = 1.96$, $p = .142$), a marginal effect

TABLE 4 Sample Size and Mean (Standard Deviation) of Transgender Children's and Parents' Reports of Depression and Anxiety as a Function of Whether the Child Is on Cross-Sex Hormones, Blockers, or no Medical Intervention

	Sample Size	Child-Report Depression	Child-Report Anxiety	Parent-Report Depression	Parent-Report Anxiety
Cross-sex hormones	5	48.7 (8.1)	48.7 (8.8)	49.3 (9.5)	51.0 (10.5)
Hormone blockers	18	48.6 (9.1)	51.4 (8.3)	50.9 (8.3)	54.0 (8.2)
No medical intervention ^a	39	48.4 (9.8)	52.6 (10.4)	49.9 (9.3)	55.7 (9.4)

Note: No differences between groups were significant ($p > .500$ for all comparisons).
^aOne child who had no medical intervention but who was experiencing puberty is excluded from this table.

of age group ($F_{2,300} = 2.66$, $p = .072$), and no significant interaction ($F_{4,300} = 0.18$, $p = .949$; Table 5 lists the full means). Children in all groups reported self-worth that was higher than the midpoint (2.5) of the scale, indicating high self-worth overall (transgender, $t_{115} = 19.14$, $p < .001$; controls, $t_{120} = 29.45$, $p < .001$; siblings, $t_{71} = 21.44$, $p < .001$).

DISCUSSION

We found remarkably good mental health outcomes in socially transitioned transgender children in the present study. Transgender children reported normative rates of depression and slightly increased rates of anxiety. Rates of depression in transgender children did not differ significantly from those in siblings of transgender children or from those in age- and gender-matched controls, although rates of anxiety were marginally higher. Parents' reports of their children's depression and anxiety largely mirrored the children's reports, although parents of transgender children reported slightly higher anxiety in their children than the children did.

These findings are consistent with a previous report from the TYP that relied solely on parent reports.²⁴ The previous study found that parents reported normative levels of depression and marginally higher rates of anxiety in their transgender children. A key concern from the previous work was that parents who allowed their children to socially transition might be biased in their reporting of mental health information from a desire to believe their children are doing well after allowing them to socially transition. The present

findings are at odds with this interpretation, because parents reported very similar rates of anxiety and depression as did their children and, if anything, reported slightly greater anxiety in their children than did the children.

In addition, we found that transgender children did not differ from age- and gender-matched controls or siblings in self-worth. Interestingly, all 3 groups of children in this study reported higher self-worth than children in other studies of gender-typical children^{40,42} using the same scale.

Our findings of normative levels of depression, slightly higher rates of anxiety, and high self-worth in socially transitioned transgender children stand in marked contrast with previous work with gender-nonconforming children who had not socially transitioned.^{25,43-45} Those studies overwhelmingly reported markedly higher rates of anxiety and depression and lower self-worth, with disproportionate numbers of children in the clinical range. However, our ability to compare our findings with past findings is limited by differences in the criteria for study inclusion—the children in the present study believed they *were* of the “opposite” gender, whereas previous work focused on more diverse groups of gender-nonconforming children, including many who wished to be the “opposite” gender or who simply preferred toys and clothing associated with the “opposite” gender.^{1,46} More specifically, past studies focused on children who met criteria for gender identity disorder or subclinical manifestations of it, a diagnosis that did not require children to feel they were a member of the “opposite” gender. Future work would benefit from comparing children who feel that they are members of the “opposite” gender who have socially transitioned with children who feel they are members of the “opposite” gender who have not socially transitioned and with children who have some degree of gender dysphoria and might wish they were—but do not actually feel they are—members of the “opposite” gender. Work with children who have non-binary identities (children who identify as “both” or “neither” gender) also is sorely needed.

The present findings highlight a key question about whether social transitions per se caused the positive mental health outcomes observed in the transgender children in the present study. Because the present study did not randomly assign children who believed themselves to be members of the opposite gender to social transitions (a process that would be unethical), we cannot definitively draw this causal inference. Another potential issue with comparing these children with gender-nonconforming children who had not transitioned from the existing literature is that there could be

TABLE 5 Sample Size and Mean (Standard Deviation) for Self-Worth Measurement

	Transgender	Control	Sibling
6–8 y			
n	53	59	35
Mean (SD)	3.50 (0.54) ^a	3.62 (0.39) ^a	3.62 (0.40) ^a
9–11 y			
n	49	48	32
Mean (SD)	3.47 (0.55) ^a	3.68 (0.35) ^a	3.64 (0.47) ^a
12–14 y			
n	14	14	5
Mean (SD)	3.30 (0.51) ^a	3.37 (0.64) ^a	3.43 (0.59) ^b

Note:
^aOne-sample *t* test indicates value is significantly above the midpoint of the scale, indicating high self-esteem ($p < .001$).
^b $p = .023$.

systematic differences between children who have and those who have not socially transitioned (e.g., the former might have more extreme gender dysphoria). Nonetheless, these findings illustrate that there is a group of previously gender-nonconforming children who have socially transitioned and who are doing quite well. These and other recent findings^{24,47} are certainly suggestive that these transitions during childhood can be associated with positive outcomes, at least initially.

If we interpret these data to suggest that social transitions might be an effective intervention for at least some transgender children, how do we explain that social transitions in adulthood are not always associated with positive mental health outcomes?^{16,22,48} One possible answer is that social transitions in childhood occur alongside various kinds of social support, which are often absent from social transitions in adulthood. Children who socially transition invariably have parental support for their identities, without which they would not be able to transition. Further, most children who socially transition in childhood have not developed secondary sex characteristics and thus are unilaterally perceived as being members of their perceived gender upon simply changing their hairstyle and clothing. In contrast, transgender adults often face family rejection, discrimination, prejudice, and even violence in their everyday lives based on their transgender identities. That socially transitioned transgender children have normative mental health could suggest that the psychopathology historically found in transgender individuals might be due to society's rejection of their transgender identities and/or years of repressing or denying their gender identity, rather than some difficulty intrinsic to identifying as a gender "opposite" one's natal sex.

We also cannot discount the possibility that the children in the present study are simply doing well while they are young but will face greater issues as they mature.⁹ As this cohort of transgender youth enters middle adolescence and adulthood, they could experience levels of rejection that they (or most of them) were protected from as children; they could face issues with dating and relationships; or they could later come to reject their transgender identity, a process that some have suggested could be associated with negative social consequences.^{9,49} In addition, the amount of time since a child's social transition, which we did not examine here, could be an important factor to consider in the mental health and adjustment of transgender children. Thus, following these children as they move into the teen and adult years will be critical not only to inform best practices on social transitions but also to illuminate the time course of mental health benefits (or decrements) of social transitions.

As one final note, the children in this study are disproportionately from higher-income backgrounds (Table 1), raising concerns about the generalizability of the present work. Further, because higher income is generally associated with better mental health outcomes in children,⁵⁰⁻⁵² this finding could suggest that socioeconomic status rather than social transitions explain the positive outcomes observed in this group. We are skeptical of this interpretation because previous work with high-income gender-nonconforming

children who had not socially transitioned found rates of anxiety and depression that were substantially higher.⁴³ That work suggests that income alone does not eliminate mental health concerns in gender-nonconforming children. In addition, as presented in Tables 2 and 3, our findings with children from lower- and middle-income families suggest some reason to believe these findings could extend beyond wealthier families. Even so, until a larger sample of lower-income children is examined, we must be cautious in generalizing these results.

For the first time, this article reports on socially transitioned transgender children's mental health as reported by the children. Transgender children reported normative rates of depression and slightly higher rates of anxiety compared with their gender-typical siblings and a matched-control group. Transgender children also reported high self-worth, matching the siblings and matched controls. Future work with larger and more diverse samples will be especially useful to understand how widespread these positive mental health outcomes are among socially transitioned transgender children and whether the low levels of psychopathology we observed will persist as these children move into their teen and adult years. This study supports other recent findings²⁴ that suggest a very strong identification with the gender "opposite" one's sex at birth is not synonymous with high levels of psychopathology⁵³ and provides converging evidence that early family support is associated with positive mental health in transgender children.^{24,47,54} &

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SUPPLEMENT 1

Additional Participant Information

During the testing period (March 2015 to February 2016), 60 transgender children 6 to 8 years old participated in a session with the TYP. Fifty-three of these children completed the self-worth measurement and are included in the present analyses. The remaining 7 participants did not complete the self-worth measurement because the experimenter administered a version of the questionnaire that did not include this measurement ($n = 4$) or because the child was too distracted to continue or asked not to continue ($n = 3$). In addition, 63 transgender children 9 to 14 years old participated in a session with the TYP during the testing period. All 63 of these children completed the self-worth and the depression and anxiety measurements.

After participation, each transgender child was matched to a control child based on identified gender (not sex) and age (within 4 months). Of the 60 matched controls who were paired with a transgender child 6 to 8 years old, 59 completed the self-worth measurement. The 1 participant who did not complete the self-worth measurement did so because the experimenter administered a version of the questionnaire that did not include this measurement. In addition, 63 control children 9 to 14 years old participated in a session with the TYP. All these children completed the depression and anxiety measurements, and 62 of these children completed the self-worth measurement. The 1 control who did not complete the self-worth measurement failed to do so because the experimenter administered a version of the questionnaire that did not include this measurement.

In addition, 76 siblings of transgender children participated in this study during the testing period and were 6 to 14 years old. The siblings of transgender children included in this sample did not necessarily have a transgender sibling represented in the present study because the associated transgender child could have been 4 years old (too young for the present work), but the sibling could have been within the age range for the present work. Of the 38 siblings who were 6 to 8 years old, 35 completed the self-worth measurement. The remaining 3 participants did not complete the self-worth measurement because the children were too distracted to continue or asked not to continue. In addition, 38 siblings 9 to 14 years old participated in a session with the TYP during the testing period. All these siblings completed the depression and anxiety measurements, and 37 of these siblings completed the self-worth measurement. The 1 child who did not complete the self-worth measurement failed to do so because the child asked to not continue the measurement.

Alternative Analyses

In an effort to be consistent with previous work, the main study used parent reports from 2 parents whenever possible. However, one concern with this approach was that it meant that parents of transgender children and siblings often had

2 reporters whose scores were averaged, whereas control participants only ever had 1 parent reporter. Therefore, we also ran analyses using only 1 parent reporter—a mother whenever one was available. Using this approach yielded identical results, as detailed below.

Using this approach, parents reported no differences among groups on depressive symptoms ($F_{2,161} = .69, p = .501$) but did report significant differences on anxiety symptoms ($F_{2,163} = 3.47, p = .033$). Post hoc Tukey tests indicated that parents reported higher rates of anxiety in transgender participants than in controls ($p = .041$), but these rates did not differ from siblings ($p = .129$), and siblings and matched controls did not differ from one another ($p = .983$). We compared these values with national averages and found no differences from national averages on depression for any group (transgender, $t_{62} = 0.48, p = .636$; control, $t_{62} = 0.63, p = .530$; siblings, $t_{37} = 1.76, p = .087$). However, parents reported higher than average anxiety in the transgender group ($t_{62} = 2.92, p = .005$). Parents reported results that did not differ from national averages for the control group ($t_{62} = 0.37, p = .714$) or sibling group ($t_{37} = 0.04, p = .972$).

As in the main article, we observed that parents reported equal rates of depression ($t_{62} = 0.47, p = .644$) but significantly more anxiety ($t_{62} = 2.55, p = .013$) than the children reported.

Analyses Based on Clinical Range (Versus Not)

We compared the percentage of children in each group with 10% (expected percentage of children who would be in the clinical range) using a χ^2 goodness-of-fit test. The percentage of transgender children in the clinical range did not differ from 10% for depression ($p = .334$) or anxiety ($p = .475$) according to the children's own reports. For siblings, the percentage in the clinical range also did not differ significantly from the expected 10% for depression ($p = .130$) or anxiety ($p = .234$) based on the children's reports. In contrast, control participants were less likely to be in the clinical range than expected by chance for depression ($\chi^2_1 = 4.95, p = .026$) and were marginally less likely to be in the clinical range than chance on anxiety ($\chi^2_1 = 3.26, p = .071$) according to the children's reports. We used the Freeman-Halton extension of the Fisher exact probability test to examine whether these differences in the percentage of children showing clinical rates of anxiety and depression differed by groups (using <http://vassarstats.net/fisher2x3.html>). Children did not differ by group in reporting clinical levels of depression ($p = .445$), although they differed marginally in their rate of clinically significant anxiety ($p = .063$), mirroring the overall depression and anxiety findings.

Using parent ratings, we found that parents reported transgender children as no more likely than chance (10%) to be in the clinical range for depression ($p = .166$) but did rate their transgender children as more likely than chance to be in the clinical range on anxiety ($\chi^2_1 = 5.73, p = .017$). Parents did not report the siblings of transgender children as any more or less likely than chance to be in the clinical range for anxiety ($p = .665$), and because no siblings were in the

clinical range for depression, no statistic could be calculated, indicating that, if anything, siblings were less likely to be in the clinical range for depression than expected. For control children, parents indicated that they were no more likely to be in the clinical range than chance for anxiety ($p = .166$), and they were marginally less likely than chance to be in the

clinical range for depression ($\chi^2_1 = 3.26, p = .071$). Rates of meeting clinical levels of depression did not differ among groups as rated by parents ($p = .727$), but rates of clinical levels of anxiety did ($p = .039$). The results of rates in the clinical range showed the same pattern as reports of overall mean anxiety and depression.

Summary of a recommendation by COHERE 16.6.2020
Finland

Medical treatment methods for dysphoria associated with variations in gender identity in minors – recommendation

In its meeting on 11 June 2020, the Council for Choices in Health Care in Finland (COHERE Finland) adopted a recommendation on medical treatment methods for dysphoria associated with variations in the gender identity of minors

The recommendation clarifies the roles of different healthcare operators in a situation where a minor is uncertain about their gender identity. The recommendation presents the medical treatment methods that fall within the range of public healthcare services when it comes to the medical treatment of gender dysphoria in minors.

In COHERE's view, psychosocial support should be provided in school and student healthcare and in primary healthcare for the treatment of gender dysphoria due to variations in gender identity in minors, and there must be sufficient competency to provide such support. Consultation with a child or youth psychiatrist and the necessary psychiatric treatment and psychotherapy should be arranged locally according to the level of treatment needed. If a child or young person experiencing gender-related anxiety has other simultaneous psychiatric symptoms requiring specialised medical care, treatment according to the nature and severity of the disorder must be arranged within the services of their own region, as no conclusions can be drawn on the stability of gender identity during the period of disorder caused by a psychiatric illness with symptoms that hamper development.

In Finland, the diagnostics of gender identity variation, the assessment of the need for medical treatments and the planning of their implementation are centralised by law in the multi-professional research clinics of Helsinki University Central Hospital (HUS) and Tampere University Hospital (TAYS). The consultation, evaluation periods and treatments provided by the TAYS or HUS working group on the gender identity of minors shall be carried out in accordance with the following principles.

Children who have not started puberty and are experiencing persistent, severe anxiety related to gender conflict and/or identification as the other sex may be sent for a consultation visit to the research group on the gender identity of minors at TAYS or HUS. Any need for support beyond the consultation visit or need for other psychiatric treatment should be addressed by local services according to the nature and severity of the problem.

If a child is diagnosed prior to the onset of puberty with a persistent experience of identifying as the other sex and shows symptoms of gender-related anxiety, which increases in severity in puberty, the child can be guided at the onset of puberty to the research group on the gender identity of minors at TAYS or HUS for an assessment of the need for treatment to suppress puberty. Based on these assessments, puberty suppression treatment may be initiated on a case-by-case basis after careful consideration and appropriate diagnostic examinations if the medical indications for the treatment are present and there are no contraindications. Therapeutic amenorrhea, i.e. prevention of menstruation, is also medically possible.

A young person who has already undergone puberty can be sent to the research clinic on the gender identity of minors at TAYS or HUS for extensive gender identity studies if the variation in gender identity and related dysphoria do not reflect the temporary search for identity typical of the development stage of adolescence and do not subside once the young person has had the opportunity to reflect on their identity but rather their identity and personality development appear to be stable.



Summary of a recommendation by COHERE 16.6.2020
Finland

Based on thorough, case-by-case consideration, the initiation of hormonal interventions that alter sex characteristics may be considered before the person is 18 years of age only if it can be ascertained that their identity as the other sex is of a permanent nature and causes severe dysphoria. In addition, it must be confirmed that the young person is able to understand the significance of irreversible treatments and the benefits and disadvantages associated with lifelong hormone therapy, and that no contraindications are present.

If a young person experiencing gender-related anxiety has experienced or is simultaneously experiencing psychiatric symptoms requiring specialised medical care, a gender identity assessment may be considered if the need for it continues after the other psychiatric symptoms have ceased and adolescent development is progressing normally. In this case, a young person can be sent by the specialised youth psychiatric care in their region for an extensive gender identity study by the TAYS or HUS research group on the gender identity of minors, which will begin the diagnostic studies. Based on the results of the studies, the need for and timeliness of medically justified treatments will be assessed individually.

Surgical treatments are not part of the treatment methods for dysphoria caused by gender-related conflicts in minors. The initiation and monitoring of hormonal treatments must be centralised at the research clinics on gender identity at HUS and TAYS.

Research data on the treatment of dysphoria due to gender identity conflicts in minors is limited. COHERE considers that, moving forward, multi-professional clinics specialising in the diagnostics and treatment of gender identity conflicts at HUS and TAYS should collect extensive information on the diagnostic process and the effects of different treatment methods on the mental wellbeing, social capacity and quality of life of children and youth. There is also a need for more information on the disadvantages of procedures and on people who regret them.

Link to the COHERE website: <https://palveluvalikoima.fi/en/frontpage>

The Council for Choices in Health Care in Finland (COHERE Finland) works in conjunction with the Ministry of Social Affairs and Health, and its task is to issue recommendations on services that should be included in the range of public health services. Further information: www.palveluvalikoima.fi.



Summary of a recommendation by COHERE 16.6.2020
Finland

Medical treatments for gender dysphoria that reduces functional capacity in transgender people – recommendation

In its meeting on 11 June 2020, the Council for Choices in Health Care in Finland (COHERE Finland) adopted a recommendation on medical treatment methods for gender dysphoria, i.e. anxiety, caused by a transgender identity.

The recommendation clarifies the roles of different healthcare operators in a situation where an adult is uncertain about their gender identity and presents the medical treatment methods included in the range of public healthcare services for the treatment of gender dysphoria caused by a transgender identity.

Gender dysphoria has increased in prevalence both in Finland and in other Western countries. Some people suffering from gender dysphoria seek diagnostic examinations, a portion of them are diagnosed as transgender, and still fewer wish to undergo treatments that would permanently modify their bodies. In Finland, the diagnostics of gender dysphoria, the assessment of the need for medical treatments and the planning of their implementation are centralised by law in the multi-professional research clinics of Helsinki University Central Hospital (HUS) and Tampere University Hospital (TAYS).

In COHERE's view, people experiencing a lack of clarity related to their gender identity should be provided with psychosocial support in line with the severity of their symptoms and the need for care as part of the primary or specialised healthcare provided by their municipality. Any assessment of the need for psychiatric and psychosocial care, and any treatment deemed necessary, should be arranged before the person is referred to the centralised research clinic so that the evaluation period can be initiated. These measures would improve the appropriate allocation of healthcare resources and ensure the timeliness of the diagnostic process and any treatment process.

It is medically justified to send people to the multi-professional research clinics at HUS and TAYS if they meet the following criteria. The person has a significant and prolonged gender conflict that causes reliably identifiable and harmful suffering in everyday situations, the person has undergone diagnostics and treatment of possible concomitant psychiatric symptoms and their continuation during and after treatment, if necessary, has been ensured, and the person has been confirmed to have the psychological conditions and sufficient functional capacity for a demanding evaluation.

Medical care in research clinics is always planned on an individual basis, and the treatments to be carried out must be medically justified in relation to the desired outcome. When deciding on treatment measures, it must be ensured that the dysphoria associated with gender identity is persistent (> 2 years), that the person can consistently describe how the dysphoria is harmful to them in everyday situations and that it can be reliably established that the dysphoria is detrimental to their social life or professional career or causes significant suffering. In addition, the personal and identity development of the person must be sufficiently structured, and appropriate arrangements must be made for the diagnostics and treatment of any simultaneous psychiatric symptoms. Treatment measures that modify the body to be more congruent with the person's gender identity can be carried out if the person can reasonably justify the need for them and is aware of the risks associated with them.

Summary of a recommendation by COHERE 16.6.2020
 Finland

At each stage of the treatment process, the prerequisites for continuing treatment are assessed together with the transgender person. When implementing hormone therapy, consideration should be given to the principles of good clinical practice, individual objectives and any adverse effects that may also lead to discontinuation of treatment. Changes caused by hormone therapy are at least partially reversible if treatment is discontinued. Surgical procedures permanently modify the body and pose a risk of scarring, loss of sensation and functional harm. Surgical procedures should be carried out only once it has been confirmed that the psychological state of the person is such that they understand the aftercare required for surgical procedures and the risk of permanent harm associated with the treatment. Surgical procedures include feminisation or masculinisation of the breasts/chest, hysterectomy and salpingo-oophorectomy and surgery modifying the external genitalia to match that of the other sex. Surgical procedures are carried out in line with the principles of promoting a good outcome and reducing adverse events as detailed in the Current Care Guidelines.

Speech therapy, facial hair removal and laryngeal surgery are included in the service range only when they are required for sufficient social capacity in the person's new gender role. The multi-professional working groups with expertise in the study and treatment of variations in gender identity at HUS and TAYS should jointly agree on uniform indications and implementation of these individual treatment procedures.

When the criteria for the provision of medical rehabilitation aids are met, it is possible for a transwoman to be provided with a wig and for a transman to be provided with a penile or erectile prosthesis based on an individual assessment by the attending physician. Based on an individual medical assessment, breast prosthesis in transwomen and binders in transmen may be suitable alternatives to breast/chest surgery.

The service range does not include corrective or other procedures desired by the patient following an outcome that is functionally acceptable based on a medical assessment or that are comparable to aesthetic surgery or that are based on other dissatisfaction associated with the body or its appearance.

Only limited research has been conducted on transgender identity and other gender identity conflicts, and comparative studies are very rare. COHERE considers that, moving forward, the multi-professional clinics specialising in the diagnostics and treatment of gender identity conflicts at HUS and TAYS should collect extensive information on the diagnostic process and the effects of different treatment methods on mental wellbeing, social and professional capacity, and quality of life. There is also a need for more information on the disadvantages of procedures and on people who regret them.

Link to the COHERE website: www.palveluvalikoima.fi/en

The Council for Choices in Health Care in Finland (COHERE Finland) works in conjunction with the Ministry of Social Affairs and Health, and its task is to issue recommendations on services that should be included in the range of public health services. Further information about service choices in health care is available on the COHERE Finland website at www.palveluvalikoima.fi/en



Research Letter | Psychiatry

Evaluation of Anxiety and Depression in a Community Sample of Transgender Youth

Dominic J. Gibson, PhD; Jessica J. Glazier, MS; Kristina R. Olson, PhD

Introduction

Most studies have found that youth who do not conform to gender norms for their assigned sex have higher rates of depression and anxiety than their cisgender peers.^{1,2} However, more recent research featuring smaller cohorts (ie, ranging from 31 to 73 participants) of socially transitioned transgender youth—youth who identify and live as a gender different from their sex assignment at birth—show normative or only slightly elevated rates of depression and anxiety.³⁻⁵ We recruited a new, larger sample of socially transitioned transgender youth, their siblings, and age- and gender-matched control participants to test whether transgender youth experience significantly higher levels of anxiety and depression than their cisgender peers.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Methods

This cross-sectional study includes responses from 3 groups of youth between ages 8 and 14 years in a large community-recruited sample (following previous recruitment strategies^{3,5}): transgender youth (148 participants), cisgender siblings of transgender children (88 participants), and cisgender age-matched controls (139 participants). We obtained written consent from parents and verbal and/or written assent from children. This study was approved by the University of Washington institutional review board. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

We measured depression and anxiety using the pediatric short form (completed by youth) and proxy form (completed by parents) of the National Institutes of Health's Patient Reported Outcomes Measurement Information System (PROMIS) scale, which measures depression and anxiety on a 100-point scale where 50 is the population mean and 40 to 60 is the reference range (see eAppendix in the Supplement). Participants must have completed 1 or both self-reported mental health measures between November 2014 and March 2020, and none of the youth in this article ever reported on their own mental health in any other study. Fifty-two parents reported on their children in a previously published report (50 at a different time point and 2 at the same time point as in this report).⁵ Data were analyzed from July to November 2020 and used R version 3.6 (R Project for Statistical Computing). $P < .05$ was considered significant and all tests were 2-sided.

Results

A total of 375 participants (227 girls [60.5%], 148 boys [39.5%]; 267 [71.2%] White participants, 15 [4.0%] Asian participants, 7 [1.9%] Black participants, 7 [1.9%] Hispanic participants, and 69 [18.4%] participants who identified as multiracial/other) between the ages of 8 and 14 years (mean [SD] age, 10.54 [1.05] years) and their parents were included (Table 1). Means, SDs, frequencies, and percentages of children who scored within the clinical range on each measure are reported in Table 2. One-way analyses of variance for each of the measures revealed no significant group differences in self-reported depressive symptoms, self-reported anxiety symptoms, or parent-reported depressive symptoms. Parent-reported anxiety differed significantly by group. Post hoc Tukey tests showed that parents reported higher rates of anxiety in transgender youth than in

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control participants (mean [SD] PROMIS score: 52.62 [9.41] vs 49.94 [8.84]; $P = .04$, $d = 0.29$) but not siblings (50.23 [9.32] vs 49.94 [8.84]; $P = .13$, $d = 0.25$). Siblings did not differ from control participants (52.41 [8.82] vs 50.53 [8.25]; $P = .97$, $d = 0.03$).

Discussion

Our results were consistent with recent smaller studies of socially transitioned transgender youth and contrast with the more severe mental health symptoms found in earlier studies of youth referred to clinics for gender-related concerns (as well as transgender teens and adults⁶), although these

Table 1. Demographic Characteristics by Group

Characteristic	Children, No. (%)		
	Transgender (n = 148)	Sibling (n = 88)	Control (n = 139)
Gender identity			
Boys	53 (36)	47 (53)	48 (35)
Girls	95 (64)	41 (47)	91 (65)
Race or ethnicity			
Asian	3 (2)	3 (3)	9 (6)
Black	3 (2)	1 (1)	3 (2)
Hispanic/Latino	4 (3)	5 (6)	0
Native American/Alaskan Native	1 (1)	1 (1)	1 (1)
Multiracial/other ^a	18 (12)	15 (17)	33 (24)
White, non-Hispanic	114 (77)	61 (69)	92 (66)
Missing	5 (3)	2 (2)	1 (1)
Age, mean (SD), y	10.1 (1.0)	10.2 (1.2)	10.1 (1.0)
Income, \$			
<25 000	5 (3)	3 (3)	2 (1)
25 001-50 000	13 (9)	6 (7)	5 (4)
50 001-75 000	26 (18)	13 (15)	8 (6)
75 001-125 000	33 (22)	29 (33)	38 (27)
>125 000	71 (48)	37 (42)	84 (60)
Missing	NA	NA	2 (1)

Abbreviation: NA, not applicable.

^a Two participants only listed other for race/ethnicity; the rest listed multiple races.

Table 2. Mean Score Estimates and Comparisons by Group for Each of the 4 Measures

	PROMIS score estimates		Group comparison		
Group	Mean (SD) score ^a	Children scoring in clinical range, No. (%) ^b	F test	P value	η ²
Child-reported depression					
Transgender	46.38 (9.13)	5 (3.4)	F ₂₃₇₁ = 1.03	.36	0.01
Sibling	48.01 (9.05)	4 (4.6)			
Control	46.46 (8.99)	3 (2.2)			
Child-reported anxiety					
Transgender	52.21 (8.92)	17 (11.5)	F ₂₃₇₂ = 1.81	.17	0.01
Sibling	52.41 (8.82)	12 (13.6)			
Control	50.53 (8.25)	9 (6.5)			
Parent-reported depression ^c					
Transgender	51.41 (8.06)	12 (8.1)	F ₂₃₇₂ = 1.45	.24	0.01
Sibling	51.1 (8.52)	8 (9.1)			
Control	49.86 (7.65)	6 (4.3)			
Parent-reported anxiety ^c					
Transgender	52.62 (9.41)	20 (13.5)	F ₂₃₇₂ = 3.55	.03	0.02
Sibling	50.23 (9.32)	6 (6.8)			
Control	49.94 (8.84)	11 (7.9)			

^a These measures are normed such that the mean (SD) score of 50 (10) is the national average. Lower scores indicate lower depression or anxiety.

^b Clinical range defined as a score of ≥ 63 , representing approximately 10% of a representative sample of youth in the age range on these measures.

^c When 2 parents provided responses for a given child, their scores were averaged.

samples differ in many ways (eg, date and location of data collection, clinic-recruited vs community samples, the present children had socially transitioned) that make direct comparisons difficult.

This study did have limitations. Although the present sample was larger than previous studies of transgender youth, it likely overrepresented families with higher levels of parental education, higher socioeconomic status, that are White, and other factors. Whether these biases reflect who is socially transitioning at the time of the study is unknown.

Nonetheless, these results demonstrate that many socially transitioned transgender youth experience levels of anxiety and depression in the normative range and equal to or only slightly higher than siblings and cisgender peers. Whether their generally strong mental health is because of their early social transition, the high levels of support they receive, or other factors is as yet unknown. The current findings do not negate the experiences of the many transgender people who face high rates of mental health challenges⁶ but do provide further evidence that being transgender is not synonymous with these challenges.

ARTICLE INFORMATION

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Correction: This article was corrected on May 11, 2021, to fix demographic information given in the Results section.

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Author Contributions: Dr Gibson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Gibson, Olson.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Gibson, Olson.

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Supervision: Olson.

Conflict of Interest Disclosures: Dr Olson reported receiving grants from National Institutes of Health, National Science Foundation, and Arcus Foundation during the conduct of the study; she reported receiving a MacArthur Foundation fellowship outside the submitted work; and she reported receiving travel fees for colloquia, talks, and conference presentations during the conduct of this study, including at the American Association for the Advancement of Science Annual Meeting; University of California, Santa Barbara Department of Psychology; University of California, Davis Center for Mind and Brain; Queen's University; Pennsylvania State University Psychology Department; University of Virginia Psychology Department; Stanford University Psychology Department; Washington University Psychology Department; University of Maryland Cognitive Science Program; Linfield College; University of Victoria; University of Arizona Psychology Department; Norwegian Conference on Gender Incongruence; American Academy of Child and Adolescent Psychiatry Annual Meeting; Institute on Gender Dysphoria Across Development; Keystone Conference; Southern Arizona Gender Alliance. Dr Olson also reported serving as an unpaid expert witness in *Center for Gender Advocacy and al v Attorney General of Québec* (court file number 500-17-082257-141), a case concerning whether minors should be able to change their gender markers; and she reported serving as an unpaid member of Big Brothers Big Sisters of America LGBTQ National Advisory Council. No other disclosures were reported.

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SUPPLEMENT.

eAppendix. Participants and Procedures

Circulating Testosterone as the Hormonal Basis of Sex Differences in Athletic Performance

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ABSTRACT Elite athletic competitions have separate male and female events due to men's physical advantages in strength, speed, and endurance so that a protected female category with objective entry criteria is required. Prior to puberty, there is no sex difference in circulating testosterone concentrations or athletic performance, but from puberty onward a clear sex difference in athletic performance emerges as circulating testosterone concentrations rise in men because testes produce 30 times more testosterone than before puberty with circulating testosterone exceeding 15-fold that of women at any age. There is a wide sex difference in circulating testosterone concentrations and a reproducible dose-response relationship between circulating testosterone and muscle mass and strength as well as circulating hemoglobin in both men and women. These dichotomies largely account for the sex differences in muscle mass and strength and circulating hemoglobin levels that result in at least an 8% to 12% ergogenic advantage in men. Suppression of elevated circulating testosterone of hyperandrogenic athletes results in negative effects on performance, which are reversed when suppression ceases. Based on the nonoverlapping, bimodal distribution of circulating testosterone concentration (measured by liquid chromatography–mass spectrometry)—and making an allowance for women with mild hyperandrogenism, notably women with polycystic ovary syndrome (who are overrepresented in elite athletics)—the appropriate eligibility criterion for female athletic events should be a circulating testosterone of <5.0 nmol/L. This would include all women other than those with untreated hyperandrogenic disorders of sexual development and noncompliant male-to-female transgender as well as testosterone-treated female-to-male transgender or androgen dopers. (*Endocrine Reviews* 39: 803 – 829, 2018)

Virtually all elite sports are segregated into male and female competitions. The main justification is to allow women a chance to win, as women have major disadvantages against men who are, on average, taller, stronger, and faster and have greater endurance due to their larger, stronger muscles and bones as well as a higher circulating hemoglobin level. Hence, elite female competition forms a protected category with entry that must be restricted by an objective eligibility criterion related, by necessity, to the relevant sex-specific physical advantages. The practical need to establish an eligibility criterion for elite female athletic competition led the International Association of Athletic Federations (IAAF) to establish a rule in 2011, endorsed by the International Olympic Committee (IOC) in 2012, for hyperandrogenic women. That

IAAF regulation stated that for athletes to be eligible to compete in female events, the athlete must be legally recognized as a female and, unless she has complete androgen insensitivity, maintain serum testosterone <10 nmol/L. That IAAF eligibility rule was challenged by an athlete to the Court for Arbitration in Sports, which ruled in 2015 that, although an eligibility criterion was justified, there was insufficient evidence of the extent of the competitive advantage enjoyed by hyperandrogenic athletes who had circulating testosterone >10 nmol/L over female athletes with circulating testosterone in the normal female range. The Court for Arbitration in Sports suspended the rule pending receipt of such evidence. In that context, the present review presents the available evidence on the hormonal basis for the sex difference

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ESSENTIAL POINTS

- It is widely accepted that elite athletic competitions should have separate male and female events
- The main justification is that men's physical advantages in strength, speed, and endurance mean that a protected female category, with objective entry criteria, is required
- Prior to puberty, there is no sex difference in circulating testosterone concentrations and athletic performance
- From male puberty onward, the sex difference in athletic performance emerges as circulating testosterone concentrations rise as the testes produce 30 times more testosterone than before puberty, resulting in men having 15- to 20-fold greater circulating testosterone than children or women at any age
- This wide, bimodal sex difference in circulating testosterone concentrations and the clear dose-response relationships between circulating testosterone and muscle mass and strength, as well as the hemoglobin level, largely account for the sex differences in athletic performance
- Based on the nonoverlapping, bimodal distribution of circulating testosterone concentration (measured by liquid chromatography–mass spectrometry) with 95% reference ranges of 7.7 to 29.4 nmol/L in healthy men and 0 to 1.7 nmol/L in healthy premenopausal women—making an allowance for women with the mild hyperandrogenism of polycystic ovary syndrome, who are overrepresented in elite athletics—the eligibility criterion for female athletic events should be a circulating testosterone concentration of <5.0 nmol/L

in athletic performance. It concludes that the evidence justifies a revised eligibility criterion of a threshold

circulating testosterone concentration of 5 nmol/L (measured by a mass spectrometry method).

Sex, Fairness, and Segregation in Sport

If sports are defined as the organized playing of competitive games according to rules (1), fixed rules are fundamental in representing the boundaries of fair sporting competition. Rule breaking, whether by breaching eligibility or competition rules, such as use of banned drugs, illegal equipment, or match fixing, creates unfair competitive advantages that violate fair play. Cheating constitutes a fraud against not just competitors but also spectators, sponsors, the sport, and the public. In the absence of genuine fair competition, elite sports would lose their wide popular appeal and ability to captivate and inspire with the authentic attraction of genuine contest between highly trained athletes.

Nevertheless, fairness is an elusive, subjective concept with malleable boundaries that may change over time as social concepts of fairness evolve. For example, until the late 19th century when organized sports trainers emerged, training itself was considered a breach of fairness because competition was envisaged at that time as a contest based solely on natural endowments. Similarly, sports once distinguished between amateurs and professionals. The concept of fairness has deep and complex philosophical roots mainly focused on notions of distributive justice. These considerations affect sports through the universal application of antidiscrimination and human rights legislation. Less attention is given to the philosophical basis of fair competition in elite sports, where the objectives are not egalitarian but aim to discover a hierarchy of achievement derived

from a mixture of unequal natural talent and individual training effort. Excellent, insightful discussion of the legal and moral complexities of sex and fair competition in elite sports from a legal scholar and former elite female athlete is available (2).

The terms *sex* and *gender* are often confused and used as if interchangeable. *Sex* is an objective, specific biological state, a term with distinct, fixed facets, notably genetic, chromosomal, gonadal, hormonal, and phenotypic (including genital) sex, each of which has a characteristic defined binary form. Whereas all facets of biological sex are almost always aligned so that assignment of sex at birth is straightforward, rare instances in which two or more facets of biological sex conflict constitute an intersex state, now referred to as disorders (or differences) of sex development (DSDs) (3). In contrast, *gender* is a subjective, malleable, self-identified social construct that defines a person's individual gender role and orientation. Prompted by biological, personal, and societal factors, volitional expression of gender can take on virtually any form limited only by the imagination, with some individuals asserting they have not just a single natal gender but two genders, none, a distinct third gender, or gender that varies (fluidly) from time to time. Hence, whereas gender is usually consistent with biological sex as assigned at birth, in a few it can differ during life. For example, if gender were the basis for eligibility for female sports, an athlete could conceivably be eligible to compete at the same Olympics in both female and male events. These features render the unassailable personal assertion of gender identity incapable of forming a fair, consistent sex classification in elite sports.

The strongest justification for sex classification in elite sports is that after puberty men produce 20 times more testosterone than women (4–7), resulting in circulating testosterone concentrations 15-fold higher than in children or women of any age. Age-grade competitive sporting records show no sex differences prior to puberty, whereas from the age of male puberty onward there is a strong and ongoing male advantage (8). The striking male postpubertal increase in circulating testosterone provides a major, ongoing, cumulative, and durable physical advantage in sporting contests by creating larger and stronger bones, greater muscle mass and strength, and higher circulating hemoglobin as well as possible psychological (behavioral) differences. In concert, these render women, on average, unable to compete effectively against men in power-based or endurance-based sports.

Sex classification in sports therefore requires proof of eligibility to compete in the protected (female) category. This deceptively simple requirement for fairness is taken for granted by peer female competitors who regard participation by males, or athletes with physical features closely resembling males, as unfair. This makes policing of eligibility inescapable for sports, to avoid unfair male participation in female events. However, such policing inevitably intrudes into highly personal matters so that it must be achieved with respect for dignity and privacy, demanding use of the least invasive, scientifically reliable means. Unsurprisingly, this dilemma has always been highly contentious since it first entered international elite sports in the early 20th century, and it has become increasingly prominent and contentious in recent decades; nevertheless, the requirement to maintain fair play in female events will not disappear as long as separate female competitions exist. During recent decades, there has been progressively better understanding of the complex biology of genetic sex determination and the impact of pubertal sexual maturation in establishing phenotypic sexual dichotomy in physical capabilities. These sex-dichotomous physical features form the basis of, but remain quite distinct from, adult gender roles and identity. During the last century, as knowledge grew, the attempts to formalize a scientific basis for the unavoidable necessity of policing eligibility for the female category have been continually challenged. Most recently, the increasing assertion of gender self-identification as a social criterion has further challenged the hegemony of biology for determining “sports sex,” Coleman’s apt term (2). Allowing subjective gender self-identification to become the sole criterion of sports sex would allow for gaming and perceptions of systematic unfairness to grow. The case for women’s sports being defined by sex rather than gender, including the consequences of acceding to gender-based classification, has been outlined (9) in arguing the importance of proper medical

management of athletes intending to compete in female events.

Separate male and female events in sports is a dominant form of classification that is superimposed on other graduated age group and weight classifications (e.g., in weightlifting, power lifting, wrestling, boxing, rowing), which reflect differences in strength, power, and speed to ensure fairness in terms of opportunity to win and, additionally, safety in contact sports. Age and weight classifications rely on objective criteria (birth date, weigh-in weight) for eligibility, and so should sex classification. Nevertheless, some power sports dependent on explosive strength and power (e.g., throwing events, sprinting) do not segregate weight classes, whereas other sports where height is an advantage (e.g., basketball, jockeys) do not have height classifications. These sports disproportionately attract athletes with greater weight and/or power-to-weight ratio or advantageous stature, respectively. If sex classification were eliminated, such open or mixed competitions would be dominated almost exclusively by men. It therefore seems highly unlikely that sex classification would ever be discarded, despite calls on philosophical or sociological grounds to end “gender” classification in sport (10).

Sex Difference in Circulating Testosterone Levels

Testosterone biosynthesis, secretion, and regulation in men and women

An androgen is a hormone capable of developing and maintaining masculine characteristics in reproductive tissues (notably the genital tract, as well as in other tissues and organs associated with secondary sexual characteristics and fertility) and contributing to the anabolic status of nonreproductive body tissues (11). The two dominant bioactive androgens circulating in mature mammals, including humans—testosterone and its more potent metabolite DHT—account for the development and maintenance of all androgen-dependent characteristics, and their circulating levels in men and nonpregnant women arise from steroids synthesized *de novo* in the testes, ovary, or adrenals (12).

The sexually undifferentiated gonads in the embryo develop into either ovaries or testes according to whether a Y chromosome (or at least the *sry* gene) is present. After birth and until puberty commences, circulating testosterone concentrations are essentially the same in boys and girls, other than briefly in the neonatal period of boys when higher levels prevail. The onset of male puberty, a brain-driven process triggered by a still mysterious hypothalamic or higher cerebral mechanism (13), initiates a hormonal cascade. In males, this leads to enhanced pituitary LH secretion that stimulates the 500 million Leydig cells in the testes

to secrete 3 to 10 mg (mean, 7 mg) of testosterone daily (4, 6, 7, 14, 15). This creates a very high local concentration of testosterone within the testis as well as a steep downhill concentration gradient into the bloodstream that maintains circulating testosterone levels at adult male levels, which are tightly regulated by strong negative hypothalamic feedback of circulating testosterone. In the absence of testes, these mechanisms do not function in females. In girls, serum testosterone increases during puberty (16), peaking at age 20 to 25 years before declining gradually with age (17, 18), but it remains <2 nmol/L at all ages, as determined by a reliable method (see below).

In adult women, circulating testosterone is derived from three roughly equal sources: direct secretion from the adrenal gland or the ovary and indirect extraglandular conversion (in liver, kidney, muscle, fat, skin) from testosterone precursors secreted by the adrenal and ovary. Only when circulating testosterone concentrations rise in male adolescents above the prepubertal concentrations does the virilization characteristic of men commence, progress, and endure throughout adult life, at least until old age (18). In combination, these different sources produce ~ 0.25 mg of testosterone daily so that throughout life women maintain circulating testosterone levels of <2 nmol/L. Circulating testosterone concentrations in women are subject to little dynamic physiological regulation. As a result, circulating testosterone concentrations in healthy premenopausal women are stable (nonfluctuating) and not subject to strong negative feedback by exogenous testosterone (as happens in men). Even the small rise (50%) at the time of the mid-cycle LH surge triggering ovulation (19) remains within the physiological range for premenopausal females.

Male and female reference ranges for circulating testosterone

A reliable threshold for circulating testosterone must be set using measurement by the reference method of liquid chromatography–mass spectrometry (LC-MS) rather than using one of the various available commercial testosterone immunoassays. The necessary reliance on steroid mass spectrometry for clinical applications in endocrinology, reproductive medicine, and sports medicine is widely recognized. It has been standard for decades in antidoping science (20), and the growing consensus is that it is required for high-quality clinical research and practice recognized by cognate professional societies (21, 22) and editorials in leading clinical endocrinology (23) and reproductive medicine (24) journals. The inherently limited specificity of testosterone immunoassays arises from antibody cross-reactivity with structurally related steroids (such as precursors and metabolites) other than the intended target. As a result, all steroid immunoassays, including for testosterone, display method-specific bias whereby, for example, the lower limit of a

testosterone reference range in healthy young men varies from 7.3 to 12.6 nmol/L according to the immunoassay used, so that no consensus definition of a lower limit could be obtained independent of the commercial immunoassay method used (25). Furthermore, testosterone immunoassays are optimized for circulating levels in men but display increasing inaccuracy at the lower, by an order of magnitude, circulating testosterone concentrations in women or children. In contrast to immunoassays, LC-MS–based methods are highly specific and do not depend on proprietary antibodies. Using LC-MS–based measurements, method-specific bias can be avoided and a fixed consensus lower reference limit defined (Table 1). Hence, for the precision required in sports medicine, whether for eligibility criteria or antidoping applications, testosterone in serum must be measured by LC-MS methods.

Prior to puberty, levels of circulating testosterone as determined by LC-MS are the same in boys and girls (16). They remain lower than 2 nmol/L in women of all ages. However, from the onset of male puberty the testes secrete 20 times more testosterone resulting in circulating testosterone levels that are 15 times greater in healthy young men than in age-similar women. Using LC-MS measurement, circulating testosterone in adults has a strikingly nonoverlapping bimodal distribution with wide and complete separation between men and women. Table 1 (25–36) summarizes data from appropriate reported studies using mass spectrometry–based methods to measure serum testosterone in healthy men and women. Based on a number-weighted pooling with conventional 95% two-sided confidence limits of the eight available studies using LC-MS measurements of serum testosterone, the reference range for healthy young men (18 to 40 years) is 7.7 nmol/L to 29.4 nmol/L. Similarly, summarizing the nine available studies for healthy menstruating women under 40 years, the 95% (two-sided) reference range is 0 to 1.7 nmol/L. These reference limits do not control for factors such as oral contraceptive use (35, 36), menstrual phase (19), SHBG (37, 38), overweight (39, 40), fasting and smoking (41), diet (40), and physical activity (42, 43) in women and men, all of which have small effects on circulating testosterone but without materially influencing the divergence between the nonoverlapping bimodal distribution of male and female reference ranges of circulating testosterone.

In creating a threshold for eligibility for female events it is also necessary to make allowance for women with polycystic ovary syndrome (PCOS) and nonclassical adrenal hyperplasia. PCOS is a relatively common disorder among women of reproductive ages with a prevalence of 6% to 10%, depending on the diagnostic criteria used (44), in which mild hyperandrogenism is a key clinical feature and has higher than expected prevalence among elite female athletes

Table 1. Serum Testosterone Measurements by LC-MS Methods in Studies of Healthy Men and Women

Study	Sample (Age 18–40 y)	N	Lower 95% CL (nmol/L)	Upper 95% CL (nmol/L)
Men				
Sikaris <i>et al.</i> , 2005 (25)	Elite, eugonadal	124	10.4	30.1
Turpeinen <i>et al.</i> , 2008 (26)	Convenience	30	10.1	31.2
Kushnir <i>et al.</i> , 2010 (27)	Convenience	132	7.2	24.2
Salameh <i>et al.</i> , 2010 (28)	Convenience	264	7.1	39.0
Neale <i>et al.</i> , 2013 (29)	Convenience	67	10.6	31.9
Kelsey <i>et al.</i> , 2014 (30)	Secondary pooled analysis	1058	7.2	25.3
Hart <i>et al.</i> , 2015 (31)	Birth cohort	423	7.4	28.0
Travison <i>et al.</i> , 2017 (32)	Pooled two cohorts	1656	7.9	31.1
Number-weighted mean			7.7	29.4
Women				
Turpeinen <i>et al.</i> , 2008 (26)	Convenience	32	0.8	2.8
Kushnir <i>et al.</i> , 2010 (27)	Convenience	104	0.3	2.0
Salameh <i>et al.</i> , 2010 (28)	Convenience	235	0.03	1.5
Haring <i>et al.</i> , 2012 (33)	Population-based	263	0.04	2.0
Neale <i>et al.</i> , 2013 (29)	Convenience	90	0	1.7
Bui <i>et al.</i> , 2013 (34)	Convenience	25	0.30	1.69
Rothman <i>et al.</i> , 2013 (19)	Convenience	31	0.4	0.92
Bermon and Garnier, 2017 (35)	Elite athletes	1652	0	1.62
Eklund <i>et al.</i> , 2017 (36)	Elite athletes and controls	223	0.26	1.73
Number-weighted mean			0.06	1.68

Abbreviation: CL, confidence limit.

(36, 45–47). Nonclassical adrenal hyperplasia is a milder and later (adult) onset variant of classical congenital adrenal hyperplasia (48) with a much higher but still rare population prevalence (1:1000 vs 1:16,000 for the classical variant) (49). Table 2 (50–64) summarizes clinical studies ($n = 16, \geq 40$ women) reporting serum testosterone concentrations measured by LC-MS in samples from women with PCOS.

The pooled data reveal that the upper limit of serum testosterone in women with PCOS is 3.1 nmol/L (95% CI, one-sided) or 4.8 nmol/L (using a 99.99% CI, one-sided) (Table 3). Hence, a conservative threshold for circulating testosterone of 5 nmol/L measured by LC-MS would identify $<1:10,000$ women with PCOS as false positives, based on circulating testosterone measurement alone. Circulating testosterone higher than this threshold is likely to be due to testosterone-secreting adrenal or ovarian tumors, intersex/DSD, badly controlled or noncompliant male-to-female (M2F) transgender athletes, or testosterone doping.

The physiological effects of testosterone depend on the circulating testosterone, not its source (endogenous or exogenous)

Testosterone, whether of a natural endogenous or manufactured exogenous source, has an identical chemical structure and biological effects, aside from minor differences in isotopic composition, which are biologically insignificant. At equivalent doses and circulating levels, exogenous testosterone exerts the same biological and clinical effects on every known androgen-responsive tissue or organ as endogenous testosterone, apart from effects on spermatogenesis, which as discussed below is only a matter of degree. Consequently, exogenous testosterone is a fully effective substitute for endogenous testosterone in therapeutic use, countering the effects of testosterone deficiency due to hypogonadism (reproductive system disorders). Any purported differences between endogenous and exogenous testosterone are due to corresponding differences in the endogenous production rate or exogenous dose. Such differences in

REVIEW

Data taken directly from paper or interpolated from other data (e.g., median, quartiles, ranges, sample size) supplied as described by Wan *et al.*, 2014 (Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 14: 135) are shown in italics.

Table 2. Summary of Serum Testosterone (nmol/L) by LC-MS in Women With PCOS From 16 Studies

Study	N	Mean	SD
Moran <i>et al.</i> , 2017 (50)	92	0.24	0.08
Münzker <i>et al.</i> , 2017 (51)	274	0.93	0.19
O'Reilly <i>et al.</i> , 2017 (52)	114	0.55	0.19
Handelsman <i>et al.</i> , 2017 (53)	152	0.38	0.25
Pasquali <i>et al.</i> , 2016 (54)	156	1.17	0.47
Yang <i>et al.</i> , 2016 (55)	1159	2.2	1.44
Tosi <i>et al.</i> , 2016 (56)	116	1.33	0.55
Daan <i>et al.</i> , 2015 (57)	170	1.64	0.53
Bui <i>et al.</i> , 2015 (58)	44	0.85	0.3
Keefe <i>et al.</i> , 2014 (59)	52	1.7	0.97
Yasmin <i>et al.</i> , 2013 (60)	165	1.99	1.02
Janse <i>et al.</i> , 2011 (61)	200	1.12	0.47
Jedel <i>et al.</i> , 2011 (62)	72	0.23	0.08
Legro <i>et al.</i> , 2010 (Mayo) (63)	596	2.12	0.89
Legro <i>et al.</i> , 2010 (Quest) (63)	596	1.98	0.97
Stener-Victorin <i>et al.</i> , 2010 (64)	74	1.53	0.62
Sum	4032		
Number-weighted mean		1.69	0.87

effective exposure lead to corresponding differences in circulating testosterone levels and its effects according to the dose-response curves for testosterone.

Similar to all hormones and drugs, over their effective range of biological activity the dose-response relationship for testosterone is usually a sigmoidal curve with lower and upper plateaus joined by a monotonically rising middle region, which may be linear in the natural scale but more often log-linear (linear on the log or similar transformed scale). In the middle portion of the typical sigmoidal dose-response curve for the same increase in testosterone dose (or concentration), the response would be increased in simple proportional (*i.e.*, linear) but more often on a logarithmic scale. In contrast, at the lower and upper plateaus of dose or concentrations, changes in testosterone exposure may evoke minimal or no response on the endpoint. For example, in women of any age circulating testosterone concentrations are along the lower plateau of the dose-response curve, so that increases in circulating testosterone concentrations within that lower plateau may have minimal or no effect. In female athletes with the mild hyperandrogenism of PCOS, higher performance has been shown (47), with their muscle mass and power performance correlating with androgen levels (36).

However, beyond these effects where endogenous testosterone concentrations are in the high-normal adult female range, it is only when the increases in circulating testosterone concentrations substantially and consistently exceed those prevailing in childhood (<2 nmol/L) and among women including those with PCOS (<5 nmol/L) that the effects would replicate the effects of rising testosterone concentrations of boys in middle to late puberty (typically >8 nmol/L), that is, the masculinizing effects of increased muscle, bone, and hemoglobin characteristics of men. As shown above, the circulating testosterone of most women never reaches consistently >5 nmol/L, a level that boys must sustain for some time to exhibit the masculinizing effects of male puberty.

In addition, the effects of testosterone are modulated in a form of fine tuning by the patterns of exposure, such as whether the circulating testosterone is delivered in the unphysiological steady-state format (*e.g.*, quasi-steady-state delivery by implant or transdermal products) or by the peak-and-trough delivery of injections, as opposed to the natural state of endogenous fluctuations in serum testosterone around the average adult male levels. However, these latter pattern effects are subtle and the dominant effect remains that of dose and average testosterone

concentrations in blood, however they arise. Furthermore, there is evidence that the androgen sensitivity of responsive tissues differs and may be optimal at different circulating testosterone concentrations (65).

Male sexual function is maintained by endogenous testosterone at adult male circulating concentrations. These effects can be replicated by exogenous testosterone if and only if it achieves comparable circulating testosterone concentrations. For example, in a well-controlled prospective study of older men with prostate cancer (66), androgen deprivation achieving castrate levels of circulating testosterone sustained during 12 months markedly suppressed sexual desire and function, whereas those effects did not occur in age-matched men having nonhormonal treatment of prostate cancer or those without prostate cancer. In healthy younger men whose endogenous testosterone was fully suppressed, sexual function completely recovered when circulating testosterone was restored to the physiological male range by administration of exogenous testosterone (67). Similar effects were also observed in healthy, middle-aged men in whom male sexual function was fully maintained (compared with placebo) during 2 years of treatment with an exogenous androgen (DHT) despite that treatment causing sustained, complete suppression of endogenous testosterone (68). This further supports the key interpretation that the biological effects of exogenous or endogenous testosterone are the same at comparable circulating levels.

Clinically, exogenous testosterone replicates fully all effects of endogenous testosterone on every reproductive and nonreproductive organ or tissue, with the sole exception of the testis. Sperm production in the testis requires a very high concentration of testosterone (typically 100-fold greater than in the general bloodstream), which is produced in nature only by the action of the pituitary hormone LH. LH stimulates the Leydig cells in the interstitial space of the testis between seminiferous tubules to produce high intratesticular concentrations of testosterone, which are necessary and sufficient to initiate and maintain sperm production in the adjacent seminiferous tubules. This

high concentration of testosterone also provides a downhill gradient to supply the rest of the body, where circulating testosterone acts on androgen-responsive tissues to produce and maintain masculine patterns of androgenization. When exogenous testosterone (or any other androgen) is administered to men, pituitary LH is suppressed by negative feedback and the sperm production halts for as long as exogenous testosterone or androgen exposure continues, after which it recovers (69). However, even the reduction in spermatogenesis and testis size when men are treated with exogenous testosterone is only a matter of degree. It is well established in rodents (70, 71) that spermatogenesis is induced by exogenous testosterone when the testosterone concentrations in the testis are high enough to replicate what occurs naturally via LH stimulation (72). However, direct replication that high-dose testosterone also initiates and maintains spermatogenesis in humans is not feasible, as these testosterone doses are 10- to 100-fold higher than could be safely given to humans. Nevertheless, confirmatory evidence in humans is available from rare cases of men with an activating mutation of the chorionic gonadotropin/LH receptor (73, 74). This mutation causes autonomous testicular testosterone secretion leading to precocious puberty arising from the premature adult male circulating testosterone concentrations that lead to complete suppression of circulating gonadotropin (LH, FSH) secretion. In this illustrative case the testis was exposed to non-physiologically high testosterone concentrations (but without any gonadotropin stimulation) that induced sperm production and allowed for natural paternity (73). This indicates that even for spermatogenesis, exogenous testosterone can replicate all biological effects of endogenous testosterone in accordance with the relevant dose-response characteristics.

The most realistic view is that increasing circulating testosterone from the childhood or female range to the adult male range will have the same physiological effects whether the source of the additional testosterone is endogenous or exogenous. This is strongly supported by well-established knowledge about the relationship of circulating testosterone concentrations

Table 3. Upper Confidence Limits on Serum Testosterone in Women With PCOS

Confidence Interval	Likelihood ^a	SD ^b	One-Sided ^c	Two-Sided ^c
95%	1:20	1.96	3.13	3.39
99%	1:100	2.35	3.47	3.73
99.9%	1:1000	3.10	4.21	4.39
99.99%	1:10,000	3.72	4.77	4.95

^aLikelihood that a woman with PCOS would exceed that limit by chance.

^bNumber of SDs for each confidence limit.

^cTwo-sided CIs are conventional for a result that could exceed or fall below confidence limits, but here we focus only on values exceeding the upper limit, so that one-sided confidence limits are appropriate.

with the timing and manifestations of male puberty. The characteristic clinical features of masculinization (e.g., muscle growth, increased height, increased hemoglobin, body hair distribution, voice change) appear only if and when circulating testosterone concentrations rise into the range of males at mid-puberty, which are higher than in women at any age even after the rise in circulating testosterone in female puberty. If and only if the pubertal rise in circulating testosterone fails will the males affected be clinically considered hypogonadal. Such a failure of male puberty may occur for genetic reasons (arising from mutations that inactivate any of the cascade of proteins whose activity is critical in the hypothalamus to trigger male puberty) or as a result of acquired conditions, caused by pathological disorders of the hypothalamus or pituitary or functional defects arising from severe deficits of energy or nutrition (e.g., extreme overtraining, undernutrition), with the latter being comparable with hypothalamic amenorrhea or anorexia nervosa in female athletes/ballet dancers. If male puberty fails, testosterone replacement therapy is fully effective in replicating all of the distinctive masculine features apart from spermatogenesis.

Elevated circulating testosterone concentration caused by DSDs

Rare genetic intersex conditions known as DSDs can lead to markedly increased circulating testosterone in women. When coupled with ambiguous genitalia at birth, they may appear as undervirilized males or virilized females. This can cause athletes who were raised and identify as women to have circulating testosterone levels comparable to those of men and greatly exceeding those of non-DSD (and nondoped) women, including those with PCOS. Key congenital disorders in this category are 46,XY DSDs, namely 5 α reductase deficiency (75), 17 β -hydroxysteroid dehydrogenase type 3 deficiency (76), and androgen insensitivity (77, 78), as well as congenital adrenal hyperplasia (79), which is a 46,XX DSD. There is evidence that the first three conditions, components of 46,XY DSDs, are 140-fold more prevalent among elite female athletes than expected in the general population (80).

Genetic 5 α reductase deficiency is due to an inactivating mutation in the 5 α reductase type II enzyme (75). This leads to a deficit of DHT during fetal life when DHT is required for converting the sex-undifferentiated embryonic and fetal tissue to form the sex-differentiated masculine form external genitalia. Although genetic males (46,XY) with 5 α reductase deficiency will develop testes, they usually remain undescended and labial fusion to form a scrotum and phallic growth does not occur. Hence, at birth the external genitalia may appear feminine, leading to a female assigned natal sex. Thus, individuals with 5 α reductase deficiency may have male chromosomal sex

(46,XY), gonadal sex (testes), and hormonal sex (adult male testosterone concentrations), but such severely undervirilized genitalia that affected individuals may be raised from birth as females rather than as undervirilized males. However, from the onset of male puberty, testicular Leydig cells start producing large amounts of testosterone, and the steep rise in circulating testosterone to adult male levels (with the permissive role of 5 α reductase activity) leads to masculine virilization, including male patterns of muscle and bone growth, hemoglobin levels, and other masculine body habitus features (hair growth pattern, voice change), as well as phallic growth (80). Such changes of male puberty prompt around half affected individuals who had female sex assigned at birth and developed as girls prior to puberty to adopt a male gender identity and role at puberty (81). Sperm are formed in the testes so that, using *in vitro* fertilization, these individuals may father children (82).

17 β -Hydroxysteroid dehydrogenase type 3 deficiency (76) has a natural history similar to that of 5 α reductase deficiency. This disorder is due to inactivating mutations in a steroidogenic enzyme expressed only in the testis and that is essential for testosterone formation in the fetus. In the absence of a functional enzyme, the testis makes little testosterone but instead secretes large amounts of androstenedione, the steroid immediately prior to the enzymatic block. In the circulation, the excess of androstenedione is converted to testosterone (mainly by the enzyme AKR1C3) (12). Although the circulating testosterone is then converted to circulating DHT, insufficient DHT is formed locally within the urogenital sinus to virilize genitalia at birth. This causes the same severe undervirilization of the external genitalia of genetically male individuals, leading to ambiguous genitalia at birth despite male chromosomal, gonadal, and hormonal sex. When puberty arrives, the testes start producing the adult male testosterone output. Again, this leads to marked virilization and subsequent assumption of a male gender identity by some affected individuals, conflicting with a female assigned natal sex and childhood upbringing.

Androgen insensitivity, which arises from mutation in the androgen receptor (AR), poses different but complex challenges for eligibility for female athletic events. As the AR is located on the X chromosome, genetic males (46,XY) are hemizygous, so that an inactivating mutation in the AR can be partially or fully insensitive to androgen action. Affected individuals have male internal genitalia (testes in the inguinal canal or abdomen with Wolffian ducts) and consequently adult male circulating testosterone concentrations after puberty. These nonlethal mutations have a wide spectrum of functional effects, ranging from full resistance to all androgen action in complete androgen insensitivity syndrome (CAIS) where individuals have a full female phenotype with

normal female external genitalia, to partial androgen insensitivity syndrome (PAIS) where some androgen action is still exerted, leading to various degrees of ambiguous genitalia, or to mild androgen insensitivity, which produces a very mild, undervirilized male phenotype (normal male genital and somatic development but with little body hair and no male pattern balding) (77). Testosterone (and dihydrotestosterone) have no consistent effect of inducing normal nitrogen retention (anabolic) responses in patients with CAIS (83–86), although some reduced androgen responsiveness is retained by patients with PAIS (84, 87–90). Athletes with CAIS can compete fairly as females because the circulating testosterone, although at adult male levels, has no physiological effect so that, in terms of androgen action and the ensuing physical somatic advantages of male sex, affected individuals are indistinguishable from females and gain no benefits of the sex difference arising from unimpeded testosterone action. A more complex issue arises with athletes having PAIS reflecting the degree of incomplete impairment of AR function. Residual androgen action in such AR mutations is harder to characterize quantitatively, as there is no standardized, objective *in vitro* test to quantify AR functionality. Hence, individuals with PAIS may have adult male circulating testosterone concentrations but variable androgen sensitivity. At present, determination of eligibility to compete in the female category requires a case-by-case evaluation, primarily based on the degree of virilization. The current best available clinical approach to determining the functional impact (degree of functionality/sensitivity) of an AR mutation is based on the degree of somatic, primarily genital, virilization assessed according to the Quigley classification of grade of androgen sensitivity (91).

Congenital adrenal hyperplasia (CAH) is a relatively common defect in adrenal steroidogenesis in the enzymatic pathway, leading to synthesis of cortisol, aldosterone, and sex steroid precursors. The disease varies in severity from life-threatening (adrenal failure) to mild (hirsutism and menstrual irregularity), or even asymptomatic and undiagnosed. The most common mutations causing CAH occur in the 21-hydroxylase enzyme, accounting for 95% of cases (79). The defect leads to a bottleneck, creating a major backing up of precursor steroids that then overflow into other steroid pathways, leading to diagnostic high levels of 17-hydroxyprogesterone and, in female patients, excessive circulating testosterone or other adrenal-source androgen precursors (*e.g.*, androstenedione, dehydroepiandrosterone) that may be converted to testosterone in tissues. A common clinical problem with management of CAH is that glucocorticoid/mineralocorticoid treatment is not always fully effective partly due to variable compliance, which may leave high circulating testosterone, including well into or even above the normal male range (92). It is unlikely

that mild nonclassical congenital adrenal hyperplasia is a major contributor to the mild hyperandrogenism prevalent among elite female athletes. The prevalence of PCOS (6% to 16%) is about 100-fold higher than mild nonclassical congenital adrenal hyperplasia (0.1%) (49), whereas a disproportionately high number of elite female athletes (especially in power sports) have PCOS (45). In one study of hyperandrogenic female athletes, even mild nonclassical adrenal hyperplasia was ruled out by normal 17-hydroxyprogesterone (36) and, in another (47), reported serum androstenedione and cortisol did not differ from controls, ruling out significant congenital adrenal hyperplasia.

Sex Difference in Muscle, Hemoglobin, Bone, and Athletic Performance Relating to Adult Circulating Testosterone Concentrations

Following puberty, testosterone production increases (16) but remains <2 nmol/L in women, whereas in men testosterone production increases 20-fold (from 0.3 mg/d to 7 mg/d), leading to 15-fold higher circulating testosterone concentrations (15 vs 1 nmol/L). The greater magnitude of sex difference in testosterone production (20-fold) compared with circulating levels (15-fold) is due to women's higher circulating SHBG, which retards testosterone clearance, creating a slower circulating half-time of testosterone. This order-of-magnitude difference in circulating testosterone concentrations is the key factor in the sex difference in athletic performance due to androgen effects principally on muscle, bone, and hemoglobin.

Muscle

Biology

It has been known since ancient times that castration influences muscle function. Modern knowledge of the molecular and cellular basis for androgen effects on skeletal muscle involves effects due to androgen (testosterone, DHT) binding to the AR that then releases chaperone proteins, dimerizes, and translocates into the nucleus to bind to androgen response elements in the promoter DNA of androgen-sensitive genes. This leads to increases in (1) muscle fiber numbers and size, (2) muscle satellite cell numbers, (3) numbers of myonuclei, and (4) size of motor neurons (93). Additionally, there is experimental evidence that testosterone increases skeletal muscle myostatin expression (94), mitochondrial biogenesis (95), myoglobin expression (96), and IGF-1 content (97), which may augment energetic and power generation of skeletal muscular activity.

Customized genetic mouse models can provide unique experimental insight into mammalian physiology that is unobtainable by human experimentation.

"Sex differences in height, where they exist, are largely dependent on postpubertal differences in circulating testosterone."

The tight evolutionary conservation of the mammalian reproductive system explains why genetic mouse models have provided consistent, high-fidelity replication of the human reproductive system (98, 99). Genetic males (46,XY) with androgen insensitivity displaying similar features occur through the spontaneous production of inactivating AR mutations in all mammalian species studied, including humans, where they are known as women with CAIS. The converse, genetic females (46,XX) resistant to all androgen action cannot occur naturally in humans or other mammals. This is because fully androgen-resistant females must have both X chromosomes carrying an inactivated AR. In turn, this requires acquiring one X chromosome from their father, and hemizygous males bearing a single X chromosome with an inactive AR produce no sperm, as a functional AR is biologically indispensable for making sperm in any mammal. However, androgen-resistant females can be bred by genetic engineering using the Cre-Lox system (100). An important finding from such studies is that androgen-resistant female mice have essentially the same muscle mass and function as wild-type androgen-sensitive females bearing normal AR, whereas androgen-resistant male mice have smaller and weaker muscle mass and function than do wild-type males and comparable instead with wild-type females (101). This indicates that androgen action, represented by circulating testosterone, is the key determinant of the higher muscle mass and strength characteristic of males compared with females. Furthermore, endogenous circulating testosterone has minimal effects on skeletal muscle mass and strength in female mice because of its low levels. Although these experiments cannot be replicated in humans, their key insight is that the higher circulating testosterone in males is the determinant of the male's greater muscle mass and function compared with females. Nevertheless, there is also evidence that hyperandrogenic women, mostly with PCOS, have increased muscle mass and strength that correlates with mildly increased circulating testosterone in the high-normal female range (36, 47).

Observational data

There is a clear sex difference in both muscle mass and strength (102–104) even adjusting for sex differences in height and weight (104, 105). On average, women have 50% to 60% of men's upper arm muscle cross-sectional area and 65% to 70% of men's thigh muscle cross-sectional area, and women have 50% to 60% of men's upper limb strength and 60% to 80% of men's leg strength (106). Young men have on average a skeletal muscle mass of >12 kg greater than age-matched women at any given body weight (104, 105). Whereas numerous genes and environmental factors (including genetics, physical activity, and diet) may contribute to muscle mass, the major cause of the sex

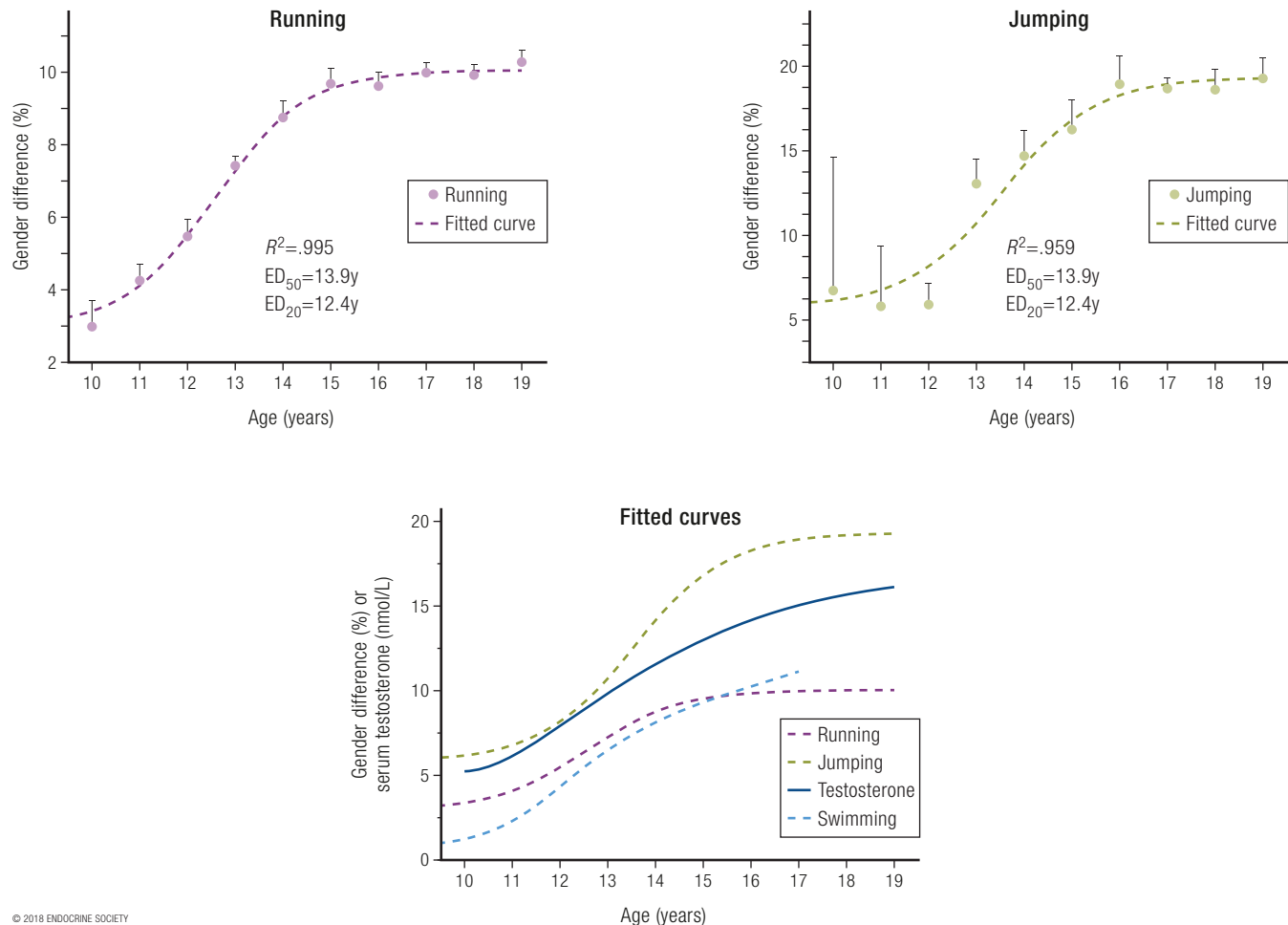
difference in muscle mass and strength is the sex difference in circulating testosterone.

Age-grade competitive sports records show minimal or no female disadvantage prior to puberty, whereas from the age of male puberty onwards there is a strong and ongoing male advantage. Corresponding to the endogenous circulating testosterone increasing in males after puberty to 15 to 20 nmol/L (sharply diverging from the circulating levels that remain <2 nmol/L in females), male athletic performances go from being equal on average to those of age-matched females to 10% to 12% better in running and swimming events, and 20% better in jumping events (8) (Fig. 1). Corroborative findings are provided by a Norwegian study that examined performance of adolescents in certain athletic events but without reference to contemporaneous circulating testosterone concentrations (107). The striking postpubertal increase in male circulating testosterone provides a major, ongoing, cumulative, and durable advantage in sporting contests by creating greater muscle mass and strength. These sex differences render women unable to compete effectively against men, especially (but not only) in power sports.

These findings are supported by studies of non-athletic women showing that muscle mass is increased in proportion to circulating testosterone in women with mildly elevated testosterone levels due to PCOS (108, 109), a condition that is more prevalent among elite female athletes who exhibit these features (36, 45, 47), often undiagnosed (46), but that may provide an ergogenic advantage (47), consistent with the graded effects of circulating testosterone on explosive performance in men and women (110).

Studies of elite female athletes further corroborate these findings. One study demonstrates dose-response effects of better performance in some (400 m running, 400 m hurdles, 800 m running, hammer throw, pole vault) but not all athletic events correlated with significantly higher endogenous testosterone in female, but not male, athletes. Even within the low circulating testosterone levels prevailing within the normal female range, in these events there was a significant advantage of 1.8% to 4.5% among those in the highest tertile compared with the lowest tertile of endogenous testosterone (35). A further study of elite female athletes corroborates and extends these observations in that endogenous androgens are associated with a more anabolic body composition as well as enhanced muscular performance (36). In this study, 106 Swedish Olympic female athletes were compared with 117 age- and weight (body mass index)-matched sedentary control women for their muscle and bone mass (by dual-energy X-ray absorptiometry), their muscular strength (squat and countermovement jumps), and testosterone and DHT, as well as androgen precursors (dehydroepiandrosterone, androstenedione) and urinary androgen glucuronide metabolites (androsterone,

Figure 1. Sex differences in performance (in percentage) according to age (in years) in running events, including 50 m to 2 miles (upper left panel), and in jumping events, including high jump, pole vault, triple jump, long jump, and standing long jump (upper right panel) [for details, see Ref. (8)]. The lower panel is a fitted sigmoidal curve plot of sex differences in performance (in percentage) according to age (in years) in running, jumping, and swimming events, as well as the rising serum testosterone concentrations from a large dataset of serum testosterone of males. Note that in the same dataset, female serum testosterone concentrations did not change over those ages, remaining the same as in prepubertal boys and girls. Data are shown as mean and SEM of the pooled sex differences by age. Reproduced with permission from Handelsman DJ. Sex differences in athletic performance emerge coinciding with the onset of male puberty. *Clin Endocrinol (Oxf)*. 2017;**87**:68–72.



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etiocholanolone, 3 and 17 3α -diols) measured by LC-MS (36). The athletes displayed higher muscle (and bone) mass than did the sedentary control women, with strength tests correlating strongly with muscle mass whether in total or just in the legs. In turn, muscle mass and strength were correlated with androgens and androgen precursors. Considering that such studies may be confounded by factors such as menstrual phase and dysfunction, as well as heterogeneous sports disciplines, which weaken the power of the study, these findings can be regarded as quite robust.

Interventional data

Dose-response studies show that in men whose endogenous testosterone is fully suppressed, add-back administration of increasing doses of testosterone that produce graded increases in circulating testosterone causes a

dose-dependent (whether expressed according to testosterone dose or circulating levels) increase in muscle mass (measured as lean body mass) and strength (65, 111). Taken together, these studies prove that testosterone doses leading to circulating concentrations from well below to well above the normal male range have unequivocal dose-dependent effects on muscle mass and strength. These data strongly and consistently suggest that the sex difference in lean body mass (muscle) is largely, if not exclusively, due to the differences in circulating testosterone between men and women. These findings have strong implications for power-dependent sport performance and largely explain the potent efficacy of androgen doping in sports.

The key findings providing conclusive evidence that testosterone has prominent dose-response effects in men are reported in studies by Bhasin and colleagues that proved a monotonic dose response,

extending from subphysiological to supraphysiological range for men for testosterone effects on muscle mass, size, and strength in healthy young men, findings that have been replicated and confirmed by an independent group (65). Both sets of studies used a common design of fully suppressing all endogenous testosterone (to castrate levels) for the full duration of the experiment by administering a GnRH analog. In the Bhasin and colleagues studies, participants were then randomized to five groups and each received weekly injections of 25 mg, 50 mg, 125 mg, 300 mg, or 600 mg of testosterone enanthate for 20 weeks. In effect, this was two subphysiological and two supraphysiological testosterone doses. In these studies, the lowest testosterone dose produced a mean serum testosterone of 253 ng/dL (8.8 nmol/L) in younger men and 176 ng/dL (6.1 nmol/L) in older men. The studies showed a consistent dose response for muscle mass and strength that was clearly related to testosterone dose and consequential blood testosterone concentrations (Fig. 2, upper panel).

The study of Finkelstein *et al.* (65) involved the same design and involved 400 healthy men aged 20 to 50 years who had complete suppression of endogenous testosterone for the 16 weeks of the study, with testosterone added back using daily doses of 0, 1.25 g, 2.5 g, 5 g, or 10 g of a topical 1% testosterone gel. This again created a graded dose-response curve for serum testosterone and for muscle mass and strength. The inclusion of a 0 (placebo) dose allowed differentiation between the 0 and lowest testosterone dose. The placebo (0) dose produced a serum testosterone of 0.7 nmol/L (the typical mean for castrated men, childhood, and women of any age). Meanwhile, the lowest testosterone dose (1.25 g of gel per day) produced a serum testosterone of 6.9 nmol/L, which is equivalent to that of a male in early to middle puberty. A key finding for this review is that, from this study of men, the increase in serum testosterone from mean of normal female concentration (0.9 nmol/L) to supraphysiological female concentrations (6.9 nmol/L) produced significant increases of 2.3% for total body lean (muscle) mass, 3.0% for thigh muscle area, and 5.5% increase in leg press strength (digitized data pooling of both cohorts from lower panel, Fig. 2).

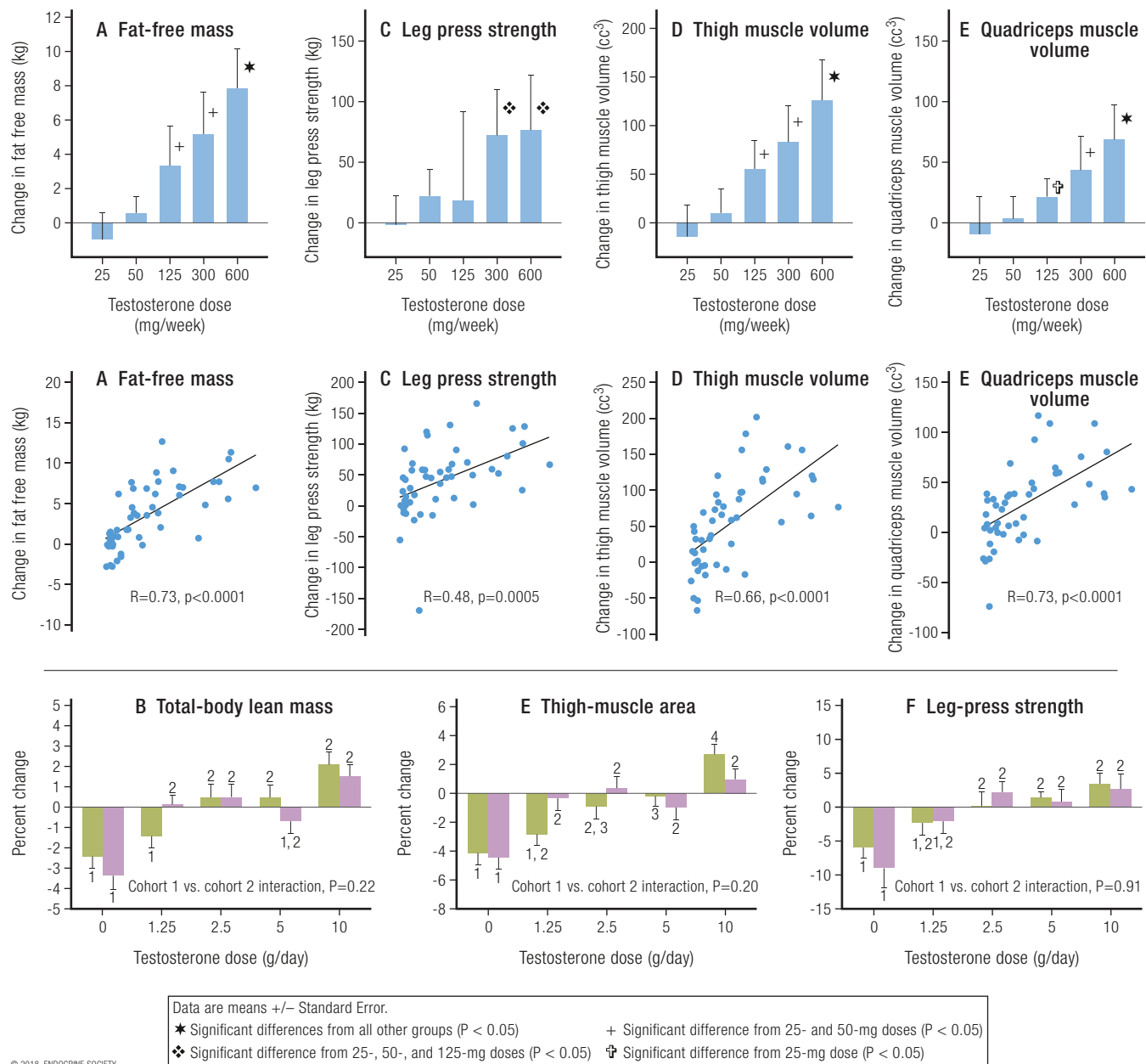
Studies of the ergogenic effects of supraphysiological concentrations of circulating testosterone require studies administering graded doses of exogenous testosterone for months. Owing to ethical concerns regarding risks of unwanted virilization and hormone-dependent cancers, however, few studies have administered supraphysiological testosterone doses to healthy women. One well-designed, randomized placebo-controlled study of postmenopausal women investigated the effects of different testosterone doses on muscle mass and performance and physical function (112). Sixty-two women (mean age, 53 years) all had a standard estrogen-replacement dose administered during a 12-week run-in period (to

eliminate any hypothetical confounding effects of estrogen deficiency), after which they were randomized to one of five groups receiving weekly injections of testosterone enanthate (doses: 0, 3 mg, 6.25 mg, 12.5 mg, and 25 mg, respectively) for 24 weeks. The increasing doses of testosterone produced an expected dose response in serum testosterone concentrations (by LC-MS), with the highest testosterone dose (25 mg/wk) producing a mean nadir concentration of 7.3 nmol/L. The women whose testosterone concentrations were increased to 7.3 nmol/L achieved significant increases in muscle mass and strength (Table 4), ranging from 4.4% for muscle (lean) mass to between 12% and 26% for measures of muscle strength (chest and leg press, loaded stair climb). As muscle strength measurement is effort-dependent, the placebo-controlled design of the Huang *et al.* (112) study supports the further interpretation that the highest dose of testosterone also had prominent mental motivational effects in the effort-dependent tests of muscle strength. These findings provide salient direct evidence of the ergogenic effects of hyperandrogenism in female athletes confirming that at least up to average circulating testosterone concentrations of 7.3 nmol/L, women display a dose-response relationship similar to that of men, with supraphysiological doses of testosterone leading to significant gains in muscle mass and power.

These effects of testosterone administration on circulating testosterone concentrations and muscle mass and strength in females may be compared with the effects in males from the Finkelstein *et al.* (65) and Bhasin and colleagues studies. In men, the lowest testosterone dose (1.25 g/d) increased mean serum testosterone to 6.9 nmol/L (equivalent to levels seen in early to middle male puberty), resulting in significant increases of total body lean (muscle) mass (2.3%), thigh muscle area (3.0%), and leg press strength (5.5%) compared with the placebo dose that resulted in a serum testosterone of 0.7 nmol/L. In the Huang *et al.* (112) study (Fig. 3), muscle mass and strength in postmenopausal women displayed a flat response at the three lower doses, when circulating testosterone concentrations remain <5 nmol/L, and displayed a significant increase only when the mean circulating testosterone concentration produced by the highest testosterone dose first increased circulating testosterone concentrations >5 nmol/L. This pattern, flat at lower doses and rising at the highest dose, represents the lower plateau and the earliest rising portion, respectively, of the sigmoidal dose-response curve of testosterone for muscle.

Data corroborating the Huang *et al.* study results comes from another well-controlled study in which postmenopausal women who were administered methyl testosterone following a run-in period of estrogen replacement displayed a significant increase in lean (muscle) mass as well as upper and lower limb

Figure 2. Strong dose-response relationship between testosterone dose and circulating concentration with muscle mass and strength in men. The upper panels [from Bhasin *et al.* (111)] display the strong dose-response relationships of muscle mass shown as (A) “lean” or “fat-free” mass or volume of (D) thigh and (E) quadriceps muscle and (C) of leg muscle strength with increasing testosterone dose (upper row) or circulating concentration (middle row). Serum testosterone concentrations are in US units (ng/dL; divide by 28.8 to get nmol/L). Adapted with permission from Bhasin S, Woodhouse L, Casaburi R, *et al.* Testosterone dose-response relationships in healthy young men. *Am J Physiol Endocrinol Metab.* 2001;281:E1172–E1181. The lower panels [from Finkelstein *et al.* (65)] show the strong dose-response relationships of (B) whole-body muscle mass, (E) thigh muscle mass, and (F) leg press strength with increasing testosterone dose. Cohorts 1 and 2 were treated with the same increasing doses of testosterone but either without (green fill, cohort 1) or with (purple fill, cohort 2) an aromatase inhibitor (anastrozole), which prevents conversion of testosterone to estradiol. The differences between cohorts (*i.e.*, use of anastrozole) was not significant for muscle mass and strength and can be ignored with results of the two cohorts being pooled. Reproduced with permission from Finkelstein JS, Lee H, Burnett-Bowie SA, Pallais JC, *et al.* Gonadal steroids and body composition, strength, and sexual function in men. *N Engl J Med* 2013;369:1011–1022.



power during a 16-week double-blind, parallel group study (113).

Similarly, two prospective studies of the first 12 months of treatment of transmen [female-to-male

(F2M) transgender] shows a consistent major increase in muscle mass and strength due to testosterone administration. In one study testosterone treatment of 17 transmen achieving adult male circulating testosterone levels

Table 4. Effects of Testosterone on Muscle Mass and Strength in Women

Androgen-Sensitive Variable	Baseline	Increase	% Increase
Lean muscle mass, kg	43 ± 6	1.9 ± 0.5	4.4
Chest press, W	100 ± 26	26 ± 7	26
Leg press, N	744 ± 172	90 ± 30	12
Loaded stair-climb power, W	406 ± 77	56 ± 13	14

With data from Huang G, Basaria S, Travison TG, *et al.* Testosterone dose-response relationships in hysterectomized women with or without oophorectomy: effects on sexual function, body composition, muscle performance and physical function in a randomized trial. *Menopause* 2014;21:612–623. Data are shown as mean and SEM derived from Table 1 and digitized from Figure 4 from Huang *et al.* (112) showing the effects of testosterone (mean circulating concentration, 7.3 nmol/L) on muscle mass and strength in women treated with the highest testosterone dose (n = 11; 25 mg of testosterone enanthate per week).

(mean, 31 nmol/L) increased muscle mass by 19.2% (114). In a second study, 23 transmen administered adult male testosterone doses also produced striking increases in total body muscle size and limb muscle size (by 6.5% to 16.6%) and grip strength (by 18%) compared with age-matched untreated control women (115). Conversely, testosterone suppression (using an estrogen-based treatment regimen) in 20 transwomen (M2F transgender) that reduced circulating testosterone levels from adult male range to adult female range led to a 9.4% reduction in muscle mass (measured as cross-sectional area).

Effects on athletic performance

Muscle growth, as well as the increase in strength and power it brings, has an obvious performance-enhancing effect, in particular in sports that depend on strength and (explosive) power, such as track and field events (107, 110). There is convincing evidence that the sex differences in muscle mass and strength are sufficient to account for the increased strength and aerobic performance of men compared with women and is in keeping with the differences in world records between the sexes (116). The basis for the sex difference in muscle mass and strength is the sex difference in circulating testosterone as clearly shown (for example) by (1) the enhanced athletic performance of men compared with prepubertal boys and women (8); (2) the close correspondence of muscle growth (muscle size) with muscle strength in ascending dose studies in men by Bhasin *et al.* (111, 117–119) and Finkelstein *et al.* (65) and in postmenopausal women by Huang *et al.* (112); (3) the effect of male castration in reducing muscle size and strength, effects that are fully rectified by testosterone replacement; and (4) the striking efficacy of androgen doping on the sports performances of German Democratic Republic female athletes (120).

Hemoglobin

Biology

It is well known that levels of circulating hemoglobin are androgen-dependent and consequently higher in men than in women by 12% on average; however, the physiological mechanism by which androgens such as

testosterone boosts circulating hemoglobin is not fully understood (121). Testosterone increases secretion of and sensitivity to erythropoietin, the main trophic hormone for erythrocyte production and thereby hemoglobin synthesis, as well as suppressing hepcidin (122), a crucial iron regulatory protein that governs the body's iron economy. Hepcidin has to balance the need for iron absorption from foods (the only source of iron required for the body's iron-containing proteins) against the fact that the body has no mechanism to shed excess iron, which can be toxic. Adequate iron availability is essential for normal erythropoiesis and synthesis of key heme, iron-containing oxygen-transporting proteins such as hemoglobin and myoglobin (123) as well as other iron-dependent proteins such as cytochromes and DNA synthesis and repair enzymes. Experimental evidence in mice shows that testosterone increases myoglobin content of muscle with potential for augmenting aerobic exercise performance (96), but this has not been evaluated in humans.

Increasing the amount of hemoglobin in the blood has the biological effect of increasing oxygen transport from lungs to tissues, where the increased availability of oxygen enhances aerobic energy expenditure. This is exploited to its greatest effect in endurance sports (1). The experiments of Ekblom *et al.* (124) in 1972 (Fig. 4) demonstrated strong linear relationships between changes in hemoglobin [due to withdrawal or retransfusion of 1, 2 or 3 U (400 mL) of blood] and aerobic capacity, established by repeated testing of maximal exercise-induced oxygen consumption before and after each procedure (124). As already noted, circulating hemoglobin levels are on average 12% higher in men than women (125). It may be estimated that as a result the average maximal oxygen transfer will be ~10% greater in men than in women, which has a direct impact on their respective athletic capacities.

Observational data

The proposition that the sex difference in circulating hemoglobin levels is likely to be due to the sex difference in average circulating testosterone concentrations is supported by the fact that male castration (*e.g.*, for advanced prostate cancer) (126) and androgen deficiency due to reproductive system disorders (127) reduce circulating

hemoglobin in men, eliminating the sex difference, whereas testosterone replacement therapy restores circulating hemoglobin to adult male levels (121, 127, 128).

An unusually informative observational study of women with CAH provides unique insight into testosterone effects on circulating hemoglobin in otherwise healthy women (92). Women with CAH require glucocorticoid replacement therapy but exhibit widely varying levels of hormonal control (79). The degree of poor control is associated with increasing levels of circulating testosterone ranging from normal female concentrations up to 36 nmol/L, and these levels correlate closely ($r = 0.56$) with levels of circulating hemoglobin (Fig. 5). Interpolating from the dose-response regression, increases in circulating testosterone measured by LC-MS from 0.9 nmol/L to 5 nmol/L, 7 nmol/L, 10 nmol/L, and 19 nmol/L were associated with increases in circulating hemoglobin of 6.5%, 7.8%, 8.9%, and 11%, respectively, establishing a strong dose-response relationship. An 11% increase in circulating hemoglobin translates to a 10% difference in maximal oxygen transfer (124), which may account for virtually all the 12% sex difference in male and female circulating hemoglobin (125). To put this into context, any drug that achieved such increases in hemoglobin would be prohibited in sports for blood doping, as this difference is sufficient to have ergogenic effects, even without taking into account any testosterone effects on muscle mass or strength (for which data were not available in that study). Conversely, among elite female athletes with circulating testosterone in the healthy premenopausal female range, circulating hemoglobin does not correlate with athletic performance (35). In women with the mild hyperandrogenism of PCOS, circulating hemoglobin and hematocrit are reported as not (129) or marginally increased (130), findings that may be influenced by the fact that PCOS is

associated with reduced or absent menstruation, thereby reducing the iron loss of regular menstruation.

Interventional data

In the Bhasin *et al.* (111) studies, in both young and older men the highest testosterone dose produced a 12% increase in blood hemoglobin compared with the lowest dose, reflecting a strong dose-response relationship (Fig. 6) (131). Analogous findings were reported for testosterone treatment effects in postmenopausal women where the highest dose (25 mg weekly) of testosterone, which increased mean serum testosterone to 7.3 nmol/L, had the largest increase (3%) in blood hemoglobin and hematocrit (112).

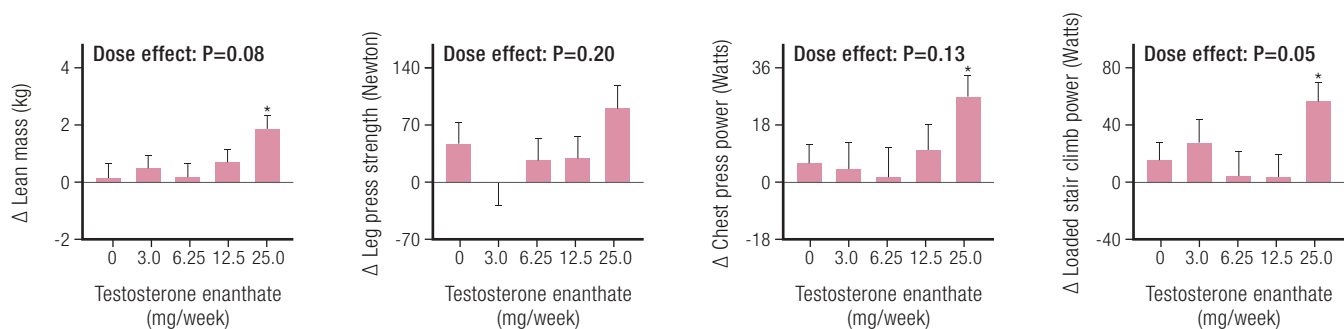
Corroborative findings are available from studies of transmen (F2M transgender), that is, natal females who subsequently receive testosterone treatment at replacement doses to create adult male circulating testosterone concentrations, who exhibit increases in circulating hemoglobin to male levels [reviewed in (132–134)]. Testosterone treatment in 17 (F2M) transmen that created mean circulating testosterone levels of 31 nmol/L also increased hemoglobin levels by 15% (114). Conversely, one prospective 12-month study of transgender (nonathlete) individuals reported that testosterone suppression (by an estrogen-based regimen) to normal female levels in 20 (M2F) transwomen reduced hemoglobin by 14%.

If such an increase in hemoglobin were produced by any chemical substance, it would be considered doping, according to the World Anti-Doping Code.

Bone

Biology

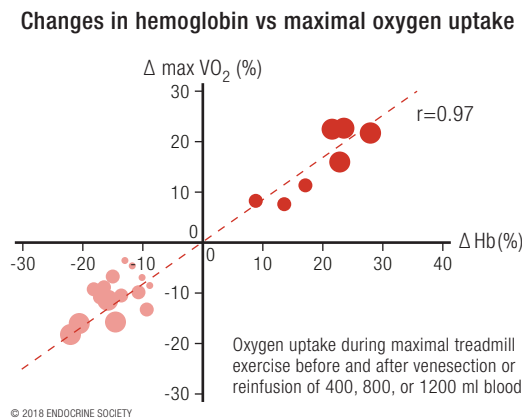
There is extensive experimental evidence from genetic mouse models showing that the sex differences in bone



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Figure 3. From Huang *et al.* (112): Dose-response effects on lean (muscle) mass and three measures of muscle strength as a result of increasing doses of weekly testosterone enanthate injections in women. Note the effects on all four parameters (three statistically significant) of the highest testosterone dose, the only one that produced circulating testosterone levels exceeding the normal female range. Reproduced with permission from Huang G, Basaria S, Travison TG, *et al.* Testosterone dose-response relationships in hysterectomized women with or without oophorectomy: effects on sexual function, body composition, muscle performance and physical function in a randomized trial. *Menopause* 2014;21:612–623.

Figure 4. Redrawn results from Ekblom *et al.* (124). Results from the transfusion of additional blood are shown in dark red circles and those after blood withdrawal in light red circles. Adapted with permission from Ekblom B, Goldbarg AN, Gullbring B. Response to exercise after blood loss and reinfusion. *J Appl Physiol* 1972;33:175–180.



size, mass, and function are due to the sex difference in circulating testosterone. These effects have been reported from studies of global and tissue or cell-selective inactivation of ARs or estrogen receptors that show that androgen effects are mediated by both direct effects on the AR as well as indirect effects mediated via aromatization of testosterone to estradiol to act on estrogen receptors [reviewed in (135)]. Bone grows in length due to epiphyseal chondral growth plates that provide cartilage, forming the matrix for lengthening of long bone, which is terminated by an estrogen-dependent mechanism that depends on aromatization of testosterone to estradiol. Similarly, bone width and density are increased through appositional growth from periosteal and endosteal expansion that depend on bone loading and androgen exposure together with other factors. An important difference between androgen effects on bone compared with effects on muscle or hemoglobin is that developmental bone effects of androgens are likely to be irreversible.

Observational data

Men have distinctively greater bone size, strength, and density than do women of the same age. As with muscle, sex differences in bone are absent prior to puberty but then accrue progressively from the onset of male puberty due to the sex difference in exposure to adult male circulating testosterone concentrations [reviewed in (135)]. The earlier onset of puberty and the related growth spurt in girls as well as earlier estrogen-dependent epiphyseal fusion explains shorter stature of girls than boys. As a result, on average men are 7% to 8% taller with longer, denser, and stronger bones, whereas women have shorter humerus and femur cross-sectional areas being 65% to 75% and 85%, respectively, those of men (106).

These changes create an advantage of greater bone strength and stronger fulcrum power from longer bones. Additionally, whereas passing through puberty enhances male physical performance, the widening of the female pelvis during puberty, balancing the evolutionary demands of obstetrics and locomotion (136, 137), retards the improvement in female physical performance, possibly driven by ovarian hormones rather than the absence of testosterone (138, 139).

Sex differences in height have been the most thoroughly investigated measure of bone size, as adult height is a stable, easily quantified measure in large population samples. Extensive twin studies show that adult height is highly heritable with predominantly additive genetic effects (140) that diverge in a sex-specific manner from the age of puberty onwards (141, 142), the effects of which are likely to be due to sex differences in adult circulating testosterone concentrations.

Bone density (total and medullary cross-sectional area) is increased in women with CAH with variably elevated serum testosterone (including into the male range) when it is only partially suppressed by glucocorticoid treatment (143), although more effective glucocorticoid suppression lowers bone density (144).

Interventional data

Well-designed, placebo-controlled direct interventional studies of supraphysiological androgen effects on bone in females are few, rarely feasible, and unlikely to be performed for ethical and practical reasons. Unlike muscle, which responds relatively rapidly to androgen effects so that muscle studies in humans can be completed within 3 to 4 months (65, 111, 112, 119, 145), comparable bone studies would typically take a year or more to reach plateau effects. Hence, such direct investigational studies in otherwise healthy women would risk side effects of virilization that may be only slowly and partly reversible, if at all, as well as potential promotion of hormone-dependent cancers making such studies ethically and practically not feasible.

Effects on athletic performance

The major effects of men's larger and stronger bones would be manifest via their taller stature as well as the larger fulcrum with greater leverage for muscular limb power exerted in jumping, throwing, or other explosive power activities. The greater cortical bone density and thereby resistance to long bone fractures is unlikely to be relevant to the athletic performance of young athletes, in whom fractures during competition are extremely rare and not expected to be linked to sex. Alternatively, stress fractures in athletes, mostly involving the legs, are more frequent in females with the male protection attributable to their larger and thicker bones (146).

Other androgen-sensitive sex dichotomous effects

Biology and observational data

Many if not most other aspects of physiology exhibit sex differences and may therefore enhance the impact of the male advantage in sports performance of the dominant determinants (muscle and hemoglobin). Examples include sex differences in exercise-induced cardiac (147, 148) and lung (149) function and mitochondrial biogenesis and energetics (95). However, the limited knowledge of the magnitude and hormonal mechanisms involved, specifically the degree of androgen dependence of these mechanisms, means that it is difficult to estimate their contribution, if any, toward the sex difference in athletic performance. The sex difference in pulmonary function may be largely explained by the androgen-sensitive sex difference in height, which is a strong predictor of lung capacity and function (149). Further physiological studies of the androgen dependence of other physiological sex differences are awaited with interest.

Psychological differences between men and women on mental function (e.g., rotational orientation) (150) as well as mood, motivation, and behavioral effects may involve androgen-sensitive effects during prenatal and perinatal as well as postpubertal effects (151, 152).

Interventional data

There is some limited direct evidence from well-designed, placebo-controlled trials that administration of testosterone or other androgens at supraphysiological doses directly affect mood and behavior, notably inducing hypomania (153). In a randomized placebo-controlled study of testosterone administration in postmenopausal women (112), in case of those receiving the highest dose (the only one causing circulating testosterone levels to exceed the normal female range), there was not only an increase in muscle mass (4.4%) but a strikingly greater increase in muscle strength (12% to 26%), suggesting an enhanced mental motivational effect of testosterone on the effort-dependent tests of muscle strength.

Alternative Mechanisms Proposed to Explain Sex Differences in Athletic Performance

Alternative explanations for the sex difference in athletic performance, other than it being due to the sex difference in postpubertal circulating testosterone, have been proposed, including (1) sex differences in height because height is a predictor of muscle mass (116), (2) genetic sex differences due to the influence of unspecified Y chromosome genes (154), and (3) sex differences in GH secretion (116).

Effects of height

One proposal has been that, as men are taller than women, height differences may explain the sex differences in muscle mass and function, which explains some athletic success (116). Numerous factors contribute to the regulation of adult muscle mass, including genetics, race, adiposity, hormones, physical activity (exercise/training), diet, birth order, and bone size (including height) [reviewed in (155)]. Among the nonhormonal factors, genetics explains a large proportion [~50% to 60% from pooled twin studies (156)] of the variability in muscle mass and strength (157, 158) and may be explained in turn by the equally high genetic contributions to circulating testosterone (37, 38). Some factors influencing muscle mass and strength such as physical activity, adiposity, and bone size are also partly androgen-dependent. Prior to puberty there is no sex difference in skeletal features, including height (159, 160). However, with the onset of puberty, girls aged 11 and 12 years are transiently taller than peer-aged boys due to their earlier onset of the female pubertal growth spurt, but from the age of 14 years onward the taller stature in males emerges and stabilizes (141). Hence, similar to muscle mass, sex differences in bone size (including length, density, and height) arise after male puberty establishes the marked dichotomy between men and women in adult circulating testosterone concentrations. Taller height is

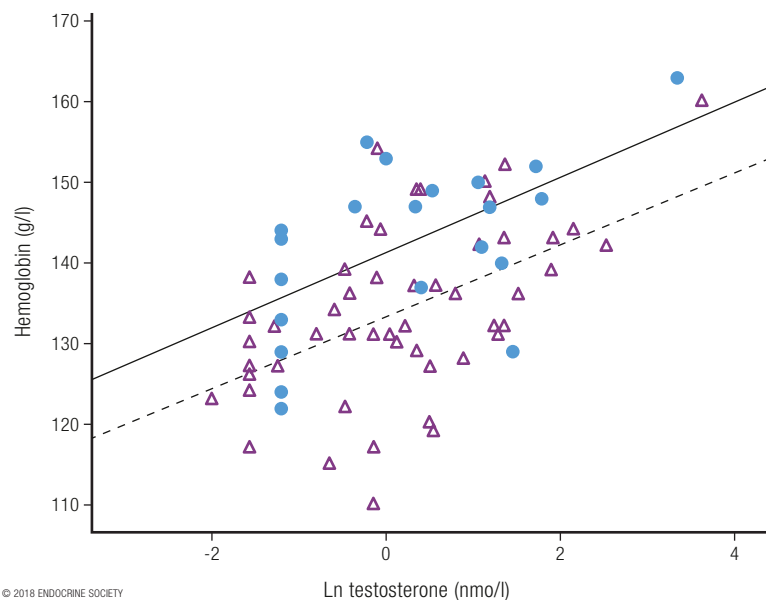


Figure 5. Plot of circulating hemoglobin against the natural logarithm of serum testosterone in women with congenital adrenal hyperplasia [from Karunasena *et al.* (92)]. The filled circles represent a cohort where serum testosterone was measured by immunoassay. The open triangles denote a second cohort, where serum testosterone was measured by LC-MS. Note the systematic overestimation of testosterone by the immunoassay used in cohort 1 vs LC-MS measurement in cohort 2. Despite that overestimation, however, the correlations were similar in both cohorts. Reproduced under a Creative Commons BY-NC-ND 4.0 license from Karunasena N, Han TS, Mallappa A, *et al.* Androgens correlate with increased erythropoiesis in women with congenital adrenal hyperplasia. Clin Endocrinol (Oxf) 2017;86:19–25.

advantageous in some sports (basketball, some football codes, combat sports), but in others (horse racing jockeys, cycling, gymnastics, weightlifting, body-building) short stature provides a greater power/strength-to-weight ratio as well as superior rotational balance, speed, and agility. However, the male advantages in speed, strength, and endurance apply regardless of whether height is advantageous. Hence, the sex differences in height, where they exist, are largely dependent on postpubertal differences in circulating testosterone when sex differences in height are first expressed.

Genetic effects of Y chromosome

It has also been proposed that the sex difference in athletic performance may be due to genetic effects of an unspecified Y chromosome gene that may dictate taller stature (154), as height is correlated with men's greater muscle mass. The small human Y chromosome has few functional genes and none with a known effect on height other than the short stature homeobox (SHOX) gene, located in the pseudoautosomal regions of the tip of the short arms of X and Y chromosomes (161). Adult height displays an apparent dose dependency on SHOX gene copy number that is a major factor contributing to explaining both the short stature of 45,XO females (Turner syndrome), who have a single copy of the SHOX gene, as well as the tall stature of 47,XXY males (Klinefelter syndrome), who have three copies (161). However, when SHOX copy number is the same, men with additional supernumerary Y chromosomes (e.g., 47,XYY) are the same height as 47,XXY men (162). Hence, there is no evidence supporting dosage-dependent Y chromosomal gene effects on height independent of SHOX gene copy number, nor does men's possession of a Y chromosome explain the height difference between adult men and women. On the contrary, the tall stature of 47,XXY men is at least partly due to the concomitant androgen deficiency leading to pubertal

delay. Pubertal delay prolongs long bone growth due to delayed epiphyseal closure, an estrogen-dependent effect that requires adequate production of testosterone as a substrate for aromatization to estradiol, resulting in tall stature. Similar eunuchoidal features and taller stature are evident in 46,XY men with congenital hypogonadotropic hypogonadism (Kallmann syndrome and its variants) with comparable congenital onset of androgen deficiency, also manifest as pubertal delay and long bone overgrowth. Hence, taller height is better explained by impaired testicular function with delayed puberty and epiphyseal closure rather than unspecified Y chromosome dosage effects. In any case, rare aneuploidies in themselves do not explain the sex difference in height in the general population of individuals with normal sex chromosomes.

Growth hormone

The proposal that the sex difference in muscle mass and function might be due to sex differences in endogenous GH secretion (116) is refuted by the extensive and conclusive clinical evidence that endogenous GH secretion in young women is consistently higher (typically twice as high) as in young men of similar age (163–170). Those findings cannot explain the male advantage in muscle mass and strength unless GH retards muscle growth/function, for which there is no evidence. Furthermore, estrogens inhibit GH-dependent, hepatic IGF-1 production, the major pathway of GH action (171, 172). The weak observational association between low circulating IGF-1 and some, but not other, measures of weak muscle strength and limited mobility among older women may reflect general age-associated debility rather than any specific hormonal effects (173). Finally, the evidence that endogenous GH plays no role in sex differences in muscle mass and function is supported by evidence from the most extensive interventional study of GH treatment to non-GH-deficient adults, daily GH administration for 8 weeks to healthy recreational athletes produced only marginally significant improvement in exercise performance of men and none in women (174). These findings are consistent with the speculation that GH (or IGF-1) may be an amplifier of testosterone effects and therefore be a consequence of the sex difference in circulating testosterone rather than its cause.

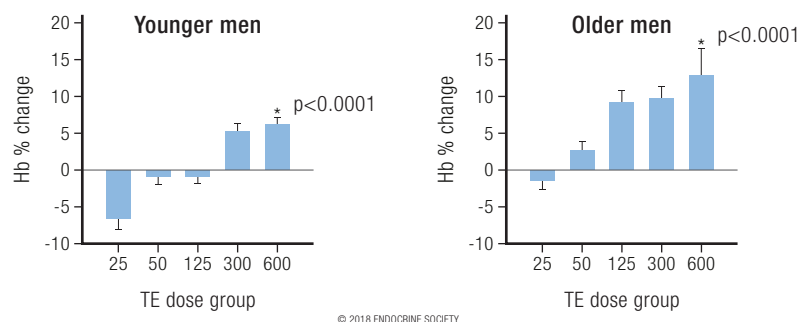


Figure 6. From Coviello *et al.* (131): Depicts the strong dose-response relationship between increasing testosterone dose with resulting change in blood hemoglobin in young and older men. Reproduced with permission from Coviello AD, Kaplan B, Lakshman KM, *et al.* Effects of graded doses of testosterone on erythropoiesis in healthy young and older men. *J Clin Endocrinol Metab* 2008;93:914–919.

The Impact of Adult Male Circulating Testosterone Concentrations on Sports Performance

Plausible estimates of the magnitude of the ergogenic advantage of adult male circulating testosterone concentrations are feasible from the limited available observational and interventional studies.

Population data on the ontogeny of puberty show that prior to puberty boys and girls have comparable athletic performance, whereas sex differences in athletic performance emerge coinciding with the rise in circulating testosterone from the onset of male puberty. Male puberty results in circulating testosterone concentrations rising from the prepubertal and female postpubertal range (<2 nmol/L) to adult male circulating testosterone concentrations (18). This is associated with a 10% to 12% better performance in running and swimming events and 20% enhancement in jumping events (8).

A minimal estimate of the impact of adult male testosterone concentrations on muscle size and strength in females is provided by the Huang *et al.* (112) study of postmenopausal women. In this study the highest testosterone dose (weekly injections of 25 mg of testosterone enanthate) increased mean circulating testosterone from 0.9 nmol/L to 7.3 nmol/L, which is equivalent to the circulating testosterone of boys in early to middle puberty. After 24 weeks of testosterone treatment, the increase in circulating testosterone concentrations led to significant increases in muscle size of 4.4% and in muscle strength of 12% to 26%. Given the limited testosterone dose (and concentration) as well as study duration, it is likely that these findings underestimate the magnitude of the impact that sex difference in circulating testosterone has on muscle mass and strength, and therefore on athletic performance.

Converse effects of reduced athletic performance in athletes who undergo suppression of circulating testosterone concentrations from those in the male into the female range have been reported. Among recreational (nonelite) athletes, an observational study showed a consistent deterioration in athletic performance of transwomen (M2F transgender) athletes corresponding closely to the suppression of circulating testosterone concentrations (175). Similarly, among elite athletes with circulating testosterone in the male range due to DSDs, comparable findings of athletic performance reduced by an average of 5.7% when circulating testosterone was suppressed from the male range to <10 nmol/L (176). Subsequently, when the IAAF hyperandrogenism rule was suspended in 2015, and so these elite athletes could train and compete with unsuppressed serum testosterone levels, their athletic performances increased by a similar amount. Additionally, circulating hemoglobin levels in these untreated DSD athletes were comparable with male athletes or with female athletes doping with erythropoietin (Fig. 7). However, when circulating testosterone was suppressed to <10 nmol/L the levels of circulating hemoglobin were 12% lower and again comparable with nondoped, non-DSD females, corresponding to the 12% magnitude of the sex difference in hemoglobin between men and women (125).

Congruent findings are also known for an elite female athlete whose serial athletic performance based on publicly available best annual times between 2008 and 2016 for the 800-m running event are depicted in relationship to the original 2011 IAAF hyperandrogenism regulation (Fig. 8).

Based on the established dose-response relationships, suppression of circulating testosterone to <10 nmol/L would not eliminate all ergogenic benefits of testosterone for athletes competing in female events. For example, according to the Huang *et al.* (112) study, reducing circulating testosterone to a mean of 7.3 nmol/L would still deliver a 4.4% increase in muscle size and a 12% to 26% increase in muscle strength compared with circulating testosterone at the normal female mean value of 0.9 nmol/L. Similarly, according to the Karunasena *et al.* (92) study, reducing circulating testosterone concentration to 7 nmol/L would still deliver 7.8% more circulating hemoglobin than the normal female mean value. Hence, the magnitude of the athletic performance advantage in DSD athletes, which depends on the magnitude of elevated circulating testosterone concentrations, is considerably greater than the 5% to 9% difference observed in reducing levels to <10 nmol/L.

The physiological mechanism underlying these observations is further strengthened by prospective controlled studies of initiation of cross-sex hormone treatment in transgender individuals (114, 177). These show that during the first 12 months muscle mass (area) was decreased by 9.4% and hemoglobin levels by 14% in 20 transwomen (M2F transgender) treated with an estrogen-based regimen that reduced circulating testosterone concentrations from the male range to the female range. Conversely, in 17 transmen (F2M transgender) treated for the first time with testosterone for 12 months (which increased circulating testosterone levels to a mean of 31 nmol/L), muscle mass increased by 19.2% and hemoglobin by 15% (114). The muscle mass findings remained stable between 1 and 3 years after initiation of treatment, although fat mass continued to change between 1 and 3 years of testosterone treatment (177). These studies did not report muscle strength, but other studies of testosterone dose-response relationships for muscle mass and strength show consistently positively correlation (65, 93, 117, 119), although with disproportionately greater effect on muscle strength than on muscle mass. Hence, the muscle mass estimates in these prospective treatment initiation studies in transgender individuals likely underestimate the muscle strength gains from elevated testosterone levels where the circulating testosterone markedly exceeds female range to be within the male range as occurs in severe hyperandrogenism of DSD females, poorly controlled transwomen (M2F transgender), or transmen (F2M transgender). These effects are also the biological

basis of the ergogenic efficacy of androgen doping in women.

Finally, to put these competitive advantages into context, the winning margin (the difference in performance by which a competitor misses a gold medal, any medal, or making the final) in elite athletic or swimming events during the last three Olympics is <1% equally for both male and female events (Table 5).

Gaps in Knowledge and Research Limitations

The major limitations on scientific knowledge of the impact of adult male circulating testosterone concentrations on the sex difference in athletic performance is the lack of well-designed studies. Ideally, these would need to replicate adult male circulating testosterone concentrations for sufficient time in women to investigate the effects on muscle, hemoglobin, bone, and other androgen-sensitive measures that display consistent sex dichotomy in the population. However, the ethical and safety concerns preventing such studies hitherto are likely to remain formidable obstacles due to the risk of unacceptable and potentially irreversible virilization as well as of promoting hormone-dependent cancers in women.

With the exception of one interventional study administering a relatively low testosterone dose (*i.e.*, low for males) to women (112), the available evidence comprises observational studies that can only examine the effects of serum testosterone within physiological female limits or sparse and mostly uncontrolled data from intersex/DSD athletes. Although the available observational findings in healthy females are informative, the key question is the magnitude and dose

response of effects at still higher circulating testosterone concentrations on the performances of women. Whereas a testosterone dose-response relationship has been established in women at relatively low (for men) testosterone dose and circulating concentrations, it remains unproven (even if clearly plausible) that the testosterone dose-response relationships established in men for muscle, hemoglobin, and bone can be extrapolated to women when they are exposed to higher circulating testosterone concentrations (*i.e.*, comparable with male levels). It is theoretically possible there could be differences between men and women in muscle responses to testosterone, as muscle cell populations might express genetic differences in androgen sensitivity (for which there are no data), or alternatively the long-term prior pattern of testosterone exposure from conception to adulthood might lead to differences in testosterone dose responsiveness after maturity. Although the dose-response relationship in women may be similar to what is seen in men, there is also anecdotal evidence that the dose-response curves may be left shifted so that testosterone has greater potency in women than in men at comparable doses and circulating levels. The prediction is supported by the anecdotal evidence from the surreptitious East German national doping program in which the supervising doctors asserted from their experience of illicit cheating that androgens had more potent ergogenic effects in women than in men (120), a speculative opinion shared by many experienced sports medicine physicians.

There is no known means of increasing endogenous testosterone in women to anything like the requisite degree to attempt to answer these questions. In healthy men, circulating testosterone originates almost exclusively from a single source (testicular Leydig cells) and is subject to tight hypothalamic negative feedback control, so that either direct stimulation (by human chorionic gonadotropin) or indirect reflex effects (*e.g.*, from estrogen blockers operating via negative feedback) to enhance Leydig cell testosterone secretion are feasible. However, similar mechanisms do not operate in women, in whom circulating testosterone originates from three different sources (adrenal, ovary, extraglandular conversion of androgen precursors), none of which is subject to tight testosterone negative feedback control. As a result, it is not feasible to produce a sufficient increase in circulating testosterone in women either by direct ovarian stimulation or indirect reflex effects to test this hypothesis even if doing so were deemed ethical and safe. Alternatively, carefully controlled, graded-dose studies in F2M transgender individuals might be informative but are largely lacking at this time.

Hence, the only feasible design of such studies would be testosterone (or another androgen) administration to healthy young women. The only well-designed, placebo-controlled study of testosterone in

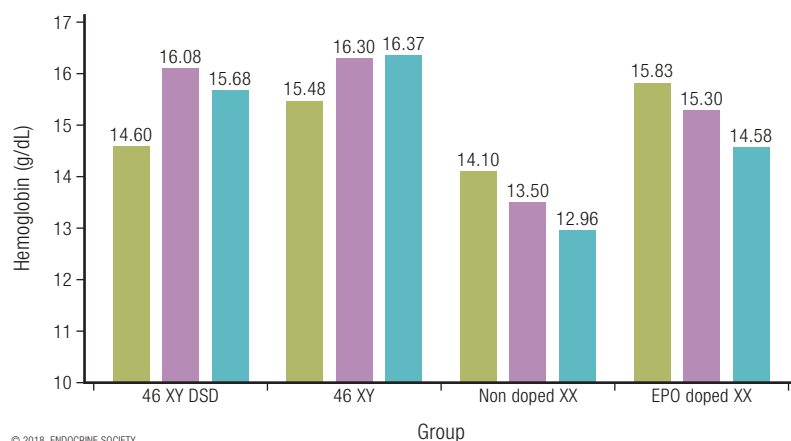


Figure 7. Mean hemoglobin concentrations (g/dL) of 12 elite athletes in 4 groups of 3 XY or XX middle-distance runners. The hemoglobin concentrations were collected as a part of the Athlete Biological Passport and analyzed according to the World Anti-Doping Agency standard methods. Each bar (athlete) is the mean of a minimum of three blood samples. In the 46,XY DSD group, blood was collected in a period when the athlete was not undergoing hormonal suppressive treatment.

otherwise healthy postmenopausal women was restricted to relatively low testosterone doses that, although clearly supraphysiological for women, were only 20% to 25% of male testosterone replacement doses (112). We are currently performing a double-blind, randomized, placebo-controlled study of the effects of moderately increased testosterone concentration on physical performance and behavior in young healthy women (ClinicalTrials.gov no. NCT03210558). However, obtaining ethical approval to administer supraphysiological testosterone doses that maintain circulating testosterone in the male range for sufficiently prolonged periods, as well as the practical difficulties in recruitment, are likely to remain obstacles to definitive resolution of this question.

In men, analogous ethical concerns over short- and long-term adverse effects delayed the definitive studies of supraphysiological testosterone doses to healthy young and older men but were eventually overcome. This was despite the fact that, uniquely among hormones, there is no known disease state in men due to pathologically excessive testosterone secretion. In contrast, in women, supraphysiological testosterone effects are known to produce virilization side effects that may be only slowly and partially, if at all, reversible. However, maintaining clearly supraphysiological testosterone concentrations would require treatment of months (muscle) or years (bone) and would replicate not only a known hyperandrogenic disease state (PCOS) but also potentially increasing risk of hormone-dependent cancers. In these circumstances, it could only be justifiable to replicate in women the salient testosterone dose-response studies available from men if the available evidence of dose-response relationship in men was not sufficiently convincing and/or there was reason to think that these dose-response characteristics would be substantially different in women. Overall, the unequivocal dose-response evidence in men together with the available overlap evidence in women appears sufficiently persuasive, so that it is doubtful that women would respond differently from men if their circulating testosterone levels were raised to the male range. More broadly, there is no more reason to require separate studies in women vs men than there is for every different ethnic subgroup of people. An aesthetic preference for splitting categories is not a sound reason to require the virtually impossible standard of establishing fresh and comprehensive empirical evidence in women of testosterone dose-response effects ranging into male circulating testosterone concentrations.

An analogy can be drawn to the World Anti-Doping Agency's practice of accepting salient surrogate evidence for banning the plethora of existing and new drugs with potential but individually unproven ergogenic effects where it is not feasible or ethical to require direct proof of the ergogenic effects. In that

context, the firmly established ergogenic efficacy of androgens (on muscle mass and strength) and increased hemoglobin (on endurance) [evidence reviewed in (1)] mean that chemical substances or methods that increase endogenous testosterone, erythropoietin, or hemoglobin are also considered ergogenic (178). By parity of reasoning, if a condition causes a female athlete's circulating testosterone levels to be in the male range, well exceeding normal female levels, with consequential increases in muscle, hemoglobin, and bone effects (at least), an ergogenic effect may reasonably be assumed.

Conclusions

The available, albeit incomplete, evidence makes it highly likely that the sex difference in circulating testosterone of adults explains most, if not all, the sex differences in sporting performance. This is based on the dose-response effects of circulating testosterone to increase muscle mass and strength, bone size and strength (density), and circulating hemoglobin, each of which alone increases athletic capacity, as well as other possible sex dichotomous, androgen-sensitive contributors such as mental effects (mood, motivation, aggression) and muscle myoglobin content. These facts explain the clear sex difference in athletic performance in most sports, on which basis it is commonly accepted that competition has to be divided into male and female categories.

The first IAAF hyperandrogenism regulation specified a hormonal eligibility criterion of a serum testosterone of <10 nmol/L for an androgen-sensitive athlete's participation in the protected category of female athletic events. This threshold was based on serum testosterone measurements by immunoassays.

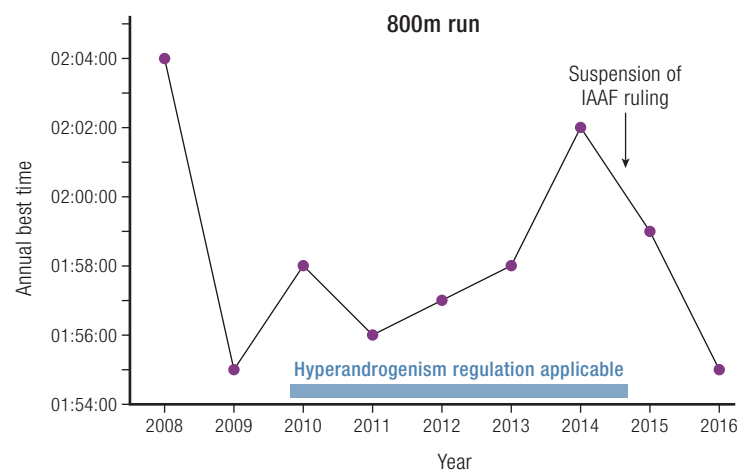


Figure 8. Best annual 800-m times of an elite female athlete between 2008 and 2016. Data provided by Dr. Richard Auchus, University of Michigan, Ann Arbor, Michigan.

REVIEW

Table 5. The Winning Margin in Elite Athletic or Swimming Events During the Last Three Olympics

Median Margin (%) ^a	n	Win Gold	Win Medal	Make Final
Athletics ^b				
Running	81	0.62	0.31	0.22
Jumping	24	0.92	0.42	0.92
Throwing	24	1.93	0.70	0.75
Swimming ^c				
Backstroke	12	0.56	0.28	0.16
Breaststroke	12	0.84	0.14	0.17
Butterfly	12	0.52	0.48	0.12
Freestyle	30	0.49	0.23	0.14
Relay	18	0.37	0.35	0.12

^aWinning margin is defined as the difference (expressed as a percentage of the faster time) between first and second place (Win Gold), between third and fourth place (Win Medal), and between the last into the final and the first that missed out (Make Final). Years (2008, 2012, 2016) and sexes were combined as there were no significant differences in winning margin between them.

^bRunning includes 100 m, 200 m, 400 m, 800 m, 1500 m, 5000 m, 10,000 m, marathon, and 3000-m steeplechase, 110-m (male)/100-m (female) and 400-m hurdles, 4 × 100-m and 4 × 400-m relays, and 20-km and 50-km walk events. Jumping includes high jump, long jump, triple jump, and pole vault events. Throwing includes javelin, shot put, discus, and hammer events. Heptathlon and decathlon were not included as their final results are in points, not times.

^cEvents comprise 100 m and 200 m for the four strokes and 50 m, 100 m, 200 m, 400 m, 800 m (female)/1500 m (male) and marathon 10 km, with the relays being the 4 × 100-m medley and 4 × 100-m and 4 × 200-m freestyle relays.

However, no reliable method-independent consensus threshold could be established using commercial testosterone immunoassays, as these assays differ systematically due to method-specific bias arising unavoidably from the specificity of the different proprietary antibodies employed (25). Based on measurements using the more accurate and specific mass spectrometry methods, if the objective is to require female athletes with congenital conditions that cause them to have serum testosterone concentrations in the normal male range to bring those levels down to the same range as other female athletes, then (allowing for PCOS athletes) the threshold used should not be >5.0 nmol/L. This represents a conservative criterion that includes all healthy young (<40 years) women, including those with PCOS. Conversely, this criterion is generous to intersex/DSD females in allowing them to maintain a higher serum testosterone (2 to 5 nmol/L) than most non-PCOS competitors in female events even though increases in muscle mass and strength and hemoglobin would be expected in this range. This is so even though the range remains below the circulating testosterone levels of middle male puberty when the major biological effects of men's higher circulating testosterone begin to be fully expressed. Ongoing compliance with the eligibility criterion is also an important variable because the estrogen-based suppression of circulating testosterone, typically using daily administered estrogen products, has a rapid onset and offset. Adequate monitoring to prevent gaming of eligibility criteria would require

regular random rather than announced blood sampling.

A related matter is how long such a threshold of circulating testosterone should be maintained prior to competition. In both intersex/DSD and transgender individuals, the developmental effects of adult male circulating testosterone concentrations will have established the sex difference in muscle, hemoglobin, and bone, some of which is fixed and irreversible (bone size) and some of which is maintained by the male circulating testosterone concentrations (muscle, hemoglobin). The limited available prospective evidence from initiation of transgender cross-sex hormone treatment suggests that the advantageous increases in muscle and hemoglobin due to male circulating testosterone concentrations are induced or reversed during the first 12 months and the androgenic effects may plateau after time. This time course is much faster than the somatic effects of male puberty, which evolve over years and for some variables (e.g., peak bone mass) are not complete for up to a decade after the start of puberty. However, the abrupt hormonal changes induced by medical treatment in intersex/DSD or transgender individuals may be telescoped compared with male puberty where circulating testosterone concentrations increase irregularly and incompletely for some years. Additional data are available from the unique investigative model of men undergoing castration for prostate cancer. Just as androgen sensitivity to testosterone may differ between tissues (65), the time course of offset of

androgen effects following withdrawal of male testosterone concentrations may also differ between the major androgen-responsive tissues. For example, circulating hemoglobin shows a progressive fall for 6 months reaching a nadir and plateau at 12 to 16 months in six studies involving 534 men undergoing medical castration for prostate cancer (179–184). Although these studies of older men with prostate cancer must be extrapolated with caution, age, stage of disease, race, and baseline circulating

testosterone concentration did not affect the rate or extent of decline in hemoglobin (179, 181). Comparable longitudinal studies of muscle loss, strength, and performance following castration for prostate cancer are well summarized (185), showing progressive loss for 24 months (see Fig. 4). Further clinical studies to define the time course of changes, mainly offset, in testosterone-dependent effects, notably on muscle and hemoglobin, are badly needed to determine the optimal duration for cross-sex hormone effects in sports.

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Disclosure Summary: DJH is a medical and scientific consultant for the IAAF and to the Australian Sports Anti-Doping Agency. He is a member of the World Anti-Doping Agency's Health, Medicine and Research Committee and of the IOC working group on hyperandrogenic female and transgender athletes. He has received institutional grant support from Besins Healthcare and Lawley for investigator-initiated clinical studies in testosterone pharmacology and has provided expert testimony in testosterone litigation. ALH is a medical and scientific consultant for the Swedish Olympic Committee and a member of the IAAF and IOC working groups on hyperandrogenic female athletes and transgender athletes. She has received grant support from the IAAF for a study on testosterone and physical performance in women. SB is a medical and scientific consultant for the IAAF and a member of the IAAF and IOC working groups on hyperandrogenic female athletes and transgender athletes. The authors have no other involvement with any entity having a financial interest in the material discussed in the manuscript. Opinions expressed in this review are the personal views of the authors and do not represent those of the IAAF, IOC, World Anti-Doping Agency, or Swedish Olympic Committee.

Abbreviations

AR, androgen receptor; CAH, congenital adrenal hyperplasia; CAIS, complete androgen insensitivity syndrome; DSD, disorder (or difference) of sex development; F2M, female-to-male; IAAF, International Association of Athletic Federations; IOC, International Olympic Committee; LC-MS, liquid chromatography–mass spectrometry; M2F, male-to-female; PAIS, partial androgen insensitivity syndrome; PCOS, polycystic ovary syndrome; SHOX, short stature homeobox.

Transgender women outpace cisgender women in athletic tests after 1 year on hormones

Pretreatment differences in athletic performance for transgender women in the U.S. Air Force vs. cisgender women continue more than 1 year after starting feminizing therapy, according to findings published in the *British Journal of Sports Medicine*.



Timothy Roberts

“Transgender women retain an advantage in upper body strength (push-ups and sit-ups) over female controls for 1 to 2 years after starting gender-affirming hormones,” **Timothy Roberts, MD, MPH**, in the division of adolescent medicine at Children's Mercy Kansas City, Missouri, told Healio. “Transgender women retain an advantage in endurance (1.5-mile run) over female controls for over 2 years after starting gender-affirming hormones. Athletic performance among transgender men matches or exceeds athletic performance for male controls after 1 year on testosterone.”

Athletic performance of transgender vs. cisgender women

	Before HT	2 years after HT
Push-ups in 1 minute	31% more	No advantage
Sit-ups in 1 minute	15% more	No advantage
1.5 mile run	21% faster	12% faster

Healio

A cohort of transgender women continued to outperform cisgender women in the 1.5-mile run 2 years after HT.

Roberts and colleagues conducted a retrospective review of medical records and fitness tests for transgender men and women who filed a request to begin gender transition or continue testosterone or estrogen while serving in the U.S. Air Force. Each individual's age, service branch, military rank, gender assigned at birth, date testosterone or estrogen started, type of testosterone or estrogen used, and days between starting testosterone or estrogen and the first serum hormone level in the adult range were obtained.

Researchers evaluated data from the Air Force's annual physical fitness assessment, which includes number of push-ups performed in 1 minute, number of sit-ups performed in 1 minute, and time required to run 1.5 miles. Pretreatment fitness was assessed using each participant's most recent score from each event before starting testosterone or estrogen. For posttreatment fitness, researchers compiled all fitness test scores occurring in the first 30 months after testosterone or

estrogen began for each individual. The time elapsed between starting treatment and the occurrence of each event was also recorded. Data from the study population were compared with the average performance among cisgender men and women younger than 30 years in the Air Force from 2004 to 2014.

Athletic advantage after 1 year

The study included 29 transgender men and 46 transgender women (mean age, 26.2 years). Pretreatment fitness scores were collected a mean 144.4 days before starting testosterone or estrogen, and the mean follow-up time was 394 days.

Compared with cisgender women, transgender women performed more push-ups (mean difference, 14.8 push-ups; 95% CI, 12.1-17.4) and more sit-ups (mean difference, 7.9 sit-ups; 95% CI, 5.7-10) prior to hormones. The transgender group continued to outperform the cisgender cohort until 2 years on treatment. For the 1.5-mile run, transgender women were faster than the cisgender women before treatment (mean difference, -147 seconds; 95% CI, -173 to -121). Times in the run worsened for transgender women after starting hormones, but the group remained faster than the cisgender cohort 2 years after treatment began (mean difference, -90 seconds; 95% CI, -169 to -10).

“Transwomen are currently mandated by World Athletics and the International Olympic Committee to have 1 year of testosterone suppression before being permitted to compete at the elite level,” Roberts said. “This may be too short if the aim is a level playing field.”

As [Healio previously reported](#), the international governing body for track and field sports released new eligibility regulations in 2018 that required women with certain forms of hyperandrogenism to lower their natural testosterone level for at least 6 months prior to competing in races ranging from 400 meters to 1 mile. The requirements state that any woman who is “androgen-sensitive” with a circulating testosterone level of at least 5 nmol/L must reduce her testosterone level to less than 5 nmol/L with the use of hormonal contraceptives, and maintain that testosterone level continuously for as long as she wishes to remain eligible to compete in restricted events, including the 400-meter, 800-meter, 1,500-meter and 1-mile races, hurdles races and combined events over the same distances.

Transgender vs. cisgender men

Transgender men performed fewer push-ups compared with cisgender men prior to testosterone (mean difference, -16.1 push-ups; 95% CI, -20.3 to -12), but the difference disappeared 1 year after the testosterone began. Transgender men and cisgender men performed similarly in sit-ups prior to testosterone, and transgender men exceeded cisgender men after 1 year of testosterone (mean difference, 5.7 sit-ups; 95% CI, 1.7-9.8). The transgender group was also slower than the cisgender cohort in the 1.5-mile run at baseline (mean difference, 131 seconds; 95% CI, 83-178), but the difference disappeared 1 year after starting testosterone.

Before starting testosterone, the transgender male group performed more push-ups and sit-ups than cisgender women, with the difference growing after testosterone began. There was no difference at baseline between transgender men and cisgender women in the 1.5-mile run, but the transgender men were faster than cisgender women 1 year after testosterone started.

“Transgender male athletes develop a competitive advantage over female athletes after starting testosterone,” Roberts said. “Transgender males should be allowed to compete in men’s athletics after starting testosterone to ensure a level playing field for female athletes.”

Roberts said the findings reveal that inadequate evidence supports the World Athletics and International Olympic Committee’s current guidelines for transgender athletes.

“We need longer-term studies of the effect of testosterone suppression on athletic performance overall and in sport-specific activities (explosive strength, endurance and cardiovascular fitness) to inform guidelines for transgender inclusion in sport,” Roberts said.

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[Gender care for minors requires teamwork, centers on family](#)

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For more information:

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PERSPECTIVE



David J. Handelsman, MBBS, PhD

This study adds to growing evidence beyond the proven male physical advantage of 10% to 15% in sports requiring power or endurance and up to 50% where explosive power or complex movement skills are pivotal (Handelsman DJ, et al. *Endocr Rev.* 2018;doi:10.1210/er.2018-00020). These sex-based benefits in muscle, bone, cardiorespiratory function and blood hemoglobin originate with male puberty, which increases testosterone production 20-fold in men compared with children and women. Barring disease or suppressive drugs, adult male circulating testosterone concentrations maintain a cumulative androgenic advantage. These testosterone-mediated physiologic advantages form the basis for exclusion of male-bodied athletes from most female events other than before puberty or in sports not requiring intense physical demands, such as chess where open competition is logical, inclusive and fair.

A major question remains whether gender-affirming hormone treatment overcomes sex-based physical advantages sufficiently to maintain fairness so that an exception can be made for transwomen (natal males) treated with estrogens. The Roberts study based on prospective analysis of the U.S. military's compulsory annual physical performance database shows convincingly that transmen (natal females) caught up with average male performance within 12 months of standard testosterone treatment as adults. By contrast, transwomen treated with estrogens after completing male puberty experienced only minimal declines in physical performance over 12 months, substantially surpassing average female performance for up to 8 years. Sporting federations should incorporate these findings into strategies for including transwomen in elite female competitions while maintaining fairness and safety for other women.

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For care with nonbinary children, there are no guidelines, there is very little experience, and all the knowledge we have is anecdotal. There is also not enough research.

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OPEN ACCESS

How does hormone transition in transgender women change body composition, muscle strength and haemoglobin? Systematic review with a focus on the implications for sport participation

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ABSTRACT

Objectives We systemically reviewed the literature to assess how long-term testosterone suppressing gender-affirming hormone therapy influenced lean body mass (LBM), muscular area, muscular strength and haemoglobin (Hgb)/haematocrit (HCT).

Design Systematic review.

Data sources Four databases (BioMed Central, PubMed, Scopus and Web of Science) were searched in April 2020 for papers from 1999 to 2020.

Eligibility criteria for selecting studies Eligible studies were those that measured at least one of the variables of interest, included transwomen and were written in English.

Results Twenty-four studies were identified and reviewed. Transwomen experienced significant decreases in all parameters measured, with different time courses noted. After 4 months of hormone therapy, transwomen have Hgb/HCT levels equivalent to those of cisgender women. After 12 months of hormone therapy, significant decreases in measures of strength, LBM and muscle area are observed. The effects of longer duration therapy (36 months) in eliciting further decrements in these measures are unclear due to paucity of data. Notwithstanding, values for strength, LBM and muscle area in transwomen remain above those of cisgender women, even after 36 months of hormone therapy.

Conclusion In transwomen, hormone therapy rapidly reduces Hgb to levels seen in cisgender women. In contrast, hormone therapy decreases strength, LBM and muscle area, yet values remain above that observed in cisgender women, even after 36 months. These findings suggest that strength may be well preserved in transwomen during the first 3 years of hormone therapy.

competed in the Olympics to date, the increasing visibility of gender-diverse people in society¹⁰ means that the sports administrators and legislators must create rules to accommodate athletes from outside the sex/gender binary.¹¹

There are many quantifiable performance-related differences between male and female athletes. In contrast, the performance-related differences between transwomen who have received gender affirming hormone treatment (GAHT) and cisgender women are less clear. GAHT for transwomen consists of an antiandrogen agent plus the introduction of exogenous oestrogen,¹² with the goal of altering the hormonal milieu and, as a result, feminisation of the body.¹³ To date, there have been no prospective studies investigating the changes in athletic performance in transgender athletes after hormonal transition. In non-athletic transgender populations, studies are commonly focused on clinical outcomes, such as bone health.¹⁴ However, studies in non-athletic transwomen undergoing GAHT also report changes in lean body mass (LBM),¹⁵ muscle cross-sectional area (CSA),¹⁶ muscular strength¹⁷ and haemoglobin (Hgb)¹⁸ and/or haematocrit (HCT).¹⁹ These parameters are of relevance to athletic performance.

In endurance sports, Hgb is of importance. Hgb is a protein carried by the red blood cells that is responsible for transporting oxygen from the lungs to peripheral tissues.²⁰ Low Hgb, or low HCT, the volume of red blood cells compared with total blood volume, can lead to a diminished supply of oxygen to the tissues, and therefore have a direct effect on endurance performance. Typical values for Hgb differ between males and females, with 'normal' values ranging between 131–179 g/L for men and 117–155 g/L for women.²¹ HCT values are also higher in males (42%–52%) than females (37%–47%).²² Testosterone exerts erythropoietic effects that results in increases in both HCT and Hgb.²³ Since GAHT significantly lowers testosterone levels in transgender women,²⁴ it is possible that they may experience reductions in HCT and Hgb, which would be anticipated to negatively affect endurance performance.

In sports demanding speed and power, muscular strength and the ability to generate high rates of force are recognised as key determinant in athletic success.²⁵ In cisgender males, increases in testosterone due to puberty promote muscular strength

INTRODUCTION

Currently the world of sport, from grassroots level to elite, is facing the challenge of how to include transgender people in sporting competitions. Regulations governing the participation of athletes from outside the sex/gender binary have existed since the 1940s.^{1–4} Presently, World Athletics requires that transgender athletes⁵ and athletes with differences of sexual development⁶ have testosterone levels ≤ 5 nmol/L in order to be eligible for the female category. There has been heavy criticism of this, and previous, testosterone-based regulations.^{7–9} Although no openly transgender athlete has



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in association with increased muscle CSA, and increased lean muscle mass.²⁶ It has been hypothesised that muscle retains a long-term memory allowing it to perform tasks that it has undertaken many times previously and myonuclei retention is thought to play an important role in such muscle memory.²⁷ Myonuclei number is increased with training and with use of anabolic steroids.²⁸ However, detraining does not diminish the myonuclei number,²⁷ and it has been hypothesised that cessation of steroids may also not lead to reductions in myonuclei number.²⁸ Hence, it is possible that strength advantages gained when training in a high-testosterone environment may not be fully reversed by testosterone suppression.

Understanding both the physiological effects of GAHT on athletic performance, and the time course of these effects, is of importance to decision-makers and those undertaking policy reviews. While it is known that testosterone levels are markedly reduced in transgender women taking testosterone suppressing GAHT,²⁹ the effects of this hormonal change on physiology, and the time course in which these changes occur, are less clear. Individual studies provide crucial, primary research on the topic, but a systematic review is warranted to provide a robust summary of the available evidence. Because bone mineral density studies have already been subject to systematic review,^{30,31} this review focuses on physiological changes induced by GAHT in transwomen that affect athletic performance; specifically, LBM, CSA, strength and Hgb/HCT.

Aim

The aim of this systematic review was to: (1) summarise the current state of knowledge as it relates to the changes, and the time course of these changes, in physiological parameters associated with athletic performance in non-athletic transwomen resulting from GAHT (suppression of testosterone and supplementation with oestrogen), and (2) consider the potential implications for the participation of transwomen in elite sport.

MATERIALS AND METHODS

Search strategy and selection criteria

This systematic review was conducted in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.³² Two electronic searches of four online databases (BioMed Central, PubMed, Scopus and Web of Science) were completed 15 months apart. The first was performed by BSK in January 2019 and the second by JH in April 2020. The two sets of search results were compared by GLW. The second search identified novel data from three additional studies using the same cohorts as three studies identified in the first search. The more recent search also identified three additional recent papers. Reference lists were also searched for additional citations pertinent to the review. The searches combined terms related to transwomen, GAHT, muscle and blood parameters (online supplemental table 1).

Study selection, quality assessment, and data extraction

Each study was initially categorised based on its design (eg, cohort, case-control) and examined for quality in line with the Effective Public Health Practise Project (EPHPP) tool.³³ This is a generic tool used to evaluate a variety of intervention study designs and is suitable for use in systematic reviews,³⁴ having content and construct validity.³⁵ Based on the EPHPP, six domains are evaluated: (1) selection bias; (2) study design; (3) confounders; (4) blinding; (5) data collection method; and (6) withdrawals/dropouts. Each domain is rated as strong (3 points),

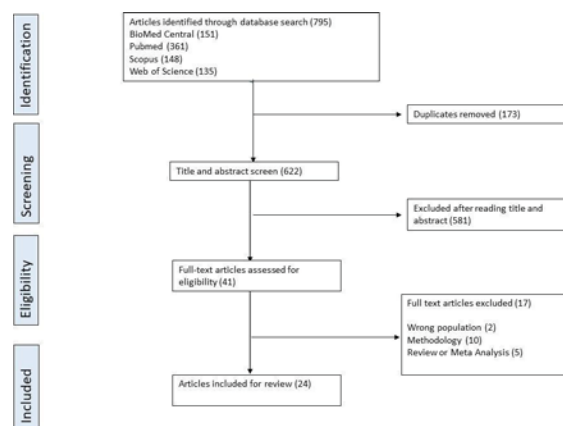


Figure 1 PRISMA flow chart illustrating search strategy. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

moderate (2 points) or weak (1 point), and domain scores are averaged to provide the overall mean rating. Based on the overall mean rating, studies are rated as weak (1.00–1.50), moderate (1.51–2.50) or strong (2.51–3.00).

For longitudinal studies, data were extracted to examine changes in LBM, CSA, strength and Hgb/HCT in transwomen taking GAHT. In cross-sectional studies, data in transwomen were compared with data from both cisgender men and cisgender women. The study authors were contacted if there were any questions regarding the presented data. In this regard, authors of the nine studies carried out by the European Network for the Investigation of Gender Incongruence (ENIGI) were contacted regarding potential overlapping participants^{15,17,19,36–41} and another author was contacted to clarify graphical data content.¹⁶

RESULTS

Search results

Figure 1 shows the search strategy following PRISMA guidelines. From an initial yield of 795 articles, 24 studies^{15–19,36–54} were included in this review. The following information was extracted from each study: name of the first author, country, year of publication, number of transfemale participants, number of cisgender male and female participants (where applicable), duration of any follow-up, type of medical treatment, method of measurement, evaluation time, and results.

Quality assessment

Based on the mean EPHPP scores, all studies were categorised as moderate in quality. The individual scores are listed in the online supplemental table 2.

Study characteristics

A summary of the study characteristics is reported in table 1. The sample sizes of the studies varied from 12 to 249. Three large studies from the ENIGI group published in 2018 and 2019^{15,17,19} contained much novel data, but also included many participants from previous studies making it impossible to accurately state the number of unique participants.

Study designs

Thirteen studies^{15,17,19,36–40,42,43,46–48} utilised a follow-up study design comparing participants' measurements before initiating hormone transition (baseline) to several months after hormone transition. Two studies^{41,51} used both follow-up and cross-sectional designs with cisgender controls. Six studies^{18,45,50,52–54}

Continued

Table 1 Characteristics of reviewed studies														
Author (year)	Study type	Country	Study quality rating	Participants (N)			Age (years)	Timing (months post GAHT)	T (nmol/L)			Measures		
				TW	CM	CW			HNTW	Mean±SD med (min–max)	Baseline post GAHT		LBM	CSA
Elbers <i>et al</i> (1999) ⁴²	Follow-up	Netherlands	Mod	20	–	–	–	Baseline 12	26±6	22	N	Y	N	N
Gooren and Bunck (2004) ⁴³	Follow-up	Netherlands	Mod	19	–	–	–	Baseline 12 36	NR	21.5	N	Y	N	Y
Mueller <i>et al</i> (2011) ⁴⁴	Prospective	Germany	Mod	84	–	–	–	Baseline 12 24	36.3±11.3	13.6	Y	N	N	N
Wierckx <i>et al</i> (2014) ⁴⁵	Follow-up	Norway and Belgium	Mod	53	–	–	–	Baseline 12	31.7±14.8 19.3±2.4	18.4	Y	N	N	Y
Gava <i>et al</i> (2016) ³⁸	Follow-up	Italy	Mod	40	–	–	–	Baseline 12	32.9±9.4 29.4±10.2	19.2	Y	N	N	N
Auer <i>et al</i> (2016) ⁴⁶	Follow-up	Belgium	Mod	20	–	–	–	Baseline 12	NR	20.5	N	N	Y	Y
Auer <i>et al</i> (2018) ⁴⁰	Follow-up	Belgium	Mod	45	–	–	–	Baseline 12	34.8±1.4	17.5	Y	N	N	N
Jarin <i>et al</i> (2017) ³⁹	Follow-up	USA	Mod	13	–	–	–	Baseline 6	18 (14–25)	13.6	N	N	N	Y
Defreyne <i>et al</i> (2018) ³⁹	Follow-up	Netherlands and Belgium	Mod	239	–	–	–	Baseline 3 6 24	28.5 (16–65)	17.4	N	N	N	Y
Vita <i>et al</i> (2018) ⁴⁸	Follow-up	Italy	Mod	21	–	–	–	Baseline 30	25.2±7.0	20.5	N	N	N	Y
Klaver <i>et al</i> (2018) ¹⁵	Follow-up	Netherlands and Belgium	Mod	179	–	–	–	Baseline 12	29.0 (18–66)	Y	Y	N	N	N
Olson-Kennedy <i>et al</i> (2018) ⁴⁹	Prospective	USA	Mod	23	–	–	–	Baseline 24	18 (12–23)	14.8	N	N	N	Y
Tack <i>et al</i> (2018) ³⁶	Follow-up	Belgium	Mod	21	–	–	–	Baseline 5–31	16.3±1.2	15.2	Y	Y	Y	N
Tack <i>et al</i> (2017) ⁴⁷	Follow-up	Belgium	Mod	21	–	–	–	Baseline 12–31	16.3±1.2	15.8	N	N	N	Y
Scharff <i>et al</i> (2019) ¹⁷	Follow-up	Netherlands and Belgium	Mod	249	–	–	–	Baseline 12	28 (23–40)	18.3	N	N	Y	N
Wiik (2020) ¹⁶	Prospective	Sweden	Mod	11	–	–	–	Baseline 4 12	27±4	18.0	N	Y	Y	Y
Van Caenegem <i>et al</i> (2014) ⁴⁵	Follow-up and cross-sectional	Belgium	Mod	49	49	–	–	Baseline 12	33±12 30 (17–67)	19.0	Y	Y	Y	N
Haraldsen <i>et al</i> (2007) ⁵¹	Follow-up and cross-sectional	Norway	Mod	12	77	–	–	Baseline 12	29.3±7.8 33.9±9.3	16.8	Y	Y	N	N

Table 1 Continued

Author (year)	Study type	Country	Study quality rating	Participants (N)			Age (years)	Timing (months post GAHT)	Measures			
				TW	CM	CW	HNTW		Mean±SD med (min-max)	LBM	CSA	MS
SoRelle <i>et al</i> (2019) ⁵²	Cross-sectional	USA	Mod	133	–	–	87	TW>6m vs HNTW	33±12 31±12	N	N	N
Greene <i>et al</i> (2019) ¹⁸	Cross-sectional	USA	Mod	93	–	–	–	TW>12m vs CW ranges	35.1 (18–69)	N	N	N
Roberts <i>et al</i> (2014) ⁵³	Cross-sectional	USA	Mod	55	20	20	–	TW>6m vs CM TW>6m vs CW	46 (27–67) 58 (21–84) 56 (23–88)	N	N	N
Lapauw <i>et al</i> (2008) ⁵⁴	Cross-sectional	Belgium	Mod	23	20	–	–	TW>48m vs CM	41±7 40±7	Y	Y	Y
Jain <i>et al</i> (2019) ⁵⁰	Cross-sectional	USA	Mod	277	–	–	102	TW vs HNTW	31±7.1 31±7.1	N	N	N
Sharula (2012) ³⁷	Cross-sectional	Japan	Mod	129	–	–	22	TW vs HNTW	33.9±10.0 31.5±9.9	N	N	N

CM, cismen; CSA, cross-sectional area; CW, ciswomen; HCT, haematocrit; Hgb, haemoglobin; HNTW, hormone-naïve transwomen; LBM, lean body mass; TW, transwomen.

used an exclusively cross-sectional design; three comparing transwomen on GAHT with cisgender controls^{18 53 54} and three comparing transwomen on GAHT with hormone-naïve transwomen.^{45 50 52} Three studies^{16 44 49} used a prospective method gathering data over 12–24 months. Aside from these three studies, data were extracted from medical charts (nine of which were from the same research group,^{15 17 19 36–41}) posing a risk of selective data reporting and publication bias.

Medical treatments

Medical treatments for endocrine transition were varied, in line with the individualised approach advised by the WPATH Standards of Care.⁵⁵ Fourteen studies^{15 17 19 36–43 46 48 54} used cyproterone acetate (50–100mg daily) as an antiandrogen. In six studies^{16 38 40 44 46 49} a form of gonadotropin-releasing hormone agonist was administered either to suppress puberty or androgens. In four studies^{18 49 50 52} spironolactone was used as an antiandrogen. Seventeen studies^{15 17–19 36–39 41 44 45 47–50 52 53} used 2–4 mg/day of oral oestradiol valerate. Eleven studies^{15–17 19 39 42 43 45 46 48 49} used transdermal 17-beta-oestradiol releasing 100 mcg/day. Four studies^{16 18 47 49} used an injection of oestradiol valerate (10mg/ampoule, every 1–4 months). Two studies^{45 54} used 0.625–2.5 mg/day of conjugated equine oestrogen. Four studies,^{42 43 51 54} all undertaken prior to 2010, used 25–50 mcg/day of ethinyl oestradiol. Ethinyl oestradiol was not used in any study after 2010, primarily due to increased risk of thrombogenesis.⁵⁶

Based on the variability in drug regimens used, there is substantial heterogeneity in the hormone levels achieved. Although the transwomen in most of the studies achieved testosterone levels within the reference range for cisgender women, there were five studies^{38 40 47 49 51} in which the transfemales had post-GAHT testosterone values greater than 5 nmol/L. Four of the five studies^{38 40 47 49} were carried out on adolescent transfemales; two of the five studies^{38 51} did not involve the use of an antiandrogen agent; one study⁴⁰ did not involve the use of any form of oestrogen. The high post-GAHT testosterone is a possible confounder, and potential physiological differences between adolescent and adult participants may also confound results.

Muscle mass and body fat changes

Table 2 summarises the studies reporting muscle mass and body fat. Eight studies^{15 36 39–41 44 46 51} used a follow-up design to assess changes in LBM; seven studies assessed after 12 months,^{15 36 39 41 44 46 51} and one⁴⁰ study reviewed patients who had been under treatment for 5–31 months. Seven of these studies,^{15 36 39–41 44 51} including the large (n=179) ENIGI study,¹⁵ and two studies^{40 51} with high post-GAHT testosterone (~8 nmol/L), showed that total LBM was decreased by 3.0%–5.4% following hormone transition (p<0.05). The one study that failed to demonstrate significant changes in LBM⁴⁶ was not an outlier in any obvious way. The large ENIGI study¹⁵ was the only study in which the limits of agreement would indicate a change in LBM at the 95% CI. All studies reported an increase in total body fat mass in transwomen after hormone transition. Three cross-sectional studies^{41 51 54} compared transwomen with cisgender men. Two studies included hormone-naïve transwomen.^{41 51} These studies reported 6.4% and 8.0% lower LBM than in cisgender men and reductions of 4% in LBM in the transwomen with 12 months of GAHT. The third cross-sectional study compared transwomen who had undergone at least 48 months of GAHT with cisgender men⁵⁴ and reported 17% lower LBM in transwomen than in cisgender men.

Table 2 Changes in total LBM in kilograms

Longitudinal studies								
Author (year)	Participants (N)		Baseline mean±SD (95% CI)	12 Months mean±SD (95% CI)	12–31 months mean±SD	% Change	P	T (nmol/L) Base-post GAHT
	TW							
Mueller <i>et al</i> (2011) ¹¹	84		59.6 (54.6–64.6)	57.2 (54.0–64.1)		−4.0	<0.005	13.6–0.6
Wierckx <i>et al</i> (2014) ⁴⁵	40 (oral oestrogen)		56.0±7.5	53±8		−5.4	<0.001	18.0–0.4
	12 (transdermal oestrogen)		62.6±9.3	59.7±8.1		−4.6	<0.05	19.7–0.5
Gava <i>et al</i> (2016) ³⁸	20 (cyproterone acetate)		51.7±8.3	49.9±7.8		−3.5	>0.05	16.3–0.7
	20 (leuprolide acetate)		50.2±7.0	49.8±6.7		−0.8	>0.05	22.2–0.7
Auer <i>et al</i> (2018) ⁴⁰	45		59.5±8.7 (56.9–62.0)	57.5±12 (53.9–60.2)		−3.4	<0.001	17.5–1.9
Klaver <i>et al</i> (2018) ¹⁵	179		57.2±8.3	55.5 (54.9–56.1)		−3.0	<0.001	
Tack <i>et al</i> (2018) ³⁶	21		47.0±6.4		44.8±6.3	−4.7	<0.01	15.2–8.8
Haraldsen <i>et al</i> (2007) ⁵¹	12		54.4±6.2	52.2		−4.0	<0.001	16.8–8.6
Van Caenegem <i>et al</i> (2015) ⁴¹	49		57.4±8.7	55.1±8.7		−4.0	<0.001	19.0–0.5
Cross-sectional studies								
Author (year)	Participants (N)		TW baseline mean±SD	TW 48 months mean±SD	CM mean±SD	% Difference	P	T (nmol/L) TW
	TW	CM						
Lapauw <i>et al</i> (2008) ⁵⁴	23	46		51.2±8.4	61.8±7.9	−17.2	<0.001	1.1
Haraldsen <i>et al</i> (2007) ⁵¹	12	77	54.4±6.2		59.1±5.7	−8.0	<0.05	16.8
Van Caenegem <i>et al</i> (2015) ⁴¹	49	49	57.4±8.7		61.3±6.8	−6.4	<0.05	19.0

Data are from dual energy X-ray absorptiometry scans.
CM, cismen; LBM, lean body mass; TW, transwomen.

CSA changes

Four follow-up studies^{16 40–42} investigated the CSA either in the quadriceps, forearm or calf regions using MRI^{16 42} or peripheral quantitative computed tomography (pQCT).^{40 41} Of note, two of the studies measured the total CSA of the individual MRI⁴² or pQCT⁴¹ image while two studies measured the isolated muscle.^{16 40} A decrease in CSA of 1.5%–11.7% was reported over periods ranging from 12 to 36 months. One of these studies⁴⁰ examined adolescent participants who only reached a final testosterone level of 8.8 nmol/L and exhibited forearm and calf CSA decreases of 4.1% and 8.9%, respectively. There were two studies^{41 42} that assessed muscle CSA at both 12 months and at either 24 or 36 months. The first study⁴² reported a 9.5% decrease in quadriceps CSA compared with baseline after 12 months and an 11.7% decrease in quadriceps CSA compared with baseline after 36 months. The second study⁴¹ reported a 1.5% decrease in tibia CSA compared with baseline after 12 months and a 3.8% decrease compared with baseline after 24 months. The same study reported that compared with baseline, forearm CSA was decreased by 8.6% after 12 months, yet at 24 months was 4.4% lower than baseline, indicating that forearm CSA was 4.2% larger at 24 months than at 12 months. There was only one study⁴² in which the limits of agreement indicated a change at the 95% CI. Two cross-sectional studies^{41 54} compared transwomen with cisgender men. One study reported 9% smaller CSA in hormone-naïve transwomen⁴¹ than in cisgender men, with the transwomen undergoing a further 4% decrease in CSA with 24 months of GAHT. The transwomen in the second study had all undergone at least 48 months of GAHT⁵⁴ and had 24% smaller CSA than cisgender men. See table 3.

Muscular strength changes

Table 4 summarises the studies reporting muscular strength. Five longitudinal studies^{16 17 37 40 41} investigated the muscular strength of transwomen. Four of the studies^{17 37 40 41} measured hand grip

strength in participants on the ENIGI study. The largest of the three (n=249) ENIGI studies¹⁷ and one other study⁴¹ found significant (p<0.001) reductions (4.3% and 7.1%, respectively) after 12 months on GAHT. Two ENIGI studies^{37 40} found no significant strength differences, although one of these studies⁴⁰ was carried out on adolescents who failed to reach typical female testosterone levels (8.8 nmol/L after GAHT). The large ENIGI study¹⁷ was the only study in which the limits of agreement would indicate a change in strength at the 95% CI. The fifth longitudinal study to assess strength measured upper leg strength using knee flexion and extension and found no significant difference after 12 months.¹⁶ Two studies^{41 54} used a cross-sectional design to compare the strength of transwomen to cisgender men. One study found 14% lower hand grip strength in hormone-naïve transwomen than in cisgender men (p<0.001)⁴¹ and a further 7% reduction in hand grip strength of the transwomen after 12 months of GAHT. The other study⁵⁴ found 24% lower hand grip and quadriceps strength in transwomen than in cisgender men after 48 months or more on GAHT (p<0.001).

Hgb and HCT changes

Nine studies^{16 19 36–38 43 47–49} reported the levels of Hgb or HCT in transwomen before and after GAHT, from a minimum of three to a maximum of 36 months post hormone therapy. Eight of these studies,^{16 19 36–38 43 48 49} including the large (n=239) ENIGI study,¹⁹ found that hormone therapy led to a significant (4.6%–14.0%) decrease in Hgb/HCT (p<0.01), while one study found no significant difference after 6 months.⁴⁷ The mean age of participants in the latter study was 18 years and the range was 14–25 years. The participants also failed to reach typical female testosterone levels (after 6 months mean testosterone=6.9 nmol/L), while in six^{16 19 36 37 43 48} of the eight other studies mean testosterone after GAHT was less than 2.0 nmol/L. The large ENIGI study¹⁹ was the only study in which the limits of agreement would indicate a change in Hgb/HCT at the 95%

Table 3 Changes in muscle CSA

Longitudinal studies

Author (year)	Participants (N) TW	CSA region (units)	Baseline CSA mean±SD (95% CI)	Follow-up CSA mean±SD (95% CI)	Number of months of GAHT	% Change	P	T (nmol/L) Base-post GAHT
Elbers <i>et al</i> (1999) ⁴²	20	Thigh (cm ²)	307±47	278±37 (269–287) 271±39	12 36	–9.5 –11.7	<0.001 <0.001	22.0–1.0 22.0–0.9
Wiik (2020) ¹⁶	11	Quadriceps (mm ²)	6193±679	5931±671 (5680–6190)	12	–4.2	<0.05	18.0–0.5
Tack <i>et al</i> (2018) ³⁶	21	Forearm (mm ²) Calf (mm ²)	3275±541 4204±1282	3142±574 3828±478	12–31 12–31	–4.1 –8.9	<0.05 >0.05	15.2–8.8
Van Caenegem <i>et al</i> (2015) ⁴¹	49	Forearm (mm ²) Tibia (mm ²)	3999±746 7742±1361	3664±783 3825±867 7623±1479 7448±1390	12 24 12 24	–8.6 –4.4 –1.5 –3.8	<0.001 <0.001 <0.01 <0.01	19.0–0.5 19.0–0.5

Cross-sectional studies

Author (year)	Participants (N)		CSA region (units)	TW mean±SD	CM mean±SD	Number of months of GAHT	% Difference	P	T (nmol/L) TW
Lapauw <i>et al</i> (2008) ⁵⁴	23	46	Forearm (mm ²) Tibia (mm ²)	3500±700 6600±1300	4600±700 8700±1100	48 48	–23.9 –24.1	<0.001 <0.001	1.1
Van Caenegem <i>et al</i> (2015) ⁴¹	49	49	Forearm (mm ²) Tibia (mm ²)	3999±746 7742±1361	4512±579 8233±1498	Baseline Baseline	–11.4 –6.0	<0.001 <0.01	19.0

Data are from MRI or pQCT.

CM, cismen; CSA, cross-sectional area; TW, transwomen.

CI. Three cross-sectional studies^{18 53 54} compared HCT in transwomen post GAHT with cisgender controls (table 5). Two studies found that transwomen on GAHT for 6 or 48 months had lower (10%) HCT than cisgender men^{53 54} ($p<0.005$), while two studies found no difference between transwomen after 6 and 12 months of GAHT and cisgender women.^{18 53} Three cross-sectional studies^{45 50 52} found significant differences^{45 50} ($p<0.05$) or large effect sizes⁵² (Cohen's $d=1.0$) in HCT between transwomen after 6 months of GAHT and hormone-naïve transwomen, and HCT decreases of 7.4%–10.9%. See table 5.

DISCUSSION

We summarise changes induced by GAHT in non-athletic transwomen in four characteristics strongly associated with athletic performance: LBM, muscle CSA, muscular strength, and Hgb/ HCT levels. Overall, the findings demonstrate a reduction in these parameters over time. However, the time course of these reductions was not consistent across the parameters assessed.

In keeping with the muscular anabolic effects of testosterone⁵⁷ and the mixed effects of oestrogens,⁵⁸ studies using dual energy X-ray absorptiometry report decreased LBM (0.8%–5.4%) in association

Table 4 Changes in strength measures

Longitudinal studies

Author (year)	Participants (N) TW	Strength measure (units)	Baseline mean±SD (95% CI)	12 months mean±SD (95% CI)	21–31 months Mean±SD	% Change	P	T (nmol/L) Base-post GAHT
Van Caenegem <i>et al</i> (2015) ⁴¹	49	Hand grip (kg)	42±9	39±9		–7.1	<0.001	19.0–0.5
Auer <i>et al</i> (2016) ⁴⁶	20	Hand grip (kg)	41.7±7.8	41.9±7		0.5	>0.05	17.5–1.9
Tack <i>et al</i> (2018) ³⁶	21	Hand grip (kg)	33.8±8.1		34.3±5.6	1.5	>0.05	15.2–8.8
Scharff (2019)	249	Hand grip (kg)	41.8±8.9	40.0±8.9 (39.2–40.8)		–4.3	<0.001	18.3–0.8
Wiik (2020) ¹⁶	11	Knee extension (N-m) Knee flexion (N-m)	239.7±44.0 99.5±16.8	242.6±41.5 (230–252) 101.5±15.5 (92–109)		1.2 2.0	>0.05 >0.05	18.0–0.5

Cross-sectional studies

Author (year)	Participants (N)		Strength measure (units)	TW baseline mean±SD	TW 48 months mean±SD	CM mean±SD	% Difference	P	T (nmol/L) TW
Van Caenegem <i>et al</i> (2015) ⁴¹	49	49	Hand grip (kg)	42±9		49±6	–14.3	<0.001	19.0
Lapauw <i>et al</i> (2008) ⁵⁴	23	46	Hand grip (kg) Knee extension (N-m)		41±8 150±49	53±8 200±44	–22.6 –25	<0.001 <0.001	1.1

CM, cismen; TW, transwomen.

Table 5 Changes in HCT and Hgb levels

Longitudinal studies											
Author (year)	Participants (N)				Measure (units)	Baseline mean±SD (95% CI)	Follow-up mean±SD (95% CI)	Number of months	% Change	P	T (nmol/L) Base-post GAHT
	TW										
Wierckx (2014)	40 (oral oestrogen)				HCT (%)	45±2.5	42±5.7	12	−7.0	<0.01	18.0–0.4
	12 (transdermal oestrogen)					45.5±1.7	42.2±2.3	12	−4.6	<0.001	19.7–0.5
Auer <i>et al</i> (2016) ⁴⁶	20				HCT (%)	45.2±2.7	42.7±1.8	12	−5.5	<0.01	17.5–1.9
Jarin <i>et al</i> (2017) ³⁹	13				HCT (%)	43.8	42.3	6	−3.4	>0.05	13.6–6.9
Vita <i>et al</i> (2018) ⁴⁸	21				HCT (%)	44.8±2.9	40.1±2.6	6–30	−10.5	<0.001	20.5–1.1
Defreyne <i>et al</i> (2018) ¹⁹	239				HCT (%)	45.0±2.5 (44.9–45.5)	41.0±3.1 (40.9– 41.7) 41.1±3.2 (40.5– 41.2) 40.7±3.2 (40.0– 40.8)	3 6 24	−8.9 −8.7 −9.6	<0.001 <0.001 <0.001	17.4–0.7 17.4–0.6 17.4–0.6
Tack <i>et al</i> (2017) ⁴⁷	21				HCT (%)	43.8±1.9	39.9±2.2	12–31	−8.9	<0.001	15.2–8.8
Gooren and Bunck (2004) ⁴³	19				Hgb (mmol/L)	9.3±0.7	8.0±0.7 8.1±0.6	12 36	−14.0 −12.9	<0.001 <0.001	21.5–1.0 21.5–0.9
Olson-Kennedy <i>et al</i> (2018) ⁴⁹	23				Hgb (g/dL)	153±11	140±12	12	−8.3	<0.001	14.8–5.9
Wiik (2020) ¹⁶	9 10				Hgb (g/L)	148.3±10.1 150.3±9.1	132.7±9.1 133.3±9.0	4 12	−10.5 −11.7	<0.001 <0.001	18.0–0.5 18.0–0.5
Cross-sectional studies											
Author (year)	Participants (N)				Measure (units)	TW mean±SD or (range)	Control mean±SD or (range)	Number of months	% Difference	P	T (nmol/L) TW
	TW	CM	CW	HNTW							
Lapauw <i>et al</i> (2008) ⁵⁴	23	46			HCT (%)	41.2±2.3	45.3±2.3	>48	−9.1	<0.001	1.1
SoRelle <i>et al</i> (2019) ⁵²	105			73	HCT (%)	(35.9– 48.7)	(39.0– 50.6)	>6	–	d=1.0	1.9
Greene <i>et al</i> (2019) ¹⁸	93				HCT (%)	(35–47)	(35.5– 46) CW	>12	–	>0.05	1.4
Roberts <i>et al</i> (2014) ⁵³	55	20	20		HCT (%)	(34.6–43.7)	(38.4– 45.7) CM (34.4– 41.9) CW	>6	– –	<0.01 >0.05	
Jain (2019)	182 (oestrogen) 95 (oestrogen +progesterone)			92	HCT (%)	42.5 40.9	45.9±2.0	>3	−7.4 −10.9	<0.05 <0.05	
Sharula (2012) ³⁷	129			22	HCT (%)	40.2±3.1	44.4±2.4	>3	−9.5	<0.001	2.5

CM, cismen; CW, ciswomen; HCT, haematocrit; Hgb, haemoglobin; HNTW, hormone-naïve transwomen; TW, transwomen.

with GAHT. Twelve months of GAHT also decreased muscle CSA (1.5%–9.7%). However, a further 12 or 24 months of GAHT did not always elicit further decreases in muscle CSA. Strength loss with 12 months of GAHT also ranged from non-significant to 7%. Taking these strength parameter data collectively, and in consideration of cisgender women demonstrating 31% lower LBM,⁵⁹ 36%⁶⁰ lower hand-grip strength and 35%⁶¹ lower knee extension strength than cisgender men, the small decrease in strength in transwomen after 12–36 months of GAHT suggests that transwomen likely retain a strength advantage over cisgender women. Whether longer duration of GAHT would yield further decrements in strength in transgender women is unknown.

In contrast to strength-related data, blood cell findings revealed a different time course of change. After 3–4 months on GAHT, the HCT¹⁹ or Hgb¹⁶ levels of transwomen matched those of cisgender women, with levels remaining stable within the ‘normal’ female range for studies lasting up to 36 months. Given the rapid fall in Hgb/HCT to ‘normal’ female levels with GAHT, it is possible that transfemale athletes experience impaired endurance performance in part due to reduced oxygen transport from the lungs to the working muscles.⁶² This postulate is consistent with findings reported in one of the few studies conducted in athletic transwomen.⁶³ In this study, the race times of eight transfemale distance runners were compared at baseline and after one or more years of GAHT. After adjusting performance for age, the eight runners were not more competitive in the female category (after GAHT) than they had been in the male

category (before GAHT). Given this, and that the changes in Hgb/HCT follow a different time course than strength changes, sport-specific regulations for transwomen in endurance ver strength sports may be needed.

Of interest, compared with cisgender men, hormone-naïve transwomen demonstrate 6.4%–8.0% lower LBM,^{41,51} 6.0%–11.4% lower muscle CSA and ~10%–14% lower handgrip strength.^{17,41,60} This disparity is noteworthy given that hormone-naïve transwomen and cisgender men have similar testosterone levels.^{16,17,19,42} Explanations for this strength difference are unclear but may include transwomen actively refraining from building muscle and/or engaging in disordered eating⁶⁴ or simply not being athletically inclined, perhaps influenced by feelings of an unwelcome presence in sporting arenas.⁶⁵ Taken together, hormone-naïve transwomen may not, on average, have the same athletic attributes as cisgender men. The need to move beyond simple comparisons of cisgender men and women to assess the sporting capabilities of transwomen is imperative.

This systematic review identified studies that assessed the changes in LBM, CSA, muscular strength and Hgb/HCT in non-athletic transgender women following GAHT. However, several limitations are noted. Although the data we present are meaningful, the effects of GAHT on these parameters, or indeed athletic performance in transgender people who engage in training and competition, remain unknown. The levels of physical activity of the transwomen compared with cisgender women in the studies were not reported. Other limitations include the studies being written in English only,

and the research being conducted in Western countries, contributing to geographical bias. Furthermore, as with much research with transgender individuals, there is a sparse data risk⁶⁶ because of small sample sizes and short study durations, indicative of the relatively small population, difficulties with recruitment and high drop-out rates over time. Indeed, the overlap of participants in the ENIGI studies and the heterogeneous methodology in the other studies precluded the possibility of meaningful meta-analysis. However, overall, the results across different study groups and methods (ie, longitudinal vs follow-up studies) are largely consistent, suggesting that the risk of selective reporting and publication bias are low and the data in the reviewed studies are reliable. This review only focused on binary transgender individuals; those who medically transition from their birth assigned gender to the opposite gender and did not consider non-binary individuals. Not only are there even more limited data on non-binary individuals, but also, for many, their affirmed gender expression does not require GAHT, thus there are no hormone-induced changes to observe which would be relevant to this review. That is not to say that non-binary inclusivity in sport is not an important issue, only that the central tenets are not focused on physiology.

As previously stated, a major limitation in this area of research is the absence of studies in transgender athletes. However, a very recent study reported changes in fitness levels of 29 transmen and 46 transwomen in the United States Air Force, from before and after 30 months of GAHT.⁶⁷ Enlisted Air Force members are required to engage in regular physical activity and to complete annual assessments of number of sit-ups and push-ups in 1 min, and 1.5 mile race time. Although not athletes per se, enlisted members could at least be considered exercise trained. The study reported that after 2 years on GAHT there were no significant differences between ciswomen and transwomen in the number of push-ups or sit-ups performed in 1 min. However, transwomen ran significantly faster during the 1.5 mile fitness test than ciswomen. These observations in trained transgender individuals are consistent with the findings of the current review in untrained transgender individuals, whereby 30 months of GAHT may be sufficient to attenuate some, but not all, influencing factors associated with muscular endurance and performance.

Overall, this review reports decreases in muscle strength, LBM and muscle CSA in response to 12–36 months, and decreases in Hb_g after 3–4 months, of GAHT in transwomen. These findings may help to shape future studies with transgender athletes and provide data for valuable and rigorous research going forward. Sporting bodies wish to be inclusive to all athletes, and there is a critical desire and need for more research to be able to develop evidence-based policies around this topic. Given that the range of physical parameters important for success varies considerably between sports, and that the physiological effects of GAHT vary in their time course (eg, muscle vs blood), future research should be sport specific as well as athlete centric. Although a level playing field in sport is illusory, it is important that opportunities for women to engage in meaningful competition within the female category exist.⁶⁸ Whether transgender and cisgender women can engage in meaningful sport, even after GAHT, is a highly debated question. However, before this question can be answered with any certainty, the intricacies and complexity of factors that feed into the development of high-performance athletes warrant further investigation of attributes beyond those assessed herein.

Contributors GLW devised the study. BSK completed an initial search in 2019 with GLW and HMD. JH completed a second search in 2020 with GLW and EOD. All authors contributed to the manuscript.

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What is already known

- There is much debate on whether (and when) transwomen should be permitted to compete in the female category in sport.

What are the new findings

- Longitudinal and cross-sectional studies identify that hormone therapy in transwomen decreases muscle cross-sectional area, lean body mass, strength and haemoglobin levels, with noted differences in the time course of change.
- Haemoglobin levels decrease to those seen in cisgender women after 4 months of hormone therapy. In contrast, despite significant decreases in muscle cross-sectional area, lean body mass and strength after 12–36 months of hormone therapy, values remain higher than that in cisgender women.
- It is possible that transwomen competing in sports may retain strength advantages over cisgender women, even after 3 years of hormone therapy.

Competing interests None declared.

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Endocrine Treatment of Gender-Dysphoric/ Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline

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***Cosponsoring Associations:** American Association of Clinical Endocrinologists, American Society of Andrology, European Society for Pediatric Endocrinology, European Society of Endocrinology, Pediatric Endocrine Society, and World Professional Association for Transgender Health.

Objective: To update the "Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline," published by the Endocrine Society in 2009.

Participants: The participants include an Endocrine Society-appointed task force of nine experts, a methodologist, and a medical writer.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation approach to describe the strength of recommendations and the quality of evidence. The task force commissioned two systematic reviews and used the best available evidence from other published systematic reviews and individual studies.

Consensus Process: Group meetings, conference calls, and e-mail communications enabled consensus. Endocrine Society committees, members and cosponsoring organizations reviewed and commented on preliminary drafts of the guidelines.

Conclusion: Gender affirmation is multidisciplinary treatment in which endocrinologists play an important role. Gender-dysphoric/gender-incongruent persons seek and/or are referred to endocrinologists to develop the physical characteristics of the affirmed gender. They require a safe and effective hormone regimen that will (1) suppress endogenous sex hormone secretion determined by the person's genetic/gonadal sex and (2) maintain sex hormone levels within the normal range for the person's affirmed gender. Hormone treatment is not recommended for prepubertal gender-dysphoric/gender-incongruent persons. Those clinicians who recommend gender-affirming endocrine treatments—appropriately trained diagnosing clinicians (required), a mental health provider for adolescents (required) and mental health

professional for adults (recommended)—should be knowledgeable about the diagnostic criteria and criteria for gender-affirming treatment, have sufficient training and experience in assessing psychopathology, and be willing to participate in the ongoing care throughout the endocrine transition. We recommend treating gender-dysphoric/gender-incongruent adolescents who have entered puberty at Tanner Stage G2/B2 by suppression with gonadotropin-releasing hormone agonists. Clinicians may add gender-affirming hormones after a multidisciplinary team has confirmed the persistence of gender dysphoria/gender incongruence and sufficient mental capacity to give informed consent to this partially irreversible treatment. Most adolescents have this capacity by age 16 years old. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to age 16 years, although there is minimal published experience treating prior to 13.5 to 14 years of age. For the care of peripubertal youths and older adolescents, we recommend that an expert multidisciplinary team comprised of medical professionals and mental health professionals manage this treatment. The treating physician must confirm the criteria for treatment used by the referring mental health practitioner and collaborate with them in decisions about gender-affirming surgery in older adolescents. For adult gender-dysphoric/gender-incongruent persons, the treating clinicians (collectively) should have expertise in transgender-specific diagnostic criteria, mental health, primary care, hormone treatment, and surgery, as needed by the patient. We suggest maintaining physiologic levels of gender-appropriate hormones and monitoring for known risks and complications. When high doses of sex steroids are required to suppress endogenous sex steroids and/or in advanced age, clinicians may consider surgically removing natal gonads along with reducing sex steroid treatment. Clinicians should monitor both transgender males (female to male) and transgender females (male to female) for reproductive organ cancer risk when surgical removal is incomplete. Additionally, clinicians should persistently monitor adverse effects of sex steroids. For gender-affirming surgeries in adults, the treating physician must collaborate with and confirm the criteria for treatment used by the referring physician. Clinicians should avoid harming individuals (via hormone treatment) who have conditions other than gender dysphoria/gender incongruence and who may not benefit from the physical changes associated with this treatment. (*J Clin Endocrinol Metab* 102: 3869–3903, 2017)

Summary of Recommendations

1.0 Evaluation of youth and adults

- 1.1. We advise that only trained mental health professionals (MHPs) who meet the following criteria should diagnose gender dysphoria (GD)/gender incongruence in adults: (1) competence in using the Diagnostic and Statistical Manual of Mental Disorders (DSM) and/or the International Statistical Classification of Diseases and Related Health Problems (ICD) for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. (Ungraded Good Practice Statement)
- 1.2. We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or the ICD for diagnostic purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psychosocially assess the person's understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. (Ungraded Good Practice Statement)
- 1.3. We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional. (Ungraded Good Practice Statement).

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- 1.4. We recommend against puberty blocking and gender-affirming hormone treatment in pre-pubertal children with GD/gender incongruence. (1 ⊕⊕⊕○)
- 1.5. We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults. (1 ⊕⊕⊕○)

2.0 Treatment of adolescents

- 2.1. We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment, and are requesting treatment should initially undergo treatment to suppress pubertal development. (2 ⊕⊕○○)
- 2.2. We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty. (2 ⊕⊕○○)
- 2.3. We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones. (1 ⊕⊕○○)
- 2.4. In adolescents who request sex hormone treatment (given this is a partly irreversible treatment), we recommend initiating treatment using a gradually increasing dose schedule after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years. (1 ⊕⊕○○).
- 2.5. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents with GD/gender incongruence, even though there are minimal published studies of gender-affirming hormone treatments administered before age 13.5 to 14 years. As with the care of adolescents ≥16 years of age, we recommend that an expert multidisciplinary team of medical and MHPs manage this treatment. (1 ⊕○○○)
- 2.6. We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment. (2 ⊕⊕○○)

3.0 Hormonal therapy for transgender adults

- 3.1. We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and

- the criteria for the endocrine phase of gender transition before beginning treatment. (1 ⊕⊕⊕○)
- 3.2. We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment. (1 ⊕⊕⊕○)
- 3.3. We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender. (2 ⊕⊕○○)
- 3.4. We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment. (2 ⊕○○○)

4.0 Adverse outcome prevention and long-term care

- 4.1. We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every 3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly. (2 ⊕⊕○○)
- 4.2. We suggest periodically monitoring prolactin levels in transgender females treated with estrogens. (2 ⊕⊕○○)
- 4.3. We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors using fasting lipid profiles, diabetes screening, and/or other diagnostic tools. (2 ⊕⊕○○)
- 4.4. We recommend that clinicians obtain bone mineral density (BMD) measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. (1 ⊕⊕○○)
- 4.5. We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for non-transgender females. (2 ⊕⊕○○)
- 4.6. We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer. (2 ⊕○○○)
- 4.7. We advise that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. (Ungraded Good Practice Statement)

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5.0 Surgery for sex reassignment and gender confirmation

- 5.1. We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically necessary and would benefit the patient's overall health and/or well-being. (1 ⊕⊕○○)
- 5.2. We advise that clinicians approve genital gender-affirming surgery only after completion of at least 1 year of consistent and compliant hormone treatment, unless hormone therapy is not desired or medically contraindicated. (Ungraded Good Practice Statement)
- 5.3. We advise that the clinician responsible for endocrine treatment and the primary care provider ensure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. (Ungraded Good Practice Statement)
- 5.4. We recommend that clinicians refer hormone-treated transgender individuals for genital surgery when: (1) the individual has had a satisfactory social role change, (2) the individual is satisfied about the hormonal effects, and (3) the individual desires definitive surgical changes. (1 ⊕○○○)
- 5.5. We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18 years old or legal age of majority in his or her country. (2 ⊕⊕○○)
- 5.6. We suggest that clinicians determine the timing of breast surgery for transgender males based upon the physical and mental health status of the individual. There is insufficient evidence to recommend a specific age requirement. (2 ⊕○○○)

Changes Since the Previous Guideline

Both the current guideline and the one published in 2009 contain similar sections. Listed here are the sections contained in the current guideline and the corresponding number of recommendations: Introduction, Evaluation of Youth and Adults (5), Treatment of Adolescents (6), Hormonal Therapy for Transgender Adults (4), Adverse Outcomes Prevention and Long-term Care (7), and Surgery for Sex Reassignment and Gender Confirmation (6). The current introduction updates the diagnostic classification of "gender dysphoria/gender incongruence." It also reviews the development of "gender identity" and summarizes its natural development. The section on

clinical evaluation of both youth and adults, defines in detail the professional qualifications required of those who diagnose and treat both adolescents and adults. We advise that decisions regarding the social transition of prepubertal youth are made with the assistance of a mental health professional or similarly experienced professional. We recommend against puberty blocking followed by gender-affirming hormone treatment of prepubertal children. Clinicians should inform pubertal children, adolescents, and adults seeking gender-confirming treatment of their options for fertility preservation. Prior to treatment, clinicians should evaluate the presence of medical conditions that may be worsened by hormone depletion and/or treatment. A multidisciplinary team, preferably composed of medical and mental health professionals, should monitor treatments. Clinicians evaluating transgender adults for endocrine treatment should confirm the diagnosis of persistent gender dysphoria/gender incongruence. Physicians should educate transgender persons regarding the time course of steroid-induced physical changes. Treatment should include periodic monitoring of hormone levels and metabolic parameters, as well as assessments of bone density and the impact upon prostate, gonads, and uterus. We also make recommendations for transgender persons who plan genital gender-affirming surgery.

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee (CGS) of the Endocrine Society deemed the diagnosis and treatment of individuals with GD/gender incongruence a priority area for revision and appointed a task force to formulate evidence-based recommendations. The task force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation group, an international group with expertise in the development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The task force used the best available research evidence to develop the recommendations. The task force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase "we recommend" and the number 1, and weak recommendations use the phrase "we suggest" and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕○○○ denotes very low-quality evidence; ⊕⊕○○, low quality; ⊕⊕⊕○, moderate quality; and ⊕⊕⊕⊕, high quality. The task force has confidence that persons who receive care according to the strong recommendations will derive, on average, more benefit than harm. Weak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the

values that the task force considered in making the recommendation. In some instances, there are remarks in which the task force offers technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the task force and their preferences; therefore, one should consider these remarks as suggestions.

In this guideline, the task force made several statements to emphasize the importance of shared decision-making, general preventive care measures, and basic principles of the treatment of transgender persons. They labeled these “Ungraded Good Practice Statement.” Direct evidence for these statements was either unavailable or not systematically appraised and considered out of the scope of this guideline. The intention of these statements is to draw attention to these principles.

The Endocrine Society maintains a rigorous conflict-of-interest review process for developing clinical practice guidelines. All task force members must declare any potential conflicts of interest by completing a conflict-of-interest form. The CGS reviews all conflicts of interest before the Society’s Council approves the members to participate on the task force and periodically during the development of the guideline. All others participating in the guideline’s development must also disclose any conflicts of interest in the matter under study, and most of these participants must be without any conflicts of interest. The CGS and the task force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined as remuneration in any amount from commercial interests; grants; research support; consulting fees; salary; ownership interests [*e.g.*, stocks and stock options (excluding diversified mutual funds)]; honoraria and other payments for participation in speakers’ bureaus, advisory boards, or boards of directors; and all other financial benefits. Completed forms are available through the Endocrine Society office.

The Endocrine Society provided the funding for this guideline; the task force received no funding or remuneration from commercial or other entities.

Commissioned Systematic Review

The task force commissioned two systematic reviews to support this guideline. The first one aimed to summarize the available evidence on the effect of sex steroid use in transgender individuals on lipids and cardiovascular outcomes. The review identified 29 eligible studies at moderate risk of bias. In transgender males (female to male), sex steroid therapy was associated with a statistically significant increase in serum triglycerides and low-density lipoprotein cholesterol levels. High-density lipoprotein cholesterol levels decreased significantly across all follow-up time periods. In transgender females (male to female), serum triglycerides were significantly higher without any changes in other parameters. Few myocardial infarction, stroke, venous thromboembolism (VTE), and death events were reported. These events were more frequent in transgender females. However, the

quality of the evidence was low. The second review summarized the available evidence regarding the effect of sex steroids on bone health in transgender individuals and identified 13 studies. In transgender males, there was no statistically significant difference in the lumbar spine, femoral neck, or total hip BMD at 12 and 24 months compared with baseline values before initiating masculinizing hormone therapy. In transgender females, there was a statistically significant increase in lumbar spine BMD at 12 months and 24 months compared with baseline values before initiation of feminizing hormone therapy. There was minimal information on fracture rates. The quality of evidence was also low.

Introduction

Throughout recorded history (in the absence of an endocrine disorder) some men and women have experienced confusion and anguish resulting from rigid, forced conformity to sexual dimorphism. In modern history, there have been numerous ongoing biological, psychological, cultural, political, and sociological debates over various aspects of gender variance. The 20th century marked the emergence of a social awakening for men and women with the belief that they are “trapped” in the wrong body (3). Magnus Hirschfeld and Harry Benjamin, among others, pioneered the medical responses to those who sought relief from and a resolution to their profound discomfort. Although the term transsexual became widely known after Benjamin wrote “The Transsexual Phenomenon” (4), it was Hirschfeld who coined the term “transsexual” in 1923 to describe people who want to live a life that corresponds with their experienced gender vs their designated gender (5). Magnus Hirschfeld (6) and others (4, 7) have described other types of trans phenomena besides transsexualism. These early researchers proposed that the gender identity of these people was located somewhere along a unidimensional continuum. This continuum ranged from all male through “something in between” to all female. Yet such a classification does not take into account that people may have gender identities outside this continuum. For instance, some experience themselves as having both a male and female gender identity, whereas others completely renounce any gender classification (8, 9). There are also reports of individuals experiencing a continuous and rapid involuntary alternation between a male and female identity (10) or men who do not experience themselves as men but do not want to live as women (11, 12). In some countries, (*e.g.*, Nepal, Bangladesh, and Australia), these nonmale or nonfemale genders are officially recognized (13). Specific treatment protocols, however, have not yet been developed for these groups.

Instead of the term transsexualism, the current classification system of the American Psychiatric Association uses the term gender dysphoria in its diagnosis of persons who are not satisfied with their designated gender (14). The current version of the World Health Organization's ICD-10 still uses the term transsexualism when diagnosing adolescents and adults. However, for the ICD-11, the World Health Organization has proposed using the term "gender incongruence" (15).

Treating persons with GD/gender incongruence (15) was previously limited to relatively ineffective elixirs or creams. However, more effective endocrinology-based treatments became possible with the availability of testosterone in 1935 and diethylstilbestrol in 1938. Reports of individuals with GD/gender incongruence who were treated with hormones and gender-affirming surgery appeared in the press during the second half of the 20th century. The Harry Benjamin International Gender Dysphoria Association was founded in September 1979 and is now called the World Professional Association for Transgender Health (WPATH). WPATH published its first Standards of Care in 1979. These standards have since been regularly updated, providing guidance for treating persons with GD/gender incongruence (16).

Prior to 1975, few peer-reviewed articles were published concerning endocrine treatment of transgender persons. Since then, more than two thousand articles about various aspects of transgender care have appeared.

It is the purpose of this guideline to make detailed recommendations and suggestions, based on existing medical literature and clinical experience, that will enable treating physicians to maximize benefit and minimize risk when caring for individuals diagnosed with GD/gender incongruence.

In the future, we need more rigorous evaluations of the effectiveness and safety of endocrine and surgical protocols. Specifically, endocrine treatment protocols for GD/gender incongruence should include the careful assessment of the following: (1) the effects of prolonged delay of puberty in adolescents on bone health, gonadal function, and the brain (including effects on cognitive, emotional, social, and sexual development); (2) the effects of treatment in adults on sex hormone levels; (3) the requirement for and the effects of progestins and other agents used to suppress endogenous sex steroids during treatment; and (4) the risks and benefits of gender-affirming hormone treatment in older transgender people.

To successfully establish and enact these protocols, a commitment of mental health and endocrine investigators is required to collaborate in long-term, large-scale

studies across countries that use the same diagnostic and inclusion criteria, medications, assay methods, and response assessment tools (*e.g.*, the European Network for the Investigation of Gender Incongruence) (17, 18).

Terminology and its use vary and continue to evolve. Table 1 contains the definitions of terms as they are used throughout this guideline.

Biological Determinants of Gender Identity Development

One's self-awareness as male or female changes gradually during infant life and childhood. This process of cognitive and affective learning evolves with interactions with parents, peers, and environment. A fairly accurate timetable exists outlining the steps in this process (19). Normative psychological literature, however, does not address if and when gender identity becomes crystallized and what factors contribute to the development of a gender identity that is not congruent with the gender of rearing. Results of studies from a variety of biomedical disciplines—genetic, endocrine, and neuroanatomic—support the concept that gender identity and/or gender expression (20) likely reflect a complex interplay of biological, environmental, and cultural factors (21, 22).

With respect to endocrine considerations, studies have failed to find differences in circulating levels of sex steroids between transgender and nontransgender individuals (23). However, studies in individuals with a disorder/difference of sex development (DSD) have informed our understanding of the role that hormones may play in gender identity outcome, even though most persons with GD/gender incongruence do not have a DSD. For example, although most 46,XX adult individuals with virilizing congenital adrenal hyperplasia caused by mutations in *CYP21A2* reported a female gender identity, the prevalence of GD/gender incongruence was much greater in this group than in the general population without a DSD. This supports the concept that there is a role for prenatal/postnatal androgens in gender development (24–26), although some studies indicate that prenatal androgens are more likely to affect gender behavior and sexual orientation rather than gender identity *per se* (27, 28).

Researchers have made similar observations regarding the potential role of androgens in the development of gender identity in other individuals with DSD. For example, a review of two groups of 46,XY persons, each with androgen synthesis deficiencies and female raised, reported transgender male (female-to-male) gender role changes in 56% to 63% and 39% to 64% of patients, respectively (29). Also, in 46,XY female-raised individuals with cloacal

Table 1. Definitions of Terms Used in This Guideline

<i>Biological sex, biological male or female:</i> These terms refer to physical aspects of maleness and femaleness. As these may not be in line with each other (e.g., a person with XY chromosomes may have female-appearing genitalia), the terms biological sex and biological male or female are imprecise and should be avoided.
<i>Cisgender:</i> This means not transgender. An alternative way to describe individuals who are not transgender is “non-transgender people.”
<i>Gender-affirming (hormone) treatment:</i> See “gender reassignment”
<i>Gender dysphoria:</i> This is the distress and unease experienced if gender identity and designated gender are not completely congruent (see Table 2). In 2013, the American Psychiatric Association released the fifth edition of the DSM-5, which replaced “gender identity disorder” with “gender dysphoria” and changed the criteria for diagnosis.
<i>Gender expression:</i> This refers to external manifestations of gender, expressed through one’s name, pronouns, clothing, haircut, behavior, voice, or body characteristics. Typically, transgender people seek to make their gender expression align with their gender identity, rather than their designated gender.
<i>Gender identity/experienced gender:</i> This refers to one’s internal, deeply held sense of gender. For transgender people, their gender identity does not match their sex designated at birth. Most people have a gender identity of man or woman (or boy or girl). For some people, their gender identity does not fit neatly into one of those two choices. Unlike gender expression (see below), gender identity is not visible to others.
<i>Gender identity disorder:</i> This is the term used for GD/gender incongruence in previous versions of DSM (see “gender dysphoria”). The ICD-10 still uses the term for diagnosing child diagnoses, but the upcoming ICD-11 has proposed using “gender incongruence of childhood.”
<i>Gender incongruence:</i> This is an umbrella term used when the gender identity and/or gender expression differs from what is typically associated with the designated gender. Gender incongruence is also the proposed name of the gender identity–related diagnoses in ICD-11. Not all individuals with gender incongruence have gender dysphoria or seek treatment.
<i>Gender variance:</i> See “gender incongruence”
<i>Gender reassignment:</i> This refers to the treatment procedure for those who want to adapt their bodies to the experienced gender by means of hormones and/or surgery. This is also called gender-confirming or gender-affirming treatment.
<i>Gender-reassignment surgery (gender-confirming/gender-affirming surgery):</i> These terms refer only to the surgical part of gender-confirming/gender-affirming treatment.
<i>Gender role:</i> This refers to behaviors, attitudes, and personality traits that a society (in a given culture and historical period) designates as masculine or feminine and/or that society associates with or considers typical of the social role of men or women.
<i>Sex designated at birth:</i> This refers to sex assigned at birth, usually based on genital anatomy.
<i>Sex:</i> This refers to attributes that characterize biological maleness or femaleness. The best known attributes include the sex-determining genes, the sex chromosomes, the H-Y antigen, the gonads, sex hormones, internal and external genitalia, and secondary sex characteristics.
<i>Sexual orientation:</i> This term describes an individual’s enduring physical and emotional attraction to another person. Gender identity and sexual orientation are not the same. Irrespective of their gender identity, transgender people may be attracted to women (gynephilic), attracted to men (androphilic), bisexual, asexual, or queer.
<i>Transgender:</i> This is an umbrella term for people whose gender identity and/or gender expression differs from what is typically associated with their sex designated at birth. Not all transgender individuals seek treatment.
<i>Transgender male (also: trans man, female-to-male, transgender male):</i> This refers to individuals assigned female at birth but who identify and live as men.
<i>Transgender woman (also: trans woman, male-to-female, transgender female):</i> This refers to individuals assigned male at birth but who identify and live as women.
<i>Transition:</i> This refers to the process during which transgender persons change their physical, social, and/or legal characteristics consistent with the affirmed gender identity. Prepubertal children may choose to transition socially.
<i>Transsexual:</i> This is an older term that originated in the medical and psychological communities to refer to individuals who have permanently transitioned through medical interventions or desired to do so.

exstrophy and penile agenesis, the occurrence of transgender male changes was significantly more prevalent than in the general population (30, 31). However, the fact that a high percentage of individuals with the same conditions did not change gender suggests that cultural factors may play a role as well.

With respect to genetics and gender identity, several studies have suggested heritability of GD/gender incongruence (32, 33). In particular, a study by Heylens *et al.* (33) demonstrated a 39.1% concordance rate for gender identity disorder (based on the DSM-IV criteria) in 23 monozygotic twin pairs but no concordance in 21 same-sex dizygotic or seven opposite-sex twin pairs. Although numerous investigators have sought to identify

specific genes associated with GD/gender incongruence, such studies have been inconsistent and without strong statistical significance (34–38).

Studies focusing on brain structure suggest that the brain phenotypes of people with GD/gender incongruence differ in various ways from control males and females, but that there is not a complete sex reversal in brain structures (39).

In summary, although there is much that is still unknown with respect to gender identity and its expression, compelling studies support the concept that biologic factors, in addition to environmental factors, contribute to this fundamental aspect of human development.

Natural History of Children With GD/Gender Incongruence

With current knowledge, we cannot predict the psychosexual outcome for any specific child. Prospective follow-up studies show that childhood GD/gender incongruence does not invariably persist into adolescence and adulthood (so-called “desisters”). Combining all outcome studies to date, the GD/gender incongruence of a minority of prepubertal children appears to persist in adolescence (20, 40). In adolescence, a significant number of these desisters identify as homosexual or bisexual. It may be that children who only showed some gender nonconforming characteristics have been included in the follow-up studies, because the DSM-IV text revision criteria for a diagnosis were rather broad. However, the persistence of GD/gender incongruence into adolescence is more likely if it had been extreme in childhood (41, 42). With the newer, stricter criteria of the DSM-5 (Table 2), persistence rates may well be different in future studies.

1.0 Evaluation of Youth and Adults

Gender-affirming treatment is a multidisciplinary effort. After evaluation, education, and diagnosis, treatment may include mental health care, hormone therapy, and/or surgical therapy. Together with an MHP, hormone-prescribing clinicians should examine the psychosocial impact of the potential changes on people’s lives, including mental health, friends, family, jobs, and their role in society. Transgender individuals should be encouraged to experience living in the new gender role and assess whether

this improves their quality of life. Although the focus of this guideline is gender-affirming hormone therapy, collaboration with appropriate professionals responsible for each aspect of treatment maximizes a successful outcome.

Diagnostic assessment and mental health care

GD/gender incongruence may be accompanied with psychological or psychiatric problems (43–51). It is therefore necessary that clinicians who prescribe hormones and are involved in diagnosis and psychosocial assessment meet the following criteria: (1) are competent in using the DSM and/or the ICD for diagnostic purposes, (2) are able to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) are trained in diagnosing psychiatric conditions, (4) undertake or refer for appropriate treatment, (5) are able to do a psychosocial assessment of the patient’s understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) regularly attend relevant professional meetings.

Because of the psychological vulnerability of many individuals with GD/gender incongruence, it is important that mental health care is available before, during, and sometimes also after transitioning. For children and adolescents, an MHP who has training/experience in child and adolescent gender development (as well as child and adolescent psychopathology) should make the diagnosis, because assessing GD/gender incongruence in children and adolescents is often extremely complex.

During assessment, the clinician obtains information from the individual seeking gender-affirming treatment. In the case

Table 2. DSM-5 Criteria for Gender Dysphoria in Adolescents and Adults

- A. A marked incongruence between one’s experienced/expressed gender and natal gender of at least 6 mo in duration, as manifested by at least two of the following:
 1. A marked incongruence between one’s experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
 2. A strong desire to be rid of one’s primary and/or secondary sex characteristics because of a marked incongruence with one’s experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
 3. A strong desire for the primary and/or secondary sex characteristics of the other gender
 4. A strong desire to be of the other gender (or some alternative gender different from one’s designated gender)
 5. A strong desire to be treated as the other gender (or some alternative gender different from one’s designated gender)
 6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one’s designated gender)
- B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.
Specify if:
 1. The condition exists with a disorder of sex development.
 2. The condition is posttransitional, in that the individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one sex-related medical procedure or treatment regimen—namely, regular sex hormone treatment or gender reassignment surgery confirming the desired gender (*e.g.*, penectomy, vaginoplasty in natal males; mastectomy or phalloplasty in natal females).

of adolescents, the clinician also obtains information from the parents or guardians regarding various aspects of the child's general and psychosexual development and current functioning. On the basis of this information, the clinician:

- decides whether the individual fulfills criteria for treatment (see Tables 2 and 3) for GD/gender incongruence (DSM-5) or transsexualism (DSM-5 and/or ICD-10);
- informs the individual about the possibilities and limitations of various kinds of treatment (hormonal/surgical and nonhormonal), and if medical treatment is desired, provides correct information to prevent unrealistically high expectations;
- assesses whether medical interventions may result in unfavorable psychological and social outcomes.

In cases in which severe psychopathology, circumstances, or both seriously interfere with the diagnostic work or make satisfactory treatment unlikely, clinicians should assist the adolescent in managing these other issues. Literature on postoperative regret suggests that besides poor quality of surgery, severe psychiatric comorbidity and lack of support may interfere with positive outcomes (52–56).

For adolescents, the diagnostic procedure usually includes a complete psychodiagnostic assessment (57) and an assessment of the decision-making capability of the youth. An evaluation to assess the family's ability to endure stress, give support, and deal with the complexities of the adolescent's situation should be part of the diagnostic phase (58).

Social transitioning

A change in gender expression and role (which may involve living part time or full time in another gender role that is consistent with one's gender identity) may test the person's resolve, the capacity to function in the affirmed gender, and the adequacy of social, economic, and psychological supports. It assists both the individual and the clinician in their judgments about how to proceed (16). During social transitioning, the person's feelings about the social transformation (including coping with the responses of others) is a major focus of the counseling. The optimal timing for social transitioning may differ between individuals. Sometimes people wait until they

start gender-affirming hormone treatment to make social transitioning easier, but individuals increasingly start social transitioning long before they receive medically supervised, gender-affirming hormone treatment.

Criteria

Adolescents and adults seeking gender-affirming hormone treatment and surgery should satisfy certain criteria before proceeding (16). Criteria for gender-affirming hormone therapy for adults are in Table 4, and criteria for gender-affirming hormone therapy for adolescents are in Table 5. Follow-up studies in adults meeting these criteria indicate a high satisfaction rate with treatment (59). However, the quality of evidence is usually low. A few follow-up studies on adolescents who fulfilled these criteria also indicated good treatment results (60–63).

Recommendations for Those Involved in the Gender-Affirming Hormone Treatment of Individuals With GD/Gender Incongruence

- 1.1. We advise that only trained MHPs who meet the following criteria should diagnose GD/gender incongruence in adults: (1) competence in using the DSM and/or the ICD for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. (Ungraded Good Practice Statement)
- 1.2. We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or ICD for diagnostic

Table 3. ICD-10 Criteria for Transsexualism

Transsexualism (F64.0) has three criteria:

1. The desire to live and be accepted as a member of the opposite sex, usually accompanied by the wish to make his or her body as congruent as possible with the preferred sex through surgery and hormone treatments.
2. The transsexual identity has been present persistently for at least 2 y.
3. The disorder is not a symptom of another mental disorder or a genetic, DSD, or chromosomal abnormality.

Table 4. Criteria for Gender-Affirming Hormone Therapy for Adults

1. Persistent, well-documented gender dysphoria/gender incongruence
2. The capacity to make a fully informed decision and to consent for treatment
3. The age of majority in a given country (if younger, follow the criteria for adolescents)
4. Mental health concerns, if present, must be reasonably well controlled

Reproduced from World Professional Association for Transgender Health (16).

purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (e.g., body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psycho-socially assess the person's understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. (Ungraded Good Practice Statement)

Evidence

Individuals with gender identity issues may have psychological or psychiatric problems (43–48, 50, 51, 64, 65). It is therefore necessary that clinicians making the diagnosis are able to make a distinction between GD/gender incongruence and conditions that have similar features. Examples of conditions with similar features are body dysmorphic disorder, body identity integrity disorder (a condition in which individuals have a sense that their anatomical configuration as an able-bodied person is somehow wrong or inappropriate) (66), or certain forms of eunuchism (in which a person is preoccupied with or engages in castration and/or penectomy for

Table 5. Criteria for Gender-Affirming Hormone Therapy for Adolescents

Adolescents are eligible for GnRH agonist treatment if:

1. A qualified MHP has confirmed that:
 - the adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed),
 - gender dysphoria worsened with the onset of puberty,
 - any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment,
 - the adolescent has sufficient mental capacity to give informed consent to this (reversible) treatment,
2. And the adolescent:
 - has been informed of the effects and side effects of treatment (including potential loss of fertility if the individual subsequently continues with sex hormone treatment) and options to preserve fertility,
 - has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,
3. And a pediatric endocrinologist or other clinician experienced in pubertal assessment
 - agrees with the indication for GnRH agonist treatment,
 - has confirmed that puberty has started in the adolescent (Tanner stage $\geq$ G2/B2),
 - has confirmed that there are no medical contraindications to GnRH agonist treatment.

Adolescents are eligible for subsequent sex hormone treatment if:

1. A qualified MHP has confirmed:
 - the persistence of gender dysphoria,
 - any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start sex hormone treatment,
 - the adolescent has sufficient mental capacity (which most adolescents have by age 16 years) to estimate the consequences of this (partly) irreversible treatment, weigh the benefits and risks, and give informed consent to this (partly) irreversible treatment,
2. And the adolescent:
 - has been informed of the (irreversible) effects and side effects of treatment (including potential loss of fertility and options to preserve fertility),
 - has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,
3. And a pediatric endocrinologist or other clinician experienced in pubertal induction:
 - agrees with the indication for sex hormone treatment,
 - has confirmed that there are no medical contraindications to sex hormone treatment.

Reproduced from World Professional Association for Transgender Health (16).

reasons that are not gender identity related) (11). Clinicians should also be able to diagnose psychiatric conditions accurately and ensure that these conditions are treated appropriately, particularly when the conditions may complicate treatment, affect the outcome of gender-affirming treatment, or be affected by hormone use.

Values and preferences

The task force placed a very high value on avoiding harm from hormone treatment in individuals who have conditions other than GD/gender incongruence and who may not benefit from the physical changes associated with this treatment and placed a low value on any potential benefit these persons believe they may derive from hormone treatment. This justifies the good practice statement.

- 1.3. We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional. (Ungraded Good Practice Statement).
- 1.4. We recommend against puberty blocking and gender-affirming hormone treatment in prepubertal children with GD/gender incongruence. (1 ⊕⊕○○)

Evidence

In most children diagnosed with GD/gender incongruence, it did not persist into adolescence. The percentages differed among studies, probably dependent on which version of the DSM clinicians used, the patient's age, the recruitment criteria, and perhaps cultural factors. However, the large majority (about 85%) of prepubertal children with a childhood diagnosis did not remain GD/gender incongruent in adolescence (20). If children have completely socially transitioned, they may have great difficulty in returning to the original gender role upon entering puberty (40). Social transition is associated with the persistence of GD/gender incongruence as a child progresses into adolescence. It may be that the presence of GD/gender incongruence in prepubertal children is the earliest sign that a child is destined to be transgender as an adolescent/adult (20). However, social transition (in addition to GD/gender incongruence) has been found to contribute to the likelihood of persistence.

This recommendation, however, does not imply that children should be discouraged from showing gender-variant behaviors or should be punished for exhibiting such behaviors. In individual cases, an early complete social transition may result in a more favorable outcome, but there are currently no criteria to identify the

GD/gender-incongruent children to whom this applies. At the present time, clinical experience suggests that persistence of GD/gender incongruence can only be reliably assessed after the first signs of puberty.

Values and preferences

The task force placed a high value on avoiding harm with gender-affirming hormone therapy in prepubertal children with GD/gender incongruence. This justifies the strong recommendation in the face of low-quality evidence.

- 1.5. We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults. (1 ⊕⊕⊕○)

Remarks

Persons considering hormone use for gender affirmation need adequate information about this treatment in general and about fertility effects of hormone treatment in particular to make an informed and balanced decision (67, 68). Because young adolescents may not feel qualified to make decisions about fertility and may not fully understand the potential effects of hormonal interventions, consent and protocol education should include parents, the referring MHP(s), and other members of the adolescent's support group. To our knowledge, there are no formally evaluated decision aids available to assist in the discussion and decision regarding the future fertility of adolescents or adults beginning gender-affirming treatment.

Treating early pubertal youth with GnRH analogs will temporarily impair spermatogenesis and oocyte maturation. Given that an increasing number of transgender youth want to preserve fertility potential, delaying or temporarily discontinuing GnRH analogs to promote gamete maturation is an option. This option is often not preferred, because mature sperm production is associated with later stages of puberty and with the significant development of secondary sex characteristics.

For those designated male at birth with GD/gender incongruence and who are in early puberty, sperm production and the development of the reproductive tract are insufficient for the cryopreservation of sperm. However, prolonged pubertal suppression using GnRH analogs is reversible and clinicians should inform these individuals that sperm production can be initiated following prolonged gonadotropin suppression. This can be accomplished by spontaneous gonadotropin recovery after

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cessation of GnRH analogs or by gonadotropin treatment and will probably be associated with physical manifestations of testosterone production, as stated above. Note that there are no data in this population concerning the time required for sufficient spermatogenesis to collect enough sperm for later fertility. In males treated for precocious puberty, spermatogenesis was reported 0.7 to 3 years after cessation of GnRH analogs (69). In adult men with gonadotropin deficiency, sperm are noted in seminal fluid by 6 to 12 months of gonadotropin treatment. However, sperm numbers when partners of these patients conceive are far below the “normal range” (70, 71).

In girls, no studies have reported long-term, adverse effects of pubertal suppression on ovarian function after treatment cessation (72, 73). Clinicians should inform adolescents that no data are available regarding either time to spontaneous ovulation after cessation of GnRH analogs or the response to ovulation induction following prolonged gonadotropin suppression.

In males with GD/gender incongruence, when medical treatment is started in a later phase of puberty or in adulthood, spermatogenesis is sufficient for cryopreservation and storage of sperm. *In vitro* spermatogenesis is currently under investigation. Restoration of spermatogenesis after prolonged estrogen treatment has not been studied.

In females with GD/gender incongruence, the effect of prolonged treatment with exogenous testosterone on ovarian function is uncertain. There have been reports of an increased incidence of polycystic ovaries in transgender males, both prior to and as a result of androgen treatment (74–77), although these reports were not confirmed by others (78). Pregnancy has been reported in transgender males who have had prolonged androgen treatment and have discontinued testosterone but have not had genital surgery (79, 80). A reproductive endocrine gynecologist can counsel patients before gender-affirming hormone treatment or surgery regarding potential fertility options (81). Techniques for cryopreservation of oocytes, embryos, and ovarian tissue continue to improve, and oocyte maturation of immature tissue is being studied (82).

2.0 Treatment of Adolescents

During the past decade, clinicians have progressively acknowledged the suffering of young adolescents with GD/gender incongruence. In some forms of GD/gender incongruence, psychological interventions may be useful and sufficient. However, for many adolescents with GD/gender incongruence, the pubertal physical changes are unbearable. As early medical intervention may prevent

psychological harm, various clinics have decided to start treating young adolescents with GD/gender incongruence with puberty-suppressing medication (a GnRH analog). As compared with starting gender-affirming treatment long after the first phases of puberty, a benefit of pubertal suppression at early puberty may be a better psychological and physical outcome.

In girls, the first physical sign of puberty is the budding of the breasts followed by an increase in breast and fat tissue. Breast development is also associated with the pubertal growth spurt, and menarche occurs ~2 years later. In boys, the first physical change is testicular growth. A testicular volume ≥ 4 mL is seen as consistent with the initiation of physical puberty. At the beginning of puberty, estradiol and testosterone levels are still low and are best measured in the early morning with an ultrasensitive assay. From a testicular volume of 10 mL, daytime testosterone levels increase, leading to virilization (83). Note that pubic hair and/or axillary hair/odor may not reflect the onset of gonadarche; instead, it may reflect adrenarche alone.

- 2.1. We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment (Table 5), and are requesting treatment should initially undergo treatment to suppress pubertal development. (2 $\oplus\oplus\oplus\oplus$)
- 2.2. We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty (Tanner stages G2/B2). (2 $\oplus\oplus\oplus\oplus$)

Evidence

Pubertal suppression can expand the diagnostic phase by a long period, giving the subject more time to explore options and to live in the experienced gender before making a decision to proceed with gender-affirming sex hormone treatments and/or surgery, some of which is irreversible (84, 85). Pubertal suppression is fully reversible, enabling full pubertal development in the natal gender, after cessation of treatment, if appropriate. The experience of full endogenous puberty is an undesirable condition for the GD/gender-incongruent individual and may seriously interfere with healthy psychological functioning and well-being. Treating GD/gender-incongruent adolescents entering puberty with GnRH analogs has been shown to improve psychological functioning in several domains (86).

Another reason to start blocking pubertal hormones early in puberty is that the physical outcome is improved compared with initiating physical transition after puberty has been completed (60, 62). Looking like a man or woman when living as the opposite sex creates difficult

barriers with enormous life-long disadvantages. We therefore advise starting suppression in early puberty to prevent the irreversible development of undesirable secondary sex characteristics. However, adolescents with GD/gender incongruence should experience the first changes of their endogenous spontaneous puberty, because their emotional reaction to these first physical changes has diagnostic value in establishing the persistence of GD/gender incongruence (85). Thus, Tanner stage 2 is the optimal time to start pubertal suppression. However, pubertal suppression treatment in early puberty will limit the growth of the penis and scrotum, which will have a potential effect on future surgical treatments (87).

Clinicians can also use pubertal suppression in adolescents in later pubertal stages to stop menses in transgender males and prevent facial hair growth in transgender females. However, in contrast to the effects in early pubertal adolescents, physical sex characteristics (such as more advanced breast development in transgender boys and lowering of the voice and outgrowth of the jaw and brow in transgender girls) are not reversible.

Values and preferences

These recommendations place a high value on avoiding an unsatisfactory physical outcome when secondary sex characteristics have become manifest and irreversible, a higher value on psychological well-being, and a lower value on avoiding potential harm from early pubertal suppression.

Remarks

Table 6 lists the Tanner stages of breast and male genital development. Careful documentation of hallmarks of pubertal development will ensure precise timing when initiating pubertal suppression once puberty has started. Clinicians can use pubertal LH and sex steroid levels to confirm that puberty has progressed sufficiently before starting pubertal suppression (88). Reference

ranges for sex steroids by Tanner stage may vary depending on the assay used. Ultrasensitive sex steroid and gonadotropin assays will help clinicians document early pubertal changes.

Irreversible and, for GD/gender-incongruent adolescents, undesirable sex characteristics in female puberty are breasts, female body habitus, and, in some cases, relative short stature. In male puberty, they are a prominent Adam’s apple; low voice; male bone configuration, such as a large jaw, big feet and hands, and tall stature; and male hair pattern on the face and extremities.

2.3. We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones. (1 ⊕ ⊕ ⊕ ⊕)

Evidence

Clinicians can suppress pubertal development and gonadal function most effectively via gonadotropin suppression using GnRH analogs. GnRH analogs are long-acting agonists that suppress gonadotropins by GnRH receptor desensitization after an initial increase of gonadotropins during ~10 days after the first and (to a lesser degree) the second injection (89). Antagonists immediately suppress pituitary gonadotropin secretion (90, 91). Long-acting GnRH analogs are the currently preferred treatment option. Clinicians may consider long-acting GnRH antagonists when evidence on their safety and efficacy in adolescents becomes available.

During GnRH analog treatment, slight development of secondary sex characteristics may regress, and in a later phase of pubertal development, it will stop. In girls, breast tissue will become atrophic, and menses will stop. In boys, virilization will stop, and testicular volume may decrease (92).

An advantage of using GnRH analogs is the reversibility of the intervention. If, after extensive exploration of his/her transition wish, the individual no longer desires transition, they can discontinue pubertal suppression. In subjects with

Table 6. Tanner Stages of Breast Development and Male External Genitalia

The description of Tanner stages for breast development:

- 1. Prepubertal
- 2. Breast and papilla elevated as small mound; areolar diameter increased
- 3. Breast and areola enlarged, no contour separation
- 4. Areola and papilla form secondary mound
- 5. Mature; nipple projects, areola part of general breast contour

For penis and testes:

- 1. Prepubertal, testicular volume <4 mL
- 2. Slight enlargement of penis; enlarged scrotum, pink, texture altered, testes 4–6 mL
- 3. Penis longer, testes larger (8–12 mL)
- 4. Penis and glans larger, including increase in breadth; testes larger (12–15 mL), scrotum dark
- 5. Penis adult size; testicular volume > 15 ml

Adapted from Lawrence (56).

precocious puberty, spontaneous pubertal development has been shown to resume after patients discontinue taking GnRH analogs (93).

Recommendations 2.1 to 2.3 are supported by a prospective follow-up study from The Netherlands. This report assessed mental health outcomes in 55 transgender adolescents/young adults (22 transgender females and 33 transgender males) at three time points: (1) before the start of GnRH agonist (average age of 14.8 years at start of treatment), (2) at initiation of gender-affirming hormones (average age of 16.7 years at start of treatment), and (3) 1 year after “gender-reassignment surgery” (average age of 20.7 years) (63). Despite a decrease in depression and an improvement in general mental health functioning, GD/gender incongruence persisted through pubertal suppression, as previously reported (86). However, following sex hormone treatment and gender-reassignment surgery, GD/gender incongruence was resolved and psychological functioning steadily improved (63). Furthermore, well-being was similar to or better than that reported by age-matched young adults from the general population, and none of the study participants regretted treatment. This study represents the first long-term follow-up of individuals managed according to currently existing clinical practice guidelines for transgender youth, and it underscores the benefit of the multidisciplinary approach pioneered in The Netherlands; however, further studies are needed.

Side effects

The primary risks of pubertal suppression in GD/gender-incongruent adolescents may include adverse effects on bone mineralization (which can theoretically be reversed with sex hormone treatment), compromised fertility if the person subsequently is treated with sex hormones, and unknown effects on brain development. Few data are available on the effect of GnRH analogs on BMD in adolescents with GD/gender incongruence. Initial data in GD/gender-incongruent subjects demonstrated no change of absolute areal BMD during 2 years of GnRH analog therapy but a decrease in BMD *z* scores (85). A recent study also suggested suboptimal bone mineral accrual during GnRH analog treatment. The study reported a decrease in areal BMD *z* scores and of bone mineral apparent density *z* scores (which takes the size of the bone into account) in 19 transgender males treated with GnRH analogs from a mean age of 15.0 years (standard deviation = 2.0 years) for a median duration of 1.5 years (0.3 to 5.2 years) and in 15 transgender females treated from 14.9 (± 1.9) years for 1.3 years (0.5 to 3.8 years), although not all changes were statistically significant (94). There was incomplete catch-up at age 22 years after sex hormone treatment from age 16.6 (± 1.4)

years for a median duration of 5.8 years (3.0 to 8.0 years) in transgender females and from age 16.4 (± 2.3) years for 5.4 years (2.8 to 7.8 years) in transgender males. Little is known about more prolonged use of GnRH analogs. Researchers reported normal BMD *z* scores at age 35 years in one individual who used GnRH analogs from age 13.7 years until age 18.6 years before initiating sex hormone treatment (65).

Additional data are available from individuals with late puberty or GnRH analog treatment of other indications. Some studies reported that men with constitutionally delayed puberty have decreased BMD in adulthood (95). However, other studies reported that these men have normal BMD (96, 97). Treating adults with GnRH analogs results in a decrease of BMD (98). In children with central precocious puberty, treatment with GnRH analogs has been found to result in a decrease of BMD during treatment by some (99) but not others (100). Studies have reported normal BMD after discontinuing therapy (69, 72, 73, 101, 102). In adolescents treated with growth hormone who are small for gestational age and have normal pubertal timing, 2-year GnRH analog treatments did not adversely affect BMD (103). Calcium supplementation may be beneficial in optimizing bone health in GnRH analog-treated individuals (104). There are no studies of vitamin D supplementation in this context, but clinicians should offer supplements to vitamin D-deficient adolescents. Physical activity, especially during growth, is important for bone mass in healthy individuals (103) and is therefore likely to be beneficial for bone health in GnRH analog-treated subjects.

GnRH analogs did not induce a change in body mass index standard deviation score in GD/gender-incongruent adolescents (94) but caused an increase in fat mass and decrease in lean body mass percentage (92). Studies in girls treated for precocious puberty also reported a stable body mass index standard deviation score during treatment (72) and body mass index and body composition comparable to controls after treatment (73).

Arterial hypertension has been reported as an adverse effect in a few girls treated with GnRH analogs for precocious/early puberty (105, 106). Blood pressure monitoring before and during treatment is recommended.

Individuals may also experience hot flashes, fatigue, and mood alterations as a consequence of pubertal suppression. There is no consensus on treatment of these side effects in this context.

It is recommended that any use of pubertal blockers (and subsequent use of sex hormones, as detailed below) include a discussion about implications for fertility (see recommendation 1.3). Transgender adolescents may

want to preserve fertility, which may be otherwise compromised if puberty is suppressed at an early stage and the individual completes phenotypic transition with the use of sex hormones.

Limited data are available regarding the effects of GnRH analogs on brain development. A single cross-sectional study demonstrated no compromise of executive function (107), but animal data suggest there may be an effect of GnRH analogs on cognitive function (108).

Values and preferences

Our recommendation of GnRH analogs places a higher value on the superior efficacy, safety, and reversibility of the pubertal hormone suppression achieved (as compared with the alternatives) and a relatively lower value on limiting the cost of therapy. Of the available alternatives, depot and oral progestin preparations are effective. Experience with this treatment dates back prior to the emergence of GnRH analogs for treating precocious puberty in papers from the 1960s and early 1970s (109–112). These compounds are usually safe, but some side effects have been reported (113–115). Only two recent studies involved transgender youth (116, 117). One of these studies described the use of oral lynestrenol monotherapy followed by the addition of testosterone treatment in transgender boys who were at Tanner stage B4 or further at the start of treatment (117). They found lynestrenol safe, but gonadotropins were not fully suppressed. The study reported metrorrhagia in approximately half of the individuals, mainly in the first 6 months. Acne, headache, hot flashes, and fatigue were other frequent side effects. Another progestin that has been studied in the United States is medroxyprogesterone. This agent is not as effective as GnRH analogs in lowering endogenous sex hormones either and may be associated with other side effects (116). Progestin preparations may be an acceptable treatment for persons without access to GnRH analogs or with a needle phobia. If GnRH analog treatment is not available (insurance denial, prohibitive cost, or other reasons), postpubertal, transgender female adolescents may be treated with an antiandrogen that directly suppresses androgen synthesis or action (see adult section).

Remarks

Measurements of gonadotropin and sex steroid levels give precise information about gonadal axis suppression, although there is insufficient evidence for any specific short-term monitoring scheme in children treated with GnRH analogs (88). If the gonadal axis is not completely suppressed—as evidenced by (for example) menses, erections, or progressive hair growth—the interval of GnRH analog treatment can be shortened or the dose increased. During treatment, adolescents should be monitored for negative effects of delaying puberty, including a halted growth spurt and impaired bone mineral accretion. Table 7 illustrates a suggested clinical protocol.

Anthropometric measurements and X-rays of the left hand to monitor bone age are informative for evaluating growth. To assess BMD, clinicians can perform dual-energy X-ray absorptiometry scans.

- 2.4. In adolescents who request sex hormone treatment (given this is a partly irreversible treatment), we recommend initiating treatment using a gradually increasing dose schedule (see Table 8) after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/ gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years (Table 5). (1 ⊕⊕○○)
- 2.5. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents with GD/ gender incongruence, even though there are minimal published studies of gender-affirming hormone treatments administered before age 13.5 to 14 years. As with the care of adolescents ≥16 years of age, we recommend that an expert multidisciplinary team of medical and MHPs manage this treatment. (1 ⊕○○○)
- 2.6. We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment (Table 9). (2 ⊕⊕○○)

Table 7. Baseline and Follow-Up Protocol During Suppression of Puberty

Every 3–6 mo
Anthropometry: height, weight, sitting height, blood pressure, Tanner stages
Every 6–12 mo
Laboratory: LH, FSH, E2/T, 25OH vitamin D
Every 1–2 y
Bone density using DXA
Bone age on X-ray of the left hand (if clinically indicated)

Adapted from Hembree *et al.* (118).

Abbreviations: DXA, dual-energy X-ray absorptiometry; E2, estradiol; FSH, follicle stimulating hormone; LH, luteinizing hormone; T, testosterone;

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Table 8. Protocol Induction of Puberty

Induction of female puberty with oral 17β -estradiol, increasing the dose every 6 mo:

5 $\mu\text{g/kg/d}$

10 $\mu\text{g/kg/d}$

15 $\mu\text{g/kg/d}$

20 $\mu\text{g/kg/d}$

Adult dose = 2–6 mg/d

In postpubertal transgender female adolescents, the dose of 17β -estradiol can be increased more rapidly:

1 mg/d for 6 mo

2 mg/d

Induction of female puberty with transdermal 17β -estradiol, increasing the dose every 6 mo (new patch is placed every 3.5 d):

6.25–12.5 $\mu\text{g/24 h}$ (cut 25- μg patch into quarters, then halves)

25 $\mu\text{g/24 h}$

37.5 $\mu\text{g/24 h}$

Adult dose = 50–200 $\mu\text{g/24 h}$

For alternatives once at adult dose, see Table 11.

Adjust maintenance dose to mimic physiological estradiol levels (see Table 15).

Induction of male puberty with testosterone esters increasing the dose every 6 mo (IM or SC):

25 $\text{mg/m}^2/2 \text{ wk}$ (or alternatively, half this dose weekly, or double the dose every 4 wk)

50 $\text{mg/m}^2/2 \text{ wk}$

75 $\text{mg/m}^2/2 \text{ wk}$

100 $\text{mg/m}^2/2 \text{ wk}$

Adult dose = 100–200 mg every 2 wk

In postpubertal transgender male adolescents the dose of testosterone esters can be increased more rapidly:

75 mg/2 wk for 6 mo

125 mg/2 wk

For alternatives once at adult dose, see Table 11.

Adjust maintenance dose to mimic physiological testosterone levels (see Table 14).

Adapted from Hembree et al. (118).

Abbreviations: IM, intramuscularly; SC, subcutaneously.

Evidence

Adolescents develop competence in decision making at their own pace. Ideally, the supervising medical professionals should individually assess this competence, although no objective tools to make such an assessment are currently available.

Many adolescents have achieved a reasonable level of competence by age 15 to 16 years (119), and in many countries 16-year-olds are legally competent with regard to medical decision making (120). However, others believe that although some capacities are generally achieved before age 16 years, other abilities (such as good risk

assessment) do not develop until well after 18 years (121). They suggest that health care procedures should be divided along a matrix of relative risk, so that younger adolescents can be allowed to decide about low-risk procedures, such as most diagnostic tests and common therapies, but not about high-risk procedures, such as most surgical procedures (121).

Currently available data from transgender adolescents support treatment with sex hormones starting at age 16 years (63, 122). However, some patients may incur potential risks by waiting until age 16 years. These include the potential risk to bone health if puberty is suppressed

Table 9. Baseline and Follow-up Protocol During Induction of Puberty

Every 3–6 mo

•Anthropometry: height, weight, sitting height, blood pressure, Tanner stages

Every 6–12 mo

•In transgender males: hemoglobin/hematocrit, lipids, testosterone, 25OH vitamin D

•In transgender females: prolactin, estradiol, 25OH vitamin D

Every 1–2 y

•BMD using DXA

•Bone age on X-ray of the left hand (if clinically indicated)

BMD should be monitored into adulthood (until the age of 25–30 y or until peak bone mass has been reached).

For recommendations on monitoring once pubertal induction has been completed, see Tables 14 and 15.

Adapted from Hembree et al. (118).

Abbreviation: DXA, dual-energy X-ray absorptiometry.

for 6 to 7 years before initiating sex hormones (*e.g.*, if someone reached Tanner stage 2 at age 9-10 years old). Additionally, there may be concerns about inappropriate height and potential harm to mental health (emotional and social isolation) if initiation of secondary sex characteristics must wait until the person has reached 16 years of age. However, only minimal data supporting earlier use of gender-affirming hormones in transgender adolescents currently exist (63). Clearly, long-term studies are needed to determine the optimal age of sex hormone treatment in GD/gender-incongruent adolescents.

The MHP who has followed the adolescent during GnRH analog treatment plays an essential role in assessing whether the adolescent is eligible to start sex hormone therapy and capable of consenting to this treatment (Table 5). Support of the family/environment is essential. Prior to the start of sex hormones, clinicians should discuss the implications for fertility (see recommendation 1.5). Throughout pubertal induction, an MHP and a pediatric endocrinologist (or other clinician competent in the evaluation and induction of pubertal development) should monitor the adolescent. In addition to monitoring therapy, it is also important to pay attention to general adolescent health issues, including healthy life style choices, such as not smoking, contraception, and appropriate vaccinations (*e.g.*, human papillomavirus).

For the induction of puberty, clinicians can use a similar dose scheme for hypogonadal adolescents with GD/gender incongruence as they use in other individuals with hypogonadism, carefully monitoring for desired and undesired effects (Table 8). In transgender female adolescents, transdermal 17 β -estradiol may be an alternative for oral 17 β -estradiol. It is increasingly used for pubertal induction in hypogonadal females. However, the absence of low-dose estrogen patches may be a problem. As a result, individuals may need to cut patches to size themselves to achieve appropriate dosing (123). In transgender male adolescents, clinicians can give testosterone injections intramuscularly or subcutaneously (124, 125).

When puberty is initiated with a gradually increasing schedule of sex steroid doses, the initial levels will not be high enough to suppress endogenous sex steroid secretion. Gonadotropin secretion and endogenous production of testosterone may resume and interfere with the effectiveness of estrogen treatment, in transgender female adolescents (126, 127). Therefore, continuation of GnRH analog treatment is advised until gonadectomy. Given that GD/gender-incongruent adolescents may opt not to have gonadectomy, long-term studies are necessary to examine the potential risks of prolonged GnRH analog treatment. Alternatively, in transgender male adolescents, GnRH analog treatment can be discontinued once an

adult dose of testosterone has been reached and the individual is well virilized. If uterine bleeding occurs, a progestin can be added. However, the combined use of a GnRH analog (for ovarian suppression) and testosterone may enable phenotypic transition with a lower dose of testosterone in comparison with testosterone alone. If there is a wish or need to discontinue GnRH analog treatment in transgender female adolescents, they may be treated with an antiandrogen that directly suppresses androgen synthesis or action (see section 3.0 "Hormonal Therapy for Transgender Adults").

Values and preferences

The recommendation to initiate pubertal induction only when the individual has sufficient mental capacity (roughly age 16 years) to give informed consent for this partly irreversible treatment places a higher value on the ability of the adolescent to fully understand and oversee the partially irreversible consequences of sex hormone treatment and to give informed consent. It places a lower value on the possible negative effects of delayed puberty. We may not currently have the means to weigh adequately the potential benefits of waiting until around age 16 years to initiate sex hormones vs the potential risks/harm to BMD and the sense of social isolation from having the timing of puberty be so out of sync with peers (128).

Remarks

Before starting sex hormone treatment, effects on fertility and options for fertility preservation should be discussed. Adult height may be a concern in transgender adolescents. In a transgender female adolescent, clinicians may consider higher doses of estrogen or a more rapid tempo of dose escalation during pubertal induction. There are no established treatments yet to augment adult height in a transgender male adolescent with open epiphyses during pubertal induction. It is not uncommon for transgender adolescents to present for clinical services after having completed or nearly completed puberty. In such cases, induction of puberty with sex hormones can be done more rapidly (see Table 8). Additionally, an adult dose of testosterone in transgender male adolescents may suffice to suppress the gonadal axis without the need to use a separate agent. At the appropriate time, the multidisciplinary team should adequately prepare the adolescent for transition to adult care.

3.0 Hormonal Therapy for Transgender Adults

The two major goals of hormonal therapy are (1) to reduce endogenous sex hormone levels, and thus reduce

the secondary sex characteristics of the individual's designated gender, and (2) to replace endogenous sex hormone levels consistent with the individual's gender identity by using the principles of hormone replacement treatment of hypogonadal patients. The timing of these two goals and the age at which to begin treatment with the sex hormones of the chosen gender is codetermined in collaboration with both the person pursuing transition and the health care providers. The treatment team should include a medical provider knowledgeable in transgender hormone therapy, an MHP knowledgeable in GD/gender incongruence and the mental health concerns of transition, and a primary care provider able to provide care appropriate for transgender individuals. The physical changes induced by this sex hormone transition are usually accompanied by an improvement in mental well-being (129, 130).

- 3.1. We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and the criteria for the endocrine phase of gender transition before beginning treatment. (1 ⊕⊕⊕⊕)
- 3.2. We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment (Table 10). (1 ⊕⊕⊕⊕)
- 3.3. We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender. (2 ⊕⊕⊕⊕)

Evidence

It is the responsibility of the treating clinician to confirm that the person fulfills criteria for treatment. The treating clinician should become familiar with the terms and criteria presented in Tables 1–5 and take a thorough history from the patient in collaboration with the other members of the treatment team. The treating clinician must ensure that the desire for transition is appropriate; the consequences, risks, and benefits of treatment are well understood; and the desire for transition persists. They also need to discuss fertility preservation options (see recommendation 1.3) (67, 68).

Transgender males

Clinical studies have demonstrated the efficacy of several different androgen preparations to induce masculinization in transgender males (Appendix A) (113, 114, 131–134). Regimens to change secondary sex characteristics follow the general principle of hormone replacement treatment of male hypogonadism (135). Clinicians can use either parenteral or transdermal preparations to achieve testosterone values in the normal male range (this is dependent on the specific assay, but is typically 320 to 1000 ng/dL) (Table 11) (136). Sustained supraphysiologic levels of testosterone increase the risk of adverse reactions (see section 4.0 “Adverse Outcome Prevention and Long-Term Care”) and should be avoided.

Similar to androgen therapy in hypogonadal men, testosterone treatment in transgender males results in increased muscle mass and decreased fat mass, increased facial hair and acne, male pattern baldness in those genetically predisposed, and increased sexual desire (137).

Table 10. Medical Risks Associated With Sex Hormone Therapy

Transgender female: estrogen

Very high risk of adverse outcomes:

- Thromboembolic disease

Moderate risk of adverse outcomes:

- Macroprolactinoma
- Breast cancer
- Coronary artery disease
- Cerebrovascular disease
- Cholelithiasis
- Hypertriglyceridemia

Transgender male: testosterone

Very high risk of adverse outcomes:

- Erythrocytosis (hematocrit > 50%)

Moderate risk of adverse outcomes:

- Severe liver dysfunction (transaminases > threefold upper limit of normal)
- Coronary artery disease
- Cerebrovascular disease
- Hypertension
- Breast or uterine cancer

Table 11. Hormone Regimens in Transgender Persons

Transgender females ^a	
Estrogen	
Oral	2.0–6.0 mg/d
Estradiol	
Transdermal	
Estradiol transdermal patch	0.025–0.2 mg/d
(New patch placed every 3–5 d)	
Parenteral	
Estradiol valerate or cypionate	5–30 mg IM every 2 wk 2–10 mg IM every week
Anti-androgens	
Spironolactone	100–300 mg/d
Cyproterone acetate ^b	25–50 mg/d
GnRH agonist	3.75 mg SQ (SC) monthly 11.25 mg SQ (SC) 3-monthly
Transgender males	
Testosterone	
Parenteral testosterone	
Testosterone enanthate or cypionate	100–200 mg SQ (IM) every 2 wk or SQ (SC) 50% per week
Testosterone undecanoate ^c	1000 mg every 12 wk
Transdermal testosterone	
Testosterone gel 1.6% ^d	50–100 mg/d
Testosterone transdermal patch	2.5–7.5 mg/d

Abbreviations: IM, intramuscularly; SQ, sequentially; SC, subcutaneously.

^aEstrogens used with or without antiandrogens or GnRH agonist.

^bNot available in the United States.

^cOne thousand milligrams initially followed by an injection at 6 wk then at 12-wk intervals.

^dAvoid cutaneous transfer to other individuals.

In transgender males, testosterone will result in clitoromegaly, temporary or permanent decreased fertility, deepening of the voice, cessation of menses (usually), and a significant increase in body hair, particularly on the face, chest, and abdomen. Cessation of menses may occur within a few months with testosterone treatment alone, although high doses of testosterone may be required. If uterine bleeding continues, clinicians may consider the addition of a progestational agent or endometrial ablation (138). Clinicians may also administer GnRH analogs or depot medroxyprogesterone to stop menses prior to testosterone treatment.

Transgender females

The hormone regimen for transgender females is more complex than the transgender male regimen (Appendix B). Treatment with physiologic doses of estrogen alone is insufficient to suppress testosterone levels into the normal range for females (139). Most published clinical studies report the need for adjunctive therapy to achieve testosterone levels in the female range (21, 113, 114, 132–134, 139, 140).

Multiple adjunctive medications are available, such as progestins with antiandrogen activity and GnRH agonists (141). Spironolactone works by directly blocking androgens during their interaction with the androgen

receptor (114, 133, 142). It may also have estrogenic activity (143). Cyproterone acetate, a progestational compound with antiandrogenic properties (113, 132, 144), is widely used in Europe. 5 α -Reductase inhibitors do not reduce testosterone levels and have adverse effects (145).

Dittrich *et al.* (141) reported that monthly doses of the GnRH agonist goserelin acetate in combination with estrogen were effective in reducing testosterone levels with a low incidence of adverse reactions in 60 transgender females. Leuprolide and transdermal estrogen were as effective as cyproterone and transdermal estrogen in a comparative retrospective study (146).

Patients can take estrogen as oral conjugated estrogens, oral 17 β -estradiol, or transdermal 17 β -estradiol. Among estrogen options, the increased risk of thromboembolic events associated with estrogens in general seems most concerning with ethinyl estradiol specifically (134, 140, 141), which is why we specifically suggest that it not be used in any transgender treatment plan. Data distinguishing among other estrogen options are less well established although there is some thought that oral routes of administration are more thrombogenic due to the “first pass effect” than are transdermal and parenteral routes, and that the risk of thromboembolic events is dose-dependent. Injectable estrogen and sublingual

estrogen may benefit from avoiding the first pass effect, but they can result in more rapid peaks with greater overall periodicity and thus are more difficult to monitor (147, 148). However, there are no data demonstrating that increased periodicity is harmful otherwise.

Clinicians can use serum estradiol levels to monitor oral, transdermal, and intramuscular estradiol. Blood tests cannot monitor conjugated estrogens or synthetic estrogen use. Clinicians should measure serum estradiol and serum testosterone and maintain them at the level for premenopausal females (100 to 200 pg/mL and <50 ng/dL, respectively). The transdermal preparations and injectable estradiol cypionate or valerate preparations may confer an advantage in older transgender females who may be at higher risk for thromboembolic disease (149).

Values

Our recommendation to maintain levels of gender-affirming hormones in the normal adult range places a high value on the avoidance of the long-term complications of pharmacologic doses. Those patients receiving endocrine treatment who have relative contraindications to hormones should have an in-depth discussion with their physician to balance the risks and benefits of therapy.

Remarks

Clinicians should inform all endocrine-treated individuals of all risks and benefits of gender-affirming hormones prior to initiating therapy. Clinicians should strongly encourage tobacco use cessation in transgender females to avoid increased risk of VTE and cardiovascular complications. We strongly discourage the unsupervised use of hormone therapy (150).

Not all individuals with GD/gender incongruence seek treatment as described (*e.g.*, male-to-eunuchs and individuals seeking partial transition). Tailoring current protocols to the individual may be done within the context of accepted safety guidelines using a multidisciplinary approach including mental health. No evidence-based protocols are available for these groups (151). We need prospective studies to better understand treatment options for these persons.

- 3.4. We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment. (2 ⊕○○○○)

Evidence

Transgender males

Physical changes that are expected to occur during the first 1 to 6 months of testosterone therapy include

cessation of menses, increased sexual desire, increased facial and body hair, increased oiliness of skin, increased muscle, and redistribution of fat mass. Changes that occur within the first year of testosterone therapy include deepening of the voice (152, 153), clitoromegaly, and male pattern hair loss (in some cases) (114, 144, 154, 155) (Table 12).

Transgender females

Physical changes that may occur in transgender females in the first 3 to 12 months of estrogen and anti-androgen therapy include decreased sexual desire, decreased spontaneous erections, decreased facial and body hair (usually mild), decreased oiliness of skin, increased breast tissue growth, and redistribution of fat mass (114, 139, 149, 154, 155, 161) (Table 13). Breast development is generally maximal at 2 years after initiating hormones (114, 139, 149, 155). Over a long period of time, the prostate gland and testicles will undergo atrophy.

Although the time course of breast development in transgender females has been studied (150), precise information about other changes induced by sex hormones is lacking (141). There is a great deal of variability among individuals, as evidenced during pubertal development. We all know that a major concern for transgender females is breast development. If we work with estrogens, the result will be often not what the transgender female expects.

Alternatively, there are transgender females who report an anecdotal improved breast development, mood, or sexual desire with the use of progestogens. However, there have been no well-designed studies of the role of progestogens in feminizing hormone regimens, so the question is still open.

Our knowledge concerning the natural history and effects of different cross-sex hormone therapies on breast

Table 12. Masculinizing Effects in Transgender Males

Effect	Onset	Maximum
Skin oiliness/acne	1–6 mo	1–2 y
Facial/body hair growth	6–12 mo	4–5 y
Scalp hair loss	6–12 mo	— ^a
Increased muscle mass/strength	6–12 mo	2–5 y
Fat redistribution	1–6 mo	2–5 y
Cessation of menses	1–6 mo	— ^b
Clitoral enlargement	1–6 mo	1–2 y
Vaginal atrophy	1–6 mo	1–2 y
Deepening of voice	6–12 mo	1–2 y

Estimates represent clinical observations: Toorians *et al.* (149), Assche-man *et al.* (156), Gooren *et al.* (157), Wierckx *et al.* (158).

^aPrevention and treatment as recommended for biological men.

^bMenorrhagia requires diagnosis and treatment by a gynecologist.

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Table 13. Feminizing Effects in Transgender Females

Effect	Onset	Maximum
Redistribution of body fat	3–6 mo	2–3 y
Decrease in muscle mass and strength	3–6 mo	1–2 y
Softening of skin/decreased oiliness	3–6 mo	Unknown
Decreased sexual desire	1–3 mo	3–6 mo
Decreased spontaneous erections	1–3 mo	3–6 mo
Male sexual dysfunction	Variable	Variable
Breast growth	3–6 mo	2–3 y
Decreased testicular volume	3–6 mo	2–3 y
Decreased sperm production	Unknown	>3 y
Decreased terminal hair growth	6–12 mo	>3 y ^a
Scalp hair	Variable	— ^b
Voice changes	None	— ^c

Estimates represent clinical observations: Toorians *et al.* (149), Asscheman *et al.* (156), Gooren *et al.* (157).

^aComplete removal of male sexual hair requires electrolysis or laser treatment or both.

^bFamilial scalp hair loss may occur if estrogens are stopped.

^cTreatment by speech pathologists for voice training is most effective.

development in transgender females is extremely sparse and based on the low quality of evidence. Current evidence does not indicate that progestogens enhance breast development in transgender females, nor does evidence prove the absence of such an effect. This prevents us from drawing any firm conclusion at this moment and demonstrates the need for further research to clarify these important clinical questions (162).

Values and preferences

Transgender persons have very high expectations regarding the physical changes of hormone treatment and are aware that body changes can be enhanced by surgical procedures (*e.g.*, breast, face, and body habitus). Clear expectations for the extent and timing of sex hormone-induced changes may prevent the potential harm and expense of unnecessary procedures.

4.0 Adverse Outcome Prevention and Long-Term Care

Hormone therapy for transgender males and females confers many of the same risks associated with sex hormone replacement therapy in nontransgender persons. The risks arise from and are worsened by inadvertent or intentional use of supraphysiologic doses of sex hormones, as well as use of inadequate doses of sex hormones to maintain normal physiology (131, 139).

- 4.1. We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every

3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly. (2 ⊕⊕○○)

Evidence

Pretreatment screening and appropriate regular medical monitoring are recommended for both transgender males and females during the endocrine transition and periodically thereafter (26, 155). Clinicians should monitor weight and blood pressure, conduct physical exams, and assess routine health questions, such as tobacco use, symptoms of depression, and risk of adverse events such as deep vein thrombosis/pulmonary embolism and other adverse effects of sex steroids.

Transgender males

Table 14 contains a standard monitoring plan for transgender males on testosterone therapy (154, 159). Key issues include maintaining testosterone levels in the physiologic normal male range and avoiding adverse events resulting from excess testosterone therapy, particularly erythrocytosis, sleep apnea, hypertension, excessive weight gain, salt retention, lipid changes, and excessive or cystic acne (135).

Because oral 17-alkylated testosterone is not recommended, serious hepatic toxicity is not anticipated with parenteral or transdermal testosterone use (163, 164). Past concerns regarding liver toxicity with testosterone have been alleviated with subsequent reports that indicate the risk of serious liver disease is minimal (144, 165, 166).

Transgender females

Table 15 contains a standard monitoring plan for transgender females on estrogens, gonadotropin suppression, or antiandrogens (160). Key issues include avoiding supraphysiologic doses or blood levels of estrogen that may lead to increased risk for thromboembolic disease, liver dysfunction, and hypertension. Clinicians should monitor serum estradiol levels using laboratories participating in external quality control, as measurements of estradiol in blood can be very challenging (167).

VTE may be a serious complication. A study reported a 20-fold increase in venous thromboembolic disease in a large cohort of Dutch transgender subjects (161). This increase may have been associated with the use of the synthetic estrogen, ethinyl estradiol (149). The incidence decreased when clinicians stopped administering ethinyl estradiol (161). Thus, the use of synthetic estrogens and conjugated estrogens is undesirable because of the inability to regulate doses by measuring serum levels and the risk of thromboembolic disease. In a German gender clinic, deep vein thrombosis occurred in 1 of 60 of transgender females treated with a GnRH analog and oral

Table 14. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Male

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of virilization and for development of adverse reactions.
2. Measure serum testosterone every 3 mo until levels are in the normal physiologic male range:^a
 - a. For testosterone enanthate/cypionate injections, the testosterone level should be measured midway between injections. The target level is 400–700 ng/dL to 400 ng/dL. Alternatively, measure peak and trough levels to ensure levels remain in the normal male range.
 - b. For parenteral testosterone undecanoate, testosterone should be measured just before the following injection. If the level is <400 ng/dL, adjust dosing interval.
 - c. For transdermal testosterone, the testosterone level can be measured no sooner than after 1 wk of daily application (at least 2 h after application).
3. Measure hematocrit or hemoglobin at baseline and every 3 mo for the first year and then one to two times a year. Monitor weight, blood pressure, and lipids at regular intervals.
4. Screening for osteoporosis should be conducted in those who stop testosterone treatment, are not compliant with hormone therapy, or who develop risks for bone loss.
5. If cervical tissue is present, monitoring as recommended by the American College of Obstetricians and Gynecologists.
6. Ovariectomy can be considered after completion of hormone transition.
7. Conduct sub- and periareolar annual breast examinations if mastectomy performed. If mastectomy is not performed, then consider mammograms as recommended by the American Cancer Society.

^aAdapted from Lapauw *et al.* (154) and Ott *et al.* (159).

estradiol (141). The patient who developed a deep vein thrombosis was found to have a homozygous C677 T mutation in the methylenetetrahydrofolate reductase gene. In an Austrian gender clinic, administering gender-affirming hormones to 162 transgender females and 89 transgender males was not associated with VTE, despite an 8.0% and 5.6% incidence of thrombophilia (159). A more recent multinational study reported only 10 cases of VTE from a cohort of 1073 subjects (168). Thrombophilia screening of transgender persons initiating hormone treatment should be restricted to those with a personal or family history of VTE (159). Monitoring D-dimer levels during treatment is not recommended (169).

- 4.2. We suggest periodically monitoring prolactin levels in transgender females treated with estrogens. (2 ⊕⊕○○)

Evidence

Estrogen therapy can increase the growth of pituitary lactotroph cells. There have been several reports of prolactinomas occurring after long-term, high-dose

estrogen therapy (170–173). Up to 20% of transgender females treated with estrogens may have elevations in prolactin levels associated with enlargement of the pituitary gland (156). In most cases, the serum prolactin levels will return to the normal range with a reduction or discontinuation of the estrogen therapy or discontinuation of cyproterone acetate (157, 174, 175).

The onset and time course of hyperprolactinemia during estrogen treatment are not known. Clinicians should measure prolactin levels at baseline and then at least annually during the transition period and every 2 years thereafter. Given that only a few case studies reported prolactinomas, and prolactinomas were not reported in large cohorts of estrogen-treated persons, the risk is likely to be very low. Because the major presenting findings of microprolactinomas (hypogonadism and sometimes gynecomastia) are not apparent in transgender females, clinicians may perform radiologic examinations of the pituitary in those patients whose prolactin levels persistently increase despite stable or reduced estrogen levels. Some transgender individuals receive psychotropic medications that can increase prolactin levels (174).

Table 15. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Female

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of feminization and for development of adverse reactions.
2. Measure serum testosterone and estradiol every 3 mo.
 - a. Serum testosterone levels should be <50 ng/dL.
 - b. Serum estradiol should not exceed the peak physiologic range: 100–200 pg/mL.
3. For individuals on spironolactone, serum electrolytes, particularly potassium, should be monitored every 3 mo in the first year and annually thereafter.
4. Routine cancer screening is recommended, as in nontransgender individuals (all tissues present).
5. Consider BMD testing at baseline (160). In individuals at low risk, screening for osteoporosis should be conducted at age 60 years or in those who are not compliant with hormone therapy.

This table presents strong recommendations and does not include lower level recommendations.

- 4.3. We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors using fasting lipid profiles, diabetes screening, and/or other diagnostic tools. (2 ⊕⊕○○)

Evidence

Transgender males

Administering testosterone to transgender males results in a more atherogenic lipid profile with lowered high-density lipoprotein cholesterol and higher triglyceride and low-density lipoprotein cholesterol values (176–179). Studies of the effect of testosterone on insulin sensitivity have mixed results (178, 180). A randomized, open-label uncontrolled safety study of transgender males treated with testosterone undecanoate demonstrated no insulin resistance after 1 year (181, 182). Numerous studies have demonstrated the effects of sex hormone treatment on the cardiovascular system (160, 179, 183, 184). Long-term studies from The Netherlands found no increased risk for cardiovascular mortality (161). Likewise, a meta-analysis of 19 randomized trials in nontransgender males on testosterone replacement showed no increased incidence of cardiovascular events (185). A systematic review of the literature found that data were insufficient (due to very low-quality evidence) to allow a meaningful assessment of patient-important outcomes, such as death, stroke, myocardial infarction, or VTE in transgender males (176). Future research is needed to ascertain the potential harm of hormonal therapies (176). Clinicians should manage cardiovascular risk factors as they emerge according to established guidelines (186).

Transgender females

A prospective study of transgender females found favorable changes in lipid parameters with increased high-density lipoprotein and decreased low-density lipoprotein concentrations (178). However, increased weight, blood pressure, and markers of insulin resistance attenuated these favorable lipid changes. In a meta-analysis, only serum triglycerides were higher at ≥24 months without changes in other parameters (187). The largest cohort of transgender females (mean age 41 years, followed for a mean of 10 years) showed no increase in cardiovascular mortality despite a 32% rate of tobacco use (161).

Thus, there is limited evidence to determine whether estrogen is protective or detrimental on lipid and glucose metabolism in transgender females (176). With aging, there is usually an increase of body weight. Therefore, as with nontransgender individuals, clinicians should

monitor and manage glucose and lipid metabolism and blood pressure regularly according to established guidelines (186).

- 4.4. We recommend that clinicians obtain BMD measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. (1 ⊕⊕○○)

Evidence

Transgender males

Baseline bone mineral measurements in transgender males are generally in the expected range for their pre-treatment gender (188). However, adequate dosing of testosterone is important to maintain bone mass in transgender males (189, 190). In one study (190), serum LH levels were inversely related to BMD, suggesting that low levels of sex hormones were associated with bone loss. Thus, LH levels in the normal range may serve as an indicator of the adequacy of sex steroid administration to preserve bone mass. The protective effect of testosterone may be mediated by peripheral conversion to estradiol, both systemically and locally in the bone.

Transgender females

A baseline study of BMD reported T scores less than −2.5 in 16% of transgender females (191). In aging males, studies suggest that serum estradiol more positively correlates with BMD than does testosterone (192, 193) and is more important for peak bone mass (194). Estrogen preserves BMD in transgender females who continue on estrogen and antiandrogen therapies (188, 190, 191, 195, 196).

Fracture data in transgender males and females are not available. Transgender persons who have undergone gonadectomy may choose not to continue consistent sex steroid treatment after hormonal and surgical sex reassignment, thereby becoming at risk for bone loss. There have been no studies to determine whether clinicians should use the sex assigned at birth or affirmed gender for assessing osteoporosis (*e.g.*, when using the FRAX tool). Although some researchers use the sex assigned at birth (with the assumption that bone mass has usually peaked for transgender people who initiate hormones in early adulthood), this should be assessed on a case-by-case basis until there are more data available. This assumption will be further complicated by the increasing prevalence of transgender people who undergo hormonal transition at a pubertal age or soon after puberty. Sex for comparison within risk assessment tools may be based on the age at which hormones were initiated and the length of exposure to hormones. In some cases, it may be

reasonable to assess risk using both the male and female calculators and using an intermediate value. Because all subjects underwent normal pubertal development, with known effects on bone size, reference values for birth sex were used for all participants (154).

- 4.5. We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for those designated female at birth. (2 ⊕⊕⊕⊕)
- 4.6. We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer. (2 ⊕⊕⊕⊕)

Evidence

Studies have reported a few cases of breast cancer in transgender females (197–200). A Dutch study of 1800 transgender females followed for a mean of 15 years (range of 1–30 years) found one case of breast cancer. The Women's Health Initiative study reported that females taking conjugated equine estrogen without progesterone for 7 years did not have an increased risk of breast cancer as compared with females taking placebo (137).

In transgender males, a large retrospective study conducted at the U.S. Veterans Affairs medical health system identified seven breast cancers (194). The authors reported that this was not above the expected rate of breast cancers in cisgender females in this cohort. Furthermore, they did report one breast cancer that developed in a transgender male patient after mastectomy, supporting the fact that breast cancer can occur even after mastectomy. Indeed, there have been case reports of breast cancer developing in subareolar tissue in transgender males, which occurred after mastectomy (201, 202).

Women with primary hypogonadism (Turner syndrome) treated with estrogen replacement exhibited a significantly decreased incidence of breast cancer as compared with national standardized incidence ratios (203, 204). These studies suggest that estrogen therapy does not increase the risk of breast cancer in the short term (<20 to 30 years). We need long-term studies to determine the actual risk, as well as the role of screening mammograms. Regular examinations and gynecologic advice should determine monitoring for breast cancer.

Prostate cancer is very rare before the age of 40, especially with androgen deprivation therapy (205). Childhood or pubertal castration results in regression of the prostate and adult castration reverses benign prostate hypertrophy (206). Although van Kesteren *et al.* (207) reported that estrogen therapy does not induce hypertrophy or premalignant changes in the prostates of

transgender females, studies have reported cases of benign prostatic hyperplasia in transgender females treated with estrogens for 20 to 25 years (208, 209). Studies have also reported a few cases of prostate carcinoma in transgender females (210–214).

Transgender females may feel uncomfortable scheduling regular prostate examinations. Gynecologists are not trained to screen for prostate cancer or to monitor prostate growth. Thus, it may be reasonable for transgender females who transitioned after age 20 years to have annual screening digital rectal examinations after age 50 years and prostate-specific antigen tests consistent with U.S. Preventive Services Task Force Guidelines (215).

- 4.7. We advise that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. (Ungraded Good Practice Statement)

Evidence

Although aromatization of testosterone to estradiol in transgender males has been suggested as a risk factor for endometrial cancer (216), no cases have been reported. When transgender males undergo hysterectomy, the uterus is small and there is endometrial atrophy (217, 218). Studies have reported cases of ovarian cancer (219, 220). Although there is limited evidence for increased risk of reproductive tract cancers in transgender males, health care providers should determine the medical necessity of a laparoscopic total hysterectomy as part of a gender-affirming surgery to prevent reproductive tract cancer (221).

Values

Given the discomfort that transgender males experience accessing gynecologic care, our recommendation for the medical necessity of total hysterectomy and oophorectomy places a high value on eliminating the risks of female reproductive tract disease and cancer and a lower value on avoiding the risks of these surgical procedures (related to the surgery and to the potential undesirable health consequences of oophorectomy) and their associated costs.

Remarks

The sexual orientation and type of sexual practices will determine the need and types of gynecologic care required following transition. Additionally, in certain countries, the approval required to change the sex in a birth certificate for transgender males may be dependent on having a complete hysterectomy. Clinicians should help patients research nonmedical administrative criteria and

provide counseling. If individuals decide not to undergo hysterectomy, screening for cervical cancer is the same as all other females.

5.0 Surgery for Sex Reassignment and Gender Confirmation

For many transgender adults, genital gender-affirming surgery may be the necessary step toward achieving their ultimate goal of living successfully in their desired gender role. The type of surgery falls into two main categories: (1) those that directly affect fertility and (2) those that do not. Those that change fertility (previously called sex reassignment surgery) include genital surgery to remove the penis and gonads in the male and removal of the uterus and gonads in the female. The surgeries that effect fertility are often governed by the legal system of the state or country in which they are performed. Other gender-conforming surgeries that do not directly affect fertility are not so tightly governed.

Gender-affirming surgical techniques have improved markedly during the past 10 years. Reconstructive genital surgery that preserves neurologic sensation is now the standard. The satisfaction rate with surgical reassignment of sex is now very high (187). Additionally, the mental health of the individual seems to be improved by participating in a treatment program that defines a pathway of gender-affirming treatment that includes hormones and surgery (130, 144) (Table 16).

Surgery that affects fertility is irreversible. The World Professional Association for Transgender Health Standards of Care (222) emphasizes that the “threshold of 18 should not be seen as an indication in itself for active intervention.” If the social transition has not been satisfactory, if the person is not satisfied with or is ambivalent about the effects of sex hormone treatment, or if the person is ambivalent about surgery then the individual should not be referred for surgery (223, 224).

Gender-affirming genital surgeries for transgender females that affect fertility include gonadectomy, penectomy, and creation of a neovagina (225, 226). Surgeons often invert the skin of the penis to form the wall of the vagina, and several literatures reviews have

reported on outcomes (227). Sometimes there is inadequate tissue to form a full neovagina, so clinicians have revisited using intestine and found it to be successful (87, 228, 229). Some newer vaginoplasty techniques may involve autologous oral epithelial cells (230, 231).

The scrotum becomes the labia majora. Surgeons use reconstructive surgery to fashion the clitoris and its hood, preserving the neurovascular bundle at the tip of the penis as the neurosensory supply to the clitoris. Some surgeons are also creating a sensate pedicled-spot adding a G spot to the neovagina to increase sensation (232). Most recently, plastic surgeons have developed techniques to fashion labia minora. To further complete the feminization, uterine transplants have been proposed and even attempted (233).

Neovaginal prolapse, rectovaginal fistula, delayed healing, vaginal stenosis, and other complications do sometimes occur (234, 235). Clinicians should strongly remind the transgender person to use their dilators to maintain the depth and width of the vagina throughout the postoperative period. Genital sexual responsivity and other aspects of sexual function are usually preserved following genital gender-affirming surgery (236, 237).

Ancillary surgeries for more feminine or masculine appearance are not within the scope of this guideline. Voice therapy by a speech language pathologist is available to transform speech patterns to the affirmed gender (148). Spontaneous voice deepening occurs during testosterone treatment of transgender males (152, 238). No studies have compared the effectiveness of speech therapy, laryngeal surgery, or combined treatment.

Breast surgery is a good example of gender-confirming surgery that does not affect fertility. In all females, breast size exhibits a very broad spectrum. For transgender females to make the best informed decision, clinicians should delay breast augmentation surgery until the patient has completed at least 2 years of estrogen therapy, because the breasts continue to grow during that time (141, 155).

Another major procedure is the removal of facial and masculine-appearing body hair using either electrolysis or

Table 16. Criteria for Gender-Affirming Surgery, Which Affects Fertility

1. Persistent, well-documented gender dysphoria
2. Legal age of majority in the given country
3. Having continuously and responsibly used gender-affirming hormones for 12 mo (if there is no medical contraindication to receiving such therapy)
4. Successful continuous full-time living in the new gender role for 12 mo
5. If significant medical or mental health concerns are present, they must be well controlled
6. Demonstrable knowledge of all practical aspects of surgery (e.g., cost, required lengths of hospitalizations, likely complications, postsurgical rehabilitation)

laser treatments. Other feminizing surgeries, such as that to feminize the face, are now becoming more popular (239–241).

In transgender males, clinicians usually delay gender-affirming genital surgeries until after a few years of androgen therapy. Those surgeries that affect fertility in this group include oophorectomy, vaginectomy, and complete hysterectomy. Surgeons can safely perform them vaginally with laparoscopy. These are sometimes done in conjunction with the creation of a neopenis. The cosmetic appearance of a neopenis is now very good, but the surgery is multistage and very expensive (242, 243). Radial forearm flap seems to be the most satisfactory procedure (228, 244). Other flaps also exist (245). Surgeons can make neopenile erections possible by reinnervation of the flap and subsequent contraction of the muscle, leading to stiffening of the neopenis (246, 247), but results are inconsistent (248). Surgeons can also stiffen the penis by imbedding some mechanical device (*e.g.*, a rod or some inflatable apparatus) (249, 250). Because of these limitations, the creation of a neopenis has often been less than satisfactory. Recently, penis transplants are being proposed (233).

In fact, most transgender males do not have any external genital surgery because of the lack of access, high cost, and significant potential complications. Some choose a metaoidioplasty that brings forward the clitoris, thereby allowing them to void in a standing position without wetting themselves (251, 252). Surgeons can create the scrotum from the labia majora with good cosmetic effect and can implant testicular prostheses (253).

The most important masculinizing surgery for the transgender male is mastectomy, and it does not affect fertility. Breast size only partially regresses with androgen therapy (155). In adults, discussions about mastectomy usually take place after androgen therapy has started. Because some transgender male adolescents present after significant breast development has occurred, they may also consider mastectomy 2 years after they begin androgen therapy and before age 18 years. Clinicians should individualize treatment based on the physical and mental health status of the individual. There are now newer approaches to mastectomy with better outcomes (254, 255). These often involve chest contouring (256). Mastectomy is often necessary for living comfortably in the new gender (256).

- 5.1. We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically

necessary and would benefit the patient's overall health and/or well-being. (1 ⊕⊕○○)

- 5.2. We advise that clinicians approve genital gender-affirming surgery only after completion of at least 1 year of consistent and compliant hormone treatment, unless hormone therapy is not desired or medically contraindicated. (Ungraded Good Practice Statement)
- 5.3. We advise that the clinician responsible for endocrine treatment and the primary care provider ensure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. (Ungraded Good Practice Statement)
- 5.4. We recommend that clinicians refer hormone-treated transgender individuals for genital surgery when: (1) the individual has had a satisfactory social role change, (2) the individual is satisfied about the hormonal effects, and (3) the individual desires definitive surgical changes. (1 ⊕○○○)
- 5.5. We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18 years old or legal age of majority in his or her country. (2 ⊕⊕○○)
- 5.6. We suggest that clinicians determine the timing of breast surgery for transgender males based upon the physical and mental health status of the individual. There is insufficient evidence to recommend a specific age requirement. (2 ⊕○○○)

Evidence

Owing to the lack of controlled studies, incomplete follow-up, and lack of valid assessment measures, evaluating various surgical approaches and techniques is difficult. However, one systematic review including a large numbers of studies reported satisfactory cosmetic and functional results for vaginoplasty/neovagina construction (257). For transgender males, the outcomes are less certain. However, the problems are now better understood (258). Several postoperative studies report significant long-term psychological and psychiatric pathology (259–261). One study showed satisfaction with breasts, genitals, and femininity increased significantly and showed the importance of surgical treatment as a key therapeutic option for transgender females (262). Another analysis demonstrated that, despite the young average age at death following surgery and the relatively larger number of individuals with somatic morbidity, the study does not allow for determination of

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causal relationships between, for example, specific types of hormonal or surgical treatment received and somatic morbidity and mortality (263). Reversal surgery in regretful male-to-female transsexuals after sexual reassignment surgery represents a complex, multistage procedure with satisfactory outcomes. Further insight into the characteristics of persons who regret their decision postoperatively would facilitate better future selection of applicants eligible for sexual reassignment surgery. We need more studies with appropriate controls that examine long-term quality of life, psychosocial outcomes, and psychiatric outcomes to determine the long-term benefits of surgical treatment.

When a transgender individual decides to have gender-affirming surgery, both the hormone prescribing clinician and the MHP must certify that the patient satisfies criteria for gender-affirming surgery (Table 16).

There is some concern that estrogen therapy may cause an increased risk for venous thrombosis during or following surgery (176). For this reason, the surgeon and the hormone-prescribing clinician should collaborate in making a decision about the use of hormones before and following surgery. One study suggests that preoperative factors (such as compliance) are less important for patient satisfaction than are the physical postoperative results (56). However, other studies and clinical experience dictate that individuals who do not follow medical instructions and do not work with their physicians toward a common goal do not achieve treatment goals (264) and experience higher rates of postoperative infections and other complications (265, 266). It is also important that the person requesting surgery feels comfortable with the anatomical changes that have occurred during hormone therapy. Dissatisfaction with social and physical outcomes during the hormone transition may be a contraindication to surgery (223).

An endocrinologist or experienced medical provider should monitor transgender individuals after surgery. Those who undergo gonadectomy will require hormone replacement therapy, surveillance, or both to prevent adverse effects of chronic hormone deficiency.

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Transgender Women in the Female Category of Sport: Perspectives on Testosterone Suppression and Performance Advantage

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Abstract

Males enjoy physical performance advantages over females within competitive sport. The sex-based segregation into male and female sporting categories does not account for transgender persons who experience incongruence between their biological sex and their experienced gender identity. Accordingly, the International Olympic Committee (IOC) determined criteria by which a transgender woman may be eligible to compete in the female category, requiring total serum testosterone levels to be suppressed below 10 nmol/L for at least 12 months prior to and during competition. Whether this regulation removes the male performance advantage has not been scrutinized. Here, we review how differences in biological characteristics between biological males and females affect sporting performance and assess whether evidence exists to support the assumption that testosterone suppression in transgender women removes the male performance advantage and thus delivers fair and safe competition. We report that the performance gap between males and females becomes significant at puberty and often amounts to 10–50% depending on sport. The performance gap is more pronounced in sporting activities relying on muscle mass and explosive strength, particularly in the upper body. Longitudinal studies examining the effects of testosterone suppression on muscle mass and strength in transgender women consistently show very modest changes, where the loss of lean body mass, muscle area and strength typically amounts to approximately 5% after 12 months of treatment. Thus, the muscular advantage enjoyed by transgender women is only minimally reduced when testosterone is suppressed. Sports organizations should consider this evidence when reassessing current policies regarding participation of transgender women in the female category of sport.

Key Points

Given that biological males experience a substantial performance advantage over females in most sports, there is currently a debate whether inclusion of transgender women in the female category of sports would compromise the objective of fair and safe competition.

Here, we report that current evidence shows the biological advantage, most notably in terms of muscle mass and strength, conferred by male puberty and thus enjoyed by most transgender women is only minimally reduced when testosterone is suppressed as per current sporting guidelines for transgender athletes.

This evidence is relevant for policies regarding participation of transgender women in the female category of sport.

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1 Introduction

Sporting performance is strongly influenced by a range of physiological factors, including muscle force and power-producing capacity, anthropometric characteristics, cardiorespiratory capacity and metabolic factors [1, 2]. Many of these physiological factors differ significantly between biological males and females as a result of genetic differences and androgen-directed development of secondary sex characteristics [3, 4]. This confers large sporting performance advantages on biological males over females [5].

When comparing athletes who compete directly against one another, such as elite or comparable levels of school-aged athletes, the physiological advantages conferred by biological sex appear, on assessment of performance data, insurmountable. Further, in sports where contact, collision or combat are important for gameplay, widely different physiological attributes may create safety and athlete welfare concerns, necessitating not only segregation of sport into male and female categories, but also, for example, into weight and age classes. Thus, to ensure that both men and women can enjoy sport in terms of fairness, safety and inclusivity, most sports are divided, in the first instance, into male and female categories.

Segregating sports by biological sex does not account for transgender persons who experience incongruence between their biological sex and their experienced gender identity, and whose legal sex may be different to that recorded at birth [6, 7]. More specifically, transgender women (observed at birth as biologically male but identifying as women) may, before or after cross-hormone treatment, wish to compete in the female category. This has raised concerns about fairness and safety within female competition, and the issue of how to fairly and safely accommodate transgender persons in sport has been subject to much discussion [6–13].

The current International Olympic Committee (IOC) policy [14] on transgender athletes states that “it is necessary to ensure insofar as possible that trans athletes are not excluded from the opportunity to participate in sporting competition”. Yet the policy also states that “the overriding sporting objective is and remains the guarantee of fair competition”. As these goals may be seen as conflicting if male performance advantages are carried through to competition in the female category, the IOC concludes that “restrictions on participation are appropriate to the extent that they are necessary and proportionate to the achievement of that objective”.

Accordingly, the IOC determined criteria by which transgender women may be eligible to compete in the female category. These include a solemn declaration that her gender identity is female and the maintenance of total

serum testosterone levels below 10 nmol/L for at least 12 months prior to competing and during competition [14]. Whilst the scientific basis for this testosterone threshold was not openly communicated by the IOC, it is surmised that the IOC believed this testosterone criterion sufficient to reduce the sporting advantages of biological males over females and deliver fair and safe competition within the female category.

Several studies have examined the effects of testosterone suppression on the changing biology, physiology and performance markers of transgender women. In this review, we aim to assess whether evidence exists to support the assumption that testosterone suppression in transgender women removes these advantages. To achieve this aim, we first review the differences in biological characteristics between biological males and females, and examine how those differences affect sporting performance. We then evaluate the studies that have measured elements of performance and physical capacity following testosterone suppression in untrained transgender women, and discuss the relevance of these findings to the supposition of fairness and safety (i.e. removal of the male performance advantage) as per current sporting guidelines.

2 The Biological Basis for Sporting Performance Advantages in Males

The physical divergence between males and females begins during early embryogenesis, when bipotential gonads are triggered to differentiate into testes or ovaries, the tissues that will produce sperm in males and ova in females, respectively [15]. Gonad differentiation into testes or ovaries determines, via the specific hormone milieu each generates, downstream in utero reproductive anatomy development [16], producing male or female body plans. We note that in rare instances, differences in sex development (DSDs) occur and the typical progression of male or female development is disrupted [17]. The categorisation of such athletes is beyond the scope of this review, and the impact of individual DSDs on sporting performance must be considered on their own merits.

In early childhood, prior to puberty, sporting participation prioritises team play and the development of fundamental motor and social skills, and is sometimes mixed sex. Athletic performance differences between males and females prior to puberty are often considered inconsequential or relatively small [18]. Nonetheless, pre-puberty performance differences are not unequivocally negligible, and could be mediated, to some extent, by genetic factors and/or activation of the hypothalamic–pituitary–gonadal axis during the neonatal period, sometimes referred to as “minipuberty”. For example, some 6500 genes are differentially expressed between males and females [19] with an estimated 3000 sex-specific

differences in skeletal muscle likely to influence composition and function beyond the effects of androgenisation [3], while increased testosterone during minipuberty in males aged 1–6 months may be correlated with higher growth velocity and an “imprinting effect” on BMI and bodyweight [20, 21]. An extensive review of fitness data from over 85,000 Australian children aged 9–17 years old showed that, compared with 9-year-old females, 9-year-old males were faster over short sprints (9.8%) and 1 mile (16.6%), could jump 9.5% further from a standing start (a test of explosive power), could complete 33% more push-ups in 30 s and had 13.8% stronger grip [22]. Male advantage of a similar magnitude was detected in a study of Greek children, where, compared with 6-year-old females, 6-year-old males completed 16.6% more shuttle runs in a given time and could jump 9.7% further from a standing position [23]. In terms of aerobic capacity, 6- to 7-year-old males have been shown to have a higher absolute and relative (to body mass) $\text{VO}_{2\text{max}}$ than 6- to 7-year-old females [24]. Nonetheless, while some biological sex differences, probably genetic in origin, are measurable and affect performance pre-puberty, we consider the effect of androgenizing puberty more influential on performance, and have focused our analysis on musculoskeletal differences hereafter.

Secondary sex characteristics that develop during puberty have evolved under sexual selection pressures to improve reproductive fitness and thus generate anatomical divergence beyond the reproductive system, leading to adult body types that are measurably different between sexes. This phenomenon is known as sex dimorphism. During puberty, testes-derived testosterone levels increase 20-fold in males, but remain low in females, resulting in circulating testosterone concentrations at least 15 times higher in males than in females of any age [4, 25]. Testosterone in males induces changes in muscle mass, strength, anthropometric variables and hemoglobin levels [4], as part of the range of sexually dimorphic characteristics observed in humans.

Broadly, males are bigger and stronger than females. It follows that, within competitive sport, males enjoy significant performance advantages over females, predicated on the superior physical capacity developed during puberty in response to testosterone. Thus, the biological effects of elevated pubertal testosterone are primarily responsible for driving the divergence of athletic performances between males and females [4]. It is acknowledged that this divergence has been compounded historically by a lag in the cultural acceptance of, and financial provision for, females in sport that may have had implications for the rate of improvement in athletic performance in females. Yet, since the 1990s, the difference in performance records between males and females has been relatively stable, suggesting that biological differences created by androgenization explain most of the male advantage, and are insurmountable [5, 26, 27].

Table 1 outlines physical attributes that are major parameters underpinning the male performance advantage [28–38]. Males have: larger and denser muscle mass, and stiffer connective tissue, with associated capacity to exert greater muscular force more rapidly and efficiently; reduced fat mass, and different distribution of body fat and lean muscle mass, which increases power to weight ratios and upper to lower limb strength in sports where this may be a crucial determinant of success; longer and larger skeletal structure, which creates advantages in sports where levers influence force application, where longer limb/digit length is favorable, and where height, mass and proportions are directly responsible for performance capacity; superior cardiovascular and respiratory function, with larger blood and heart volumes, higher hemoglobin concentration, greater cross-sectional area of the trachea and lower oxygen cost of respiration [3, 4, 39, 40]. Of course, different sports select for different physiological characteristics—an advantage in one discipline may be neutral or even a disadvantage in another—but examination of a variety of record and performance metrics in any discipline reveals there are few sporting disciplines where males do not possess performance advantage over females as a result of the physiological characteristics affected by testosterone.

3 Sports Performance Differences Between Males and Females

3.1 An Overview of Elite Adult Athletes

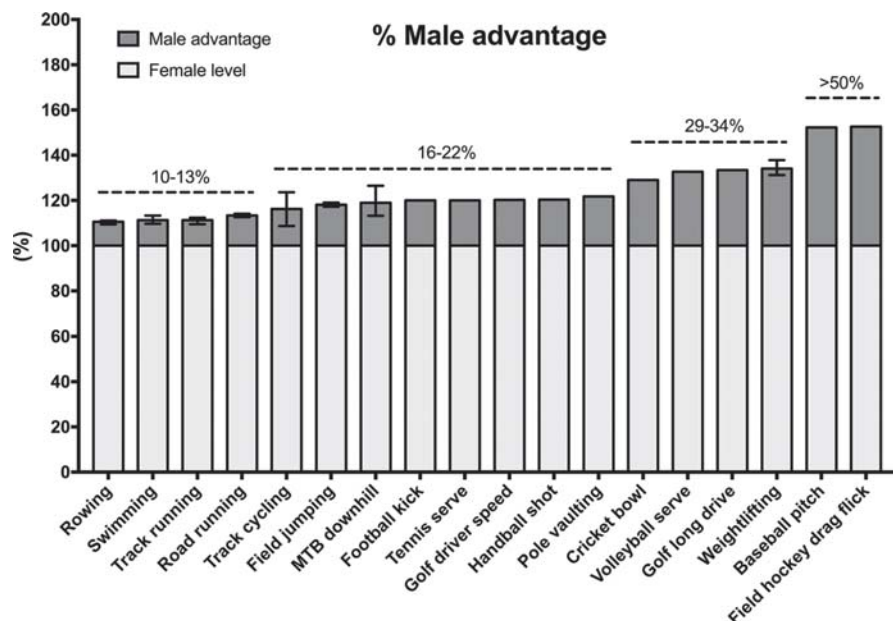
A comparison of adult elite male and female achievements in sporting activities can quantify the extent of the male performance advantage. We searched publicly available sports federation databases and/or tournament/competition records to identify sporting metrics in various events and disciplines, and calculated the performance of males relative to females. Although not an exhaustive list, examples of performance gaps in a range of sports with various durations, physiological performance determinants, skill components and force requirements are shown in Fig. 1.

The smallest performance gaps were seen in rowing, swimming and running (11–13%), with low variation across individual events within each of those categories. The performance gap increases to an average of 16% in track cycling, with higher variation across events (from 9% in the 4000 m team pursuit to 24% in the flying 500 m time trial). The average performance gap is 18% in jumping events (long jump, high jump and triple jump). Performance differences larger than 20% are generally present when considering sports and activities that involve extensive upper body contributions. The gap between fastest recorded tennis serve

Table 1 Selected physical difference between untrained/moderately trained males and females. Female levels are set as the reference value

Variable	Magnitude of sex difference (%)	References
Body composition		
Lean body mass	45	Lee et al. [28]
Fat%	– 30	
Muscle mass		
Lower body	33	Janssen et al. [29]
Upper body	40	
Muscle strength		
Grip strength	57	Bohannon et al. [30]
Knee extension peak torque	54	Neder et al. [31]
Anthropometry and bone geometry		
Femur length	9.4	Jantz et al. [32]
Humerus length	12.0	Brinckmann et al. [33]
Radius length	14.6	
Pelvic width relative to pelvis height	– 6.1	
Tendon properties		
Force	83	Lepley et al. [34]
Stiffness	41	
VO _{2max}		
Absolute values	50	Pate et al. [35]
Relative values	25	
Respiratory function		
Pulmonary ventilation (maximal)	48	Åstrand et al. [36]
Cardiovascular function		
Left ventricular mass	31	Åstrand et al. [36]
Cardiac output (rest)	22	Best et al. [37]
Cardiac output (maximal)	30	Tong et al. [38]
Stroke volume (rest)	43	
Stroke volume (maximal)	34	
Hemoglobin concentration	11	

Fig. 1 The male performance advantage over females across various selected sporting disciplines. The female level is set to 100%. In sport events with multiple disciplines, the male value has been averaged across disciplines, and the error bars represent the range of the advantage. The metrics were compiled from publicly available sports federation databases and/or tournament/competition records. *MTB* mountain bike



is 20%, while the gaps between fastest recorded baseball pitches and field hockey drag flicks exceed 50%.

Sports performance relies to some degree on the magnitude, speed and repeatability of force application, and, with respect to the speed of force production (power), vertical jump performance is on average 33% greater in elite men than women, with differences ranging from 27.8% for endurance sports to in excess of 40% for precision and combat sports [41]. Because implement mass differs, direct comparisons are not possible in throwing events in track and field athletics. However, the performance gap is known to be substantial, and throwing represents the widest sex difference in motor performance from an early age [42]. In Olympic javelin throwers, this is manifested in differences in the peak linear velocities of the shoulder, wrist, elbow and hand, all of which are 13–21% higher for male athletes compared with females [43].

The increasing performance gap between males and females as upper body strength becomes more critical for performance is likely explained to a large extent by the observation that males have disproportionately greater strength in their upper compared to lower body, while females show the inverse [44, 45]. This different distribution of strength compounds the general advantage of increased muscle mass in upper body dominant disciplines. Males also have longer arms than females, which allows greater torque production from the arm lever when, for example, throwing a ball, punching or pushing.

3.2 Olympic Weightlifting

In Olympic weightlifting, where weight categories differ between males and females, the performance gap is between 31 and 37% across the range of competitive body weights between 1998 and 2020 (Fig. 1). It is important to note that at all weight categories below the top/open category, performances are produced within weight categories

with an upper limit, where strength can be correlated with “fighting weight”, and we focused our analysis of performance gaps in these categories.

To explore strength–mass relationships further, we compared Olympic weightlifting data between equivalent weight categories which, to some extent, limit athlete height, to examine the hypothesis that male performance advantage may be largely (or even wholly) mediated by increased height and lever-derived advantages (Table 2). Between 1998 and 2018, a 69 kg category was common to both males and females, with the male record holder (69 kg, 1.68 m) lifting a combined weight 30.1% heavier than the female record holder (69 kg, 1.64 m). Weight category changes in 2019 removed the common 69 kg category and created a common 55 kg category. The current male record holder (55 kg, 1.52 m) lifts 29.5% heavier than the female record holder (55 kg, 1.52 m). These comparisons demonstrate that males are approximately 30% stronger than females of equivalent stature and mass. However, importantly, male vs. female weightlifting performance gaps increase with increasing bodyweight. For example, in the top/open weight category of Olympic weightlifting, in the absence of weight (and associated height) limits, maximum male lifting strength exceeds female lifting strength by nearly 40%. This is further manifested in powerlifting, where the male record (total of squat, bench press and deadlift) is 65% higher than the female record in the open weight category of the World Open Classic Records. Further analysis of Olympic weightlifting data shows that the 55-kg male record holder is 6.5% stronger than the 69-kg female record holder (294 kg vs 276 kg), and that the 69-kg male record is 3.2% higher than the record held in the female open category by a 108-kg female (348 kg vs 348 kg). This Olympic weightlifting analysis reveals key differences between male and female strength capacity. It shows that, even after adjustment for mass, biological males are significantly stronger (30%) than females, and

Table 2 Olympic weightlifting data between equivalent male–female and top/open weight categories

	Sex	Weight (kg)	Height (m)	Combined record (kg)	Strength to weight ratio	Relative performance (%)
2019 record in the 55 kg weight-limited category						
Liao Qiuyun	F	55	1.52	227	4.13	
Om Yun-chol	M	55	1.52	294	5.35	29.5
1998–2018 record in the 69-kg weight-limited category						
Oxsana Slivenko	F	69	1.64	276	4.00	
Liao Hui	M	69	1.68	359	5.20	30.1
Comparative performances for top/open categories (all time heaviest combined lifts)						
Tatiana Kashirina	F	108	1.77	348	3.22	
Lasha Talakhadze	M	168	1.97	484	2.88	39.1

F female, M male

that females who are 60% heavier than males do not overcome these strength deficits.

3.3 Perspectives on Elite Athlete Performance Differences

Figure 1 illustrates the performance gap between adult elite males and adult elite females across various sporting disciplines and activities. The translation of these advantages, assessed as the performance difference between the very best males and very best females, are significant when extended and applied to larger populations. In running events, for example, where the male–female gap is approximately 11%, it follows that many thousands of males are faster than the very best females. For example, approximately 10,000 males have personal best times that are faster than the current Olympic 100 m female champion (World Athletics, personal communication, July 2019). This has also been described elsewhere [46, 47], and illustrates the true effect of an 11% typical difference on population comparisons between males and females. This is further apparent upon examination of selected junior male records, which surpass adult elite female performances by the age of 14–15 years (Table 3), demonstrating superior male athletic performance over elite females within a few years of the onset of puberty.

These data overwhelmingly confirm that testosterone-driven puberty, as the driving force of development of male secondary sex characteristics, underpins sporting advantages that are so large no female could reasonably hope to succeed without sex segregation in most sporting competitions. To ensure, in light of these analyses, that female athletes can be included in sporting competitions in a fair and safe manner, most sports have a female category the purpose of which is the protection of both fairness and, in some sports, safety/welfare of athletes who do not benefit from the physiological changes induced by male levels of testosterone from puberty onwards.

Table 3 Selected junior male records in comparison with adult elite female records

Event	Schoolboy male record	Elite female (adult) record
100 m	10.20 (age 15)	10.49
800 m	1:51.23 (age 14)	1:53.28
1500 m	3:48.37 (age 14)	3:50.07
Long jump	7.85 m (age 15)	7.52 m
Discus throw	77.68 m (age 15)	76.80 m

M meters

Time format: minutes:seconds.hundredths of a second

3.4 Performance Differences in Non-elite Individuals

The male performance advantages described above in athletic cohorts are similar in magnitude in untrained people. Even when expressed relative to fat-free weight, VO_{2max} is 12–15% higher in males than in females [48]. Records of lower-limb muscle strength reveal a consistent 50% difference in peak torque between males and females across the lifespan [31]. Hubal et al. [49] tested 342 women and 243 men for isometric (maximal voluntary contraction) and dynamic strength (one-repetition maximum; 1RM) of the elbow flexor muscles and performed magnetic resonance imaging (MRI) of the biceps brachii to determine cross-sectional area. The males had 57% greater muscle size, 109% greater isometric strength, and 89% greater 1RM strength than age-matched females. This reinforces the finding in athletic cohorts that sex differences in muscle size and strength are more pronounced in the upper body.

Recently, sexual dimorphism in arm force and power was investigated in a punch motion in moderately-trained individuals [50]. The power produced during a punch was 162% greater in males than in females, and the least powerful man produced more power than the most powerful woman. This highlights that sex differences in parameters such as mass, strength and speed may combine to produce even larger sex differences in sport-specific actions, which often are a product of how various physical capacities combine. For example, power production is the product of force and velocity, and momentum is defined as mass multiplied by velocity. The momentum and kinetic energy that can be transferred to another object, such as during a tackle or punch in collision and combat sports are, therefore, dictated by: the mass; force to accelerate that mass, and; resultant velocity attained by that mass. As there is a male advantage for each of these factors, the net result is likely synergistic in a sport-specific action, such as a tackle or a throw, that widely surpasses the sum of individual magnitudes of advantage in isolated fitness variables. Indeed, already at 17 years of age, the average male throws a ball further than 99% of 17-year-old females [51], despite no single variable (arm length, muscle mass etc.) reaching this numerical advantage. Similarly, punch power is 162% greater in men than women even though no single parameter that produces punching actions achieves this magnitude of difference [50].

4 Is the Male Performance Advantage Lost when Testosterone is Suppressed in Transgender Women?

The current IOC criteria for inclusion of transgender women in female sports categories require testosterone suppression below 10 nmol/L for 12 months prior to and during competition. Given the IOC's stated position that the "overriding sporting objective is and remains the guarantee of fair competition" [14], it is reasonable to assume that the rationale for this requirement is that it reduces the male performance advantages described previously to an acceptable degree, thus permitting fair and safe competition. To determine whether this medical intervention is sufficient to remove (or reduce) the male performance advantage, which we described above, we performed a systematic search of the scientific literature addressing anthropometric and muscle characteristics of transgender women. Search terms and filtering of peer-reviewed data are given in Supplementary Table S1.

4.1 Anthropometrics

Given its importance for the general health of the transgender population, there are multiple studies of bone health, and reviews of these data. To summarise, transgender women often have low baseline (pre-intervention) bone mineral density (BMD), attributed to low levels of physical activity, especially weight-bearing exercise, and low vitamin D levels [52, 53]. However, transgender women generally maintain bone mass over the course of at least 24 months of testosterone suppression. There may even be small but significant increases in BMD at the lumbar spine [54, 55]. Some retrieved studies present data pertaining to maintained BMD in transgender women after many years of testosterone suppression. One such study concluded that "BMD is preserved over a median of 12.5 years" [56]. In support, no increase in fracture rates was observed over 12 months of testosterone suppression [54]. Current advice, including that from the International Society for Clinical Densitometry, is that transgender women, in the absence of other risk factors, do not require monitoring of BMD [52, 57]. This is explicable under current standard treatment regimes, given the established positive effect of estrogen, rather than testosterone, on bone turnover in males [58].

Given the maintenance of BMD and the lack of a plausible biological mechanism by which testosterone suppression might affect skeletal measurements such as bone length and hip width, we conclude that height and skeletal parameters remain unaltered in transgender women, and

that sporting advantage conferred by skeletal size and bone density would be retained despite testosterone reductions compliant with the IOC's current guidelines. This is of particular relevance to sports where height, limb length and handspan are key (e.g. basketball, volleyball, handball) and where high movement efficiency is advantageous. Male bone geometry and density may also provide protection against some sport-related injuries—for example, males have a lower incidence of knee injuries, often attributed to low quadriceps (Q) angle conferred by a narrow pelvic girdle [59, 60].

4.2 Muscle and Strength Metrics

As discussed earlier, muscle mass and strength are key parameters underpinning male performance advantages. Strength differences range between 30 and 100%, depending upon the cohort studied and the task used to assess strength. Thus, given the important contribution made by strength to performance, we sought studies that have assessed strength and muscle/lean body mass changes in transgender women after testosterone reduction. Studies retrieved in our literature search covered both longitudinal and cross-sectional analyses. Given the superior power of the former study type, we will focus on these.

The pioneer work by Gooren and colleagues, published in part in 1999 [61] and in full in 2004 [62], reported the effects of 1 and 3 years of testosterone suppression and estrogen supplementation in 19 transgender women (age 18–37 years). After the first year of therapy, testosterone levels were reduced to 1 nmol/L, well within typical female reference ranges, and remained low throughout the study course. As determined by MRI, thigh muscle area had decreased by – 9% from baseline measurement. After 3 years, thigh muscle area had decreased by a further – 3% from baseline measurement (total loss of – 12% over 3 years of treatment). However, when compared with the baseline measurement of thigh muscle area in transgender men (who are born female and experience female puberty), transgender women retained significantly higher thigh muscle size. The final thigh muscle area, after three years of testosterone suppression, was 13% larger in transwomen than in the transmen at baseline ($p < 0.05$). The authors concluded that testosterone suppression in transgender women does not reverse muscle size to female levels.

Including Gooren and Bunck [62], 12 longitudinal studies [53, 63–73] have examined the effects of testosterone suppression on lean body mass or muscle size in transgender women. The collective evidence from these studies suggests that 12 months, which is the most commonly examined intervention period, of testosterone suppression to female-typical reference levels results in a modest (approximately – 5%) loss of lean body mass or muscle size (Table 4). No

Table 4 Longitudinal studies of muscle and strength changes in adult transgender women undergoing cross-sex hormone therapy

Study	Participants (age)	Therapy	Confirmed serum testosterone levels	Muscle/strength data	Comparison with reference females
Polderman et al. [73]	<i>N</i> = 12 TW 18–36 yr (age range)	T suppression + E supplementation	< 2 nmol/L at 4 mo	<i>LBM</i> 4 mo – 2.2%	<i>LBM</i> 4 mo 16%
Gooren and Bunck [62]	<i>N</i> = 19 TW 26 ± 6 yr	T suppression + E supplementation	≤ 1 nmol/L at 1 and 3 yr	<i>Thigh area</i> 1 yr – 9% / 3 yr – 12%	<i>Thigh area</i> 1 yr 16%/3 yr 13%
Haraldsen et al. [63]	<i>N</i> = 12 TW 29 ± 8 yr	E supplementation	< 10 nmol/L at 3 mo and 1 yr	<i>LBM</i> 3 mo/1 yr—small changes, unclear magnitude	
Mueller et al. [64]	<i>N</i> = 84 TW 36 ± 11 yr	T suppression + E supplementation	≤ 1 nmol/L at 1 and 2 yr	<i>LBM</i> 1 yr – 4%/2 yr – 7%	
Wierckx et al. [65]	<i>N</i> = 53 TW 31 ± 14 yr	T suppression + E supplementation	< 10 nmol/L at 1 yr	<i>LBM</i> 1 yr – 5%	<i>LBM</i> 1 yr 39%
Van Caenegem et al. [53] (and Van Caenegem et al. [76])	<i>N</i> = 49 TW 33 ± 14 yr	T suppression + E supplementation	≤ 1 nmol/L at 1 and 2 yr	<i>LBM</i> 1 yr – 4%/2 yr – 0.5% <i>Grip strength</i> 1 yr – 7%/2 yr – 9% <i>Calf area</i> 1 yr – 2%/2 yr – 4% <i>Forearm area</i> 1 yr – 8%/2 yr – 4%	<i>LBM</i> 1 yr 24%/2 yr 28% <i>Grip strength</i> 1 yr 26%/2 yr 23% <i>Calf area</i> 1 yr 16%/2 yr 13% <i>Forearm area</i> 1 yr 29%/2 yr 34%
Gava et al. [66]	<i>N</i> = 40 TW 31 ± 10 yr	T suppression + E supplementation	< 5 nmol/L at 6 mo and ≤ 1 nmol/L at 1 yr	<i>LBM</i> 1 yr – 2%	
Auer et al. [67]	<i>N</i> = 45 TW 35 ± 1 (SE) yr	T suppression + E supplementation	< 5 nmol/L at 1 yr	<i>LBM</i> 1 yr – 3%	<i>LBM</i> 1 yr 27%
Klaver et al. [68]	<i>N</i> = 179 TW 29 (range 18–66)	T suppression + E supplementation	≤ 1 nmol/L at 1 yr	<i>LBM</i> 1 yr Total – 3% Arm region – 6% Trunk region – 2% Android region 0% Gynoid region – 3% Leg region – 4%	<i>LBM</i> 1 yr Total 18% Arm region 28% Leg region 19%
Figuera et al. [69]	<i>N</i> = 46 TW 34 ± 10	E supplementation with or without T suppression	< 5 nmol/L at 3 mo ≤ 1 nmol/L at 31 mo	<i>ALM</i> 31 mo – 4% from the 3 mo visit	
Scharff et al. [70]	<i>N</i> = 249 TW 28 (inter quartile range 23–40)	T suppression + E supplementation	≤ 1 nmol/L at 1 yr	<i>Grip strength</i> 1 yr – 4%	<i>Grip strength</i> 1 yr 21%
Wiik et al. [71]	<i>N</i> = 11 TW 27 ± 4	T suppression + E supplementation	≤ 1 nmol/L at 4 mo and at 1 yr	<i>Thigh volume</i> 1 yr – 5% <i>Quad area</i> 1 yr – 4% <i>Knee extension strength</i> 1 yr 2% <i>Knee flexion strength</i> 1 yr 3%	<i>Thigh volume</i> 1 yr 33% <i>Quad area</i> 26% <i>Knee extension strength</i> 41% <i>Knee flexion strength</i> 33%

Studies reporting measures of lean mass, muscle volume, muscle area or strength are included. Muscle/strength data are calculated in reference to baseline cohort data and, where reported, reference female (or transgender men before treatment) cohort data. Tack et al. [72] was not included in the table since some of the participants had not completed full puberty at treatment initiation. van Caenegem et al. [76] reports reference female values measured in a separately-published, parallel cohort of transgender men

N number of participants, *TW* transgender women, *Yr* year, *Mo* month, *T* testosterone, *E* estrogen. ± Standard deviation (unless otherwise indicated in text), *LBM* lean body mass, *ALM* appendicular lean mass

study has reported muscle loss exceeding the -12% found by Gooren and Bunck after 3 years of therapy. Notably, studies have found very consistent changes in lean body mass (using dual-energy X-ray absorptiometry) after 12 months of treatment, where the change has always been between -3 and -5% on average, with slightly greater reductions in the arm compared with the leg region [68]. Thus, given the large baseline differences in muscle mass between males and females (Table 1; approximately 40%), the reduction achieved by 12 months of testosterone suppression can reasonably be assessed as small relative to the initial superior mass. We, therefore, conclude that the muscle mass advantage males possess over females, and the performance implications thereof, are not removed by the currently studied durations (4 months, 1, 2 and 3 years) of testosterone suppression in transgender women. In sports where muscle mass is important for performance, inclusion is therefore only possible if a large imbalance in fairness, and potentially safety in some sports, is to be tolerated.

To provide more detailed information on not only gross body composition but also thigh muscle volume and contractile density, Wiik et al. [71] recently carried out a comprehensive battery of MRI and computed tomography (CT) examinations before and after 12 months of successful testosterone suppression and estrogen supplementation in 11 transgender women. Thigh volume (both anterior and posterior thigh) and quadriceps cross-sectional area decreased -4 and -5% , respectively, after the 12-month period, supporting previous results of modest effects of testosterone suppression on muscle mass (see Table 4). The more novel measure of radiological attenuation of the quadriceps muscle, a valid proxy of contractile density [74, 75], showed no significant change in transgender women after 12 months of treatment, whereas the parallel group of transgender men demonstrated a $+6\%$ increase in contractile density with testosterone supplementation.

As indicated earlier (e.g. Table 1), the difference in muscle strength between males and females is often more pronounced than the difference in muscle mass. Unfortunately, few studies have examined the effects of testosterone suppression on muscle strength or other proxies of performance in transgender individuals. The first such study was published online approximately 1 year prior to the release of the current IOC policy. In this study, as well as reporting changes in muscle size, van Caenegem et al. [53] reported that hand-grip strength was reduced from baseline measurements by -7% and -9% after 12 and 24 months, respectively, of cross-hormone treatment in transgender women. Comparison with data in a separately-published, parallel cohort of transgender men [76] demonstrated a retained hand-grip strength advantage after 2 years of 23% over female baseline measurements (a calculated average of

baseline data obtained from control females and transgender men).

In a recent multicenter study [70], examination of 249 transgender women revealed a decrease of -4% in grip strength after 12 months of cross-hormone treatment, with no variation between different testosterone level, age or BMI tertiles (all transgender women studied were within female reference ranges for testosterone). Despite this modest reduction in strength, transgender women retained a 17% grip strength advantage over transgender men measured at baseline. The authors noted that handgrip strength in transgender women was in approximately the 25th percentile for males but was over the 90th percentile for females, both before and after hormone treatment. This emphasizes that the strength advantage for males over females is inherently large. In another study exploring handgrip strength, albeit in late puberty adolescents, Tack et al. noted no change in grip strength after hormonal treatment (average duration 11 months) of 21 transgender girls [72].

Although grip strength provides an excellent proxy measurement for general strength in a broad population, specific assessment within different muscle groups is more valuable in a sports-specific framework. Wiik et al., [71] having determined that thigh muscle mass reduces only modestly, and that no significant changes in contractile density occur with 12 months of testosterone suppression, provided, for the first time, data for isokinetic strength measurements of both knee extension and knee flexion. They reported that muscle strength after 12 months of testosterone suppression was comparable to baseline strength. As a result, transgender women remained about 50% stronger than both the group of transgender men at baseline and a reference group of females. The authors suggested that small neural learning effects during repeated testing may explain the apparent lack of small reductions in strength that had been measured in other studies [71].

These longitudinal data comprise a clear pattern of very modest to negligible changes in muscle mass and strength in transgender women suppressing testosterone for at least 12 months. Muscle mass and strength are key physical parameters that constitute a significant, if not majority, portion of the male performance advantage, most notably in those sports where upper body strength, overall strength, and muscle mass are crucial determinants of performance. Thus, our analysis strongly suggests that the reduction in testosterone levels required by many sports federation transgender policies is insufficient to remove or reduce the male advantage, in terms of muscle mass and strength, by any meaningful degree. The relatively consistent finding of a minor (approximately -5%) muscle loss after the first year of treatment is also in line with studies on androgen-deprivation therapy in males with prostate cancer, where the annual loss

of lean body mass has been reported to range between -2 and -4% [77].

Although less powerful than longitudinal studies, we identified one major cross-sectional study that measured muscle mass and strength in transgender women. In this study, 23 transgender women and 46 healthy age- and height-matched control males were compared [78]. The transgender women were recruited at least 3 years after sex reassignment surgery, and the mean duration of cross-hormone treatment was 8 years. The results showed that transgender women had 17% less lean mass and 25% lower peak quadriceps muscle strength than the control males [78]. This cross-sectional comparison suggests that prolonged testosterone suppression, well beyond the time period mandated by sports federations substantially reduces muscle mass and strength in transgender women. However, the typical gap in lean mass and strength between males and females at baseline (Table 1) exceeds the reductions reported in this study [78]. The final average lean body mass of the transgender women was 51.2 kg, which puts them in the 90th percentile for women [79]. Similarly, the final grip strength was 41 kg, 25% higher than the female reference value [80]. Collectively, this implies a retained physical advantage even after 8 years of testosterone suppression. Furthermore, given that cohorts of transgender women often have slightly lower baseline measurements of muscle and strength than control males [53], and baseline measurements were unavailable for the transgender women of this cohort, the above calculations using control males reference values may be an overestimate of actual loss of muscle mass and strength, emphasizing both the need for caution when analyzing cross-sectional data in the absence of baseline assessment and the superior power of longitudinal studies quantifying within-subject changes.

4.3 Endurance Performance and Cardiovascular Parameters

No controlled longitudinal study has explored the effects of testosterone suppression on endurance-based performance. Sex differences in endurance performance are generally smaller than for events relying more on muscle mass and explosive strength. Using an age grading model designed to normalize times for masters/veteran categories, Harper [81] analyzed self-selected and self-reported race times for eight transgender women runners of various age categories who had, over an average 7 year period (range 1–29 years), competed in sub-elite middle and long distance races within both the male and female categories. The age-graded scores for these eight runners were the same in both categories, suggesting that cross-hormone treatment reduced running performance by approximately the size of the typical male advantage. However, factors affecting performances in the interim, including training and injury, were uncontrolled

for periods of years to decades and there were uncertainties regarding which race times were self-reported vs. which race times were actually reported and verified, and factors such as standardization of race course and weather conditions were unaccounted for. Furthermore, one runner improved substantially post-transition, which was attributed to improved training [81]. This demonstrates that performance decrease after transition is not inevitable if training practices are improved. Unfortunately, no study to date has followed up these preliminary self-reports in a more controlled setting, so it is impossible to make any firm conclusions from this data set alone.

Circulating hemoglobin levels are androgen-dependent [82] and typically reported as 12% higher in males compared with females [4]. Hemoglobin levels appear to decrease by 11–14% with cross-hormone therapy in transgender women [62, 71], and indeed comparably sized reductions have been reported in athletes with DSDs where those athletes are sensitive to and been required to reduce testosterone [47, 83]. Oxygen-carrying capacity in transgender women is most likely reduced with testosterone suppression, with a concomitant performance penalty estimated at 2–5% for the female athletic population [83]. Furthermore, there is a robust relationship between hemoglobin mass and VO_{2max} [84, 85] and reduction in hemoglobin is generally associated with reduced aerobic capacity [86, 87]. However, hemoglobin mass is not the only parameter contributing to VO_{2max} , where central factors such as total blood volume, heart size and contractility, and peripheral factors such as capillary supply and mitochondrial content also plays a role in the final oxygen uptake [88]. Thus, while a reduction in hemoglobin is strongly predicted to impact aerobic capacity and reduce endurance performance in transgender women, it is unlikely to completely close the baseline gap in aerobic capacity between males and females.

The typical increase in body fat noted in transgender women [89, 90] may also be a disadvantage for sporting activities (e.g. running) where body weight (or fat distribution) presents a marginal disadvantage. Whether this body composition change negatively affects performance results in transgender women endurance athletes remains unknown. It is unclear to what extent the expected increase in body fat could be offset by nutritional and exercise countermeasures, as individual variation is likely to be present. For example, in the Wiik et al. study [71], 3 out of the 11 transgender women were completely resistant to the marked increase in total adipose tissue noted at the group level. This inter-individual response to treatment represents yet another challenge for sports governing bodies who most likely, given the many obstacles with case-by-case assessments, will form policies based on average effect sizes.

Altogether, the effects of testosterone suppression on performance markers for endurance athletes remain

insufficiently explored. While the negative effect on hemoglobin concentration is well documented, the effects on $\text{VO}_{2\text{max}}$, left ventricular size, stroke volume, blood volume, cardiac output lactate threshold, and exercise economy, all of which are important determinants of endurance performance, remain unknown. However, given the plausible disadvantages with testosterone suppression mentioned in this section, together with the more marginal male advantage in endurance-based sports, the balance between inclusion and fairness is likely closer to equilibrium in weight-bearing endurance-based sports compared with strength-based sports where the male advantage is still substantial.

5 Discussion

The data presented here demonstrate that superior anthropometric, muscle mass and strength parameters achieved by males at puberty, and underpinning a considerable portion of the male performance advantage over females, are not removed by the current regimen of testosterone suppression permitting participation of transgender women in female sports categories. Rather, it appears that the male performance advantage remains substantial. Currently, there is no consensus on an acceptable degree of residual advantage held by transgender women that would be tolerable in the female category of sport. There is significant dispute over this issue, especially since the physiological determinants of performance vary across different sporting disciplines. However, given the IOC position that fair competition is the overriding sporting objective [14], any residual advantage carried by transgender women raises obvious concerns about fair and safe competition in the numerous sports where muscle mass, strength and power are key performance determinants.

5.1 Perspectives on Athletic Status of Transgender Women

Whilst available evidence is strong and convincing that strength, skeletal- and muscle-mass derived advantages will largely remain after cross-hormone therapy in transgender women, it is acknowledged that the findings presented here are from healthy adults with regular or even low physical activity levels [91], and not highly trained athletes. Thus, further research is required in athletic transgender populations.

However, despite the current absence of empirical evidence in athletic transgender women, it is possible to evaluate potential outcomes in athletic transgender women compared with untrained cohorts. The first possibility is that athletic transgender women will experience similar reductions (approximately -5%) in muscle mass and strength as untrained transgender women, and will thus

retain significant advantages over a comparison group of females. As a result of higher baseline characteristics in these variables, the retained advantage may indeed be even larger. A second possibility is that by virtue of greater muscle mass and strength at baseline, pre-trained transgender women will experience larger relative decreases in muscle mass and strength if they converge with untrained transgender women, particularly if training is halted during transition. Finally, training before and during the period of testosterone suppression may attenuate the anticipated reductions, such that relative decreases in muscle mass and strength will be smaller or non-existent in transgender women who undergo training, compared to untrained (and non-training) controls.

It is well established that resistance training counteracts substantial muscle loss during atrophy conditions that are far more severe than testosterone suppression. For example, resistance exercise every third day during 90-days bed rest was sufficient to completely offset the 20% reduction in knee extensor muscle size noted in the resting control subjects [92]. More relevant to the question of transgender women, however, is to examine training effects in studies where testosterone has been suppressed in biological males. Kvorning et al. investigated, in a randomized placebo-controlled trial, how suppression of endogenous testosterone for 12 weeks influenced muscle hypertrophy and strength gains during a training program (3 days/week) that took place during the last 8 weeks of the 3-month suppression period [93]. Despite testosterone suppression to female levels of 2 nmol/L, there was a significant $+4\%$ increase in leg lean mass and a $+2\%$ increase in total lean body mass, and a measurable though insignificant increase in isometric knee extension strength. Moreover, in select exercises used during the training program, 10RM leg press and bench press increased $+32\%$ and $+17\%$, respectively. While some of the training adaptations were lower than in the placebo group, this study demonstrates that training during a period of testosterone suppression not only counteracts muscle loss, but can actually increase muscle mass and strength.

Males with prostate cancer undergoing androgen deprivation therapy provide a second avenue to examine training effects during testosterone suppression. Testosterone levels are typically reduced to castrate levels, and the loss of lean mass has typically ranged between -2 and -4% per year [77], consistent with the findings described previously in transgender women. A recent meta-analysis concluded that exercise interventions including resistance exercise were generally effective for maintaining muscle mass and increasing muscle strength in prostate cancer patients undergoing androgen deprivation therapy [94]. It is important to emphasize that the efficacy of the different training programs may vary. For example, a 12-week training study of prostate cancer patients undergoing androgen deprivation therapy

included drop-sets to combine heavy loads and high volume while eliciting near-maximal efforts in each set [95]. This strategy resulted in significantly increased lean body mass (+3%), thigh muscle volume (+6%), knee extensor 1RM strength (+28%) and leg press muscle endurance (+110%).

In addition to the described effects of training during testosterone suppression, the effect of training prior to testosterone suppression may also contribute to the attenuation of any muscle mass and strength losses, via a molecular mechanism referred to as ‘muscle memory’ [96]. Specifically, it has been suggested that myonuclei acquired by skeletal muscle cells during training are maintained during subsequent atrophy conditions [97]. Even though this model of muscle memory has been challenged recently [98], it may facilitate an improved training response upon retraining [99]. Mechanistically, the negative effects of testosterone suppression on muscle mass are likely related to reduced levels of resting protein synthesis [100], which, together with protein breakdown, determines the net protein balance of skeletal muscle. However, testosterone may not be required to elicit a robust muscle protein synthesis response to resistance exercise [100]. Indeed, relative increases in muscle mass in men and women from resistance training are comparable, despite marked differences in testosterone levels [101], and the acute rise in testosterone apparent during resistance exercise does not predict muscle hypertrophy nor strength gains [102]. This suggests that even though testosterone is important for muscle mass, especially during puberty, the maintenance of muscle mass through resistance training is not crucially dependent on circulating testosterone levels.

Thus, in well-controlled studies in biological males who train while undergoing testosterone reduction, training is protective of, and may even enhance, muscle mass and strength attributes. Considering transgender women athletes who train during testosterone suppression, it is plausible to conclude that any losses will be similar to or even smaller in magnitude than documented in the longitudinal studies described in this review. Furthermore, pre-trained transgender women are likely to have greater muscle mass at baseline than untrained transgender women; it is possible that even with the same, rather than smaller, relative decreases in muscle mass and strength, the magnitude of retained advantage will be greater. In contrast, if pre-trained transgender women undergo testosterone suppression while refraining from intense training, it appears likely that muscle mass and strength will be lost at either the same or greater rate than untrained individuals, although there is no rationale to expect a weaker endpoint state. The degree of change in athletic transgender women is influenced by the athlete’s baseline resistance-training status, the efficacy of the implemented program and other factors such as genetic make-up and nutritional habits, but we argue that it is implausible that

athletic transgender women would achieve final muscle mass and strength metrics that are on par with reference females at comparable athletic level.

5.2 The Focus on Muscle Mass and Strength

We acknowledge that changes in muscle mass are not always correlated in magnitude to changes in strength measurements because muscle mass (or total mass) is not the only contributor to strength [103]. Indeed, the importance of the nervous system, e.g. muscle agonist activation (recruitment and firing frequency) and antagonist co-activation, for muscle strength must be acknowledged [104]. In addition, factors such as fiber types, biomechanical levers, pennation angle, fascicle length and tendon/extracellular matrix composition may all influence the ability to develop muscular force [105]. While there is currently limited to no information on how these factors are influenced by testosterone suppression, the impact seems to be minute, given the modest changes noted in muscle strength during cross-hormone treatment.

It is possible that estrogen replacement may affect the sensitivity of muscle to anabolic signaling and have a protective effect on muscle mass [106] explaining, in part, the modest change in muscle mass with testosterone suppression and accompanying cross-hormone treatment. Indeed, this is supported by research conducted on estrogen replacement therapy in other targeted populations [107, 108] and in several different animal models, including mice after gonadectomy [109] and ovariectomy [110].

In terms of other performance proxies relevant to sports performance, there is no research evaluating the effects of transgender hormone treatment on factors such as agility, jumping or sprint performance, competition strength performance (e.g. bench press), or discipline-specific performance. Other factors that may impact sports performance, known to be affected by testosterone and some of them measurably different between males and females, include visuospatial abilities, aggressiveness, coordination and flexibility.

5.3 Testosterone-Based Criteria for Inclusion of Transgender Women in Female Sports

The appropriate testosterone limit for participation of transgender women in the female category has been a matter of debate recently, where sports federations such as World Athletics recently lowered the eligibility criterion of free circulating testosterone (measured by means of liquid chromatography coupled with mass spectrometry) to <5 nmol/L. This was based, at least in part, on a thorough review by Handelsman et al. [4], where the authors concluded that, given the nonoverlapping distribution of circulating testosterone between males and females, and making an allowance

for females with mild hyperandrogenism (e.g. with polycystic ovary syndrome), the appropriate testosterone limit should be 5 rather than 10 nmol/L.

From the longitudinal muscle mass/strength studies summarised here, however, it is apparent that most therapeutic interventions result in almost complete suppression of testosterone levels, certainly well below 5 nmol/L (Table 4). Thus, with regard to transgender women athletes, we question whether current circulating testosterone level cut-off can be a meaningful decisive factor, when in fact not even suppression down to around 1 nmol/L removes the anthropometric and muscle mass/strength advantage in any significant way.

In terms of duration of testosterone suppression, it may be argued that although 12 months of treatment is not sufficient to remove the male advantage, perhaps extending the time frame of suppression would generate greater parity with female metrics. However, based on the studies reviewed here, evidence is lacking that this would diminish the male advantage to a tolerable degree. On the contrary, it appears that the net loss of lean mass and grip strength is not substantially decreased at year 2 or 3 of cross-hormone treatment (Table 4), nor evident in cohorts after an average 8 years after transition. This indicates that a plateau or a new steady state is reached within the first or second year of treatment, a phenomenon also noted in transgender men, where the increase in muscle mass seems to stabilise between the first and the second year of testosterone treatment [111].

6 Conclusions

We have shown that under testosterone suppression regimes typically used in clinical settings, and which comfortably exceed the requirements of sports federations for inclusion of transgender women in female sports categories by reducing testosterone levels to well below the upper tolerated limit, evidence for loss of the male performance advantage, established by testosterone at puberty and translating in elite athletes to a 10–50% performance advantage, is lacking. Rather, the data show that strength, lean body mass, muscle size and bone density are only trivially affected. The reductions observed in muscle mass, size, and strength are very small compared to the baseline differences between males and females in these variables, and thus, there are major performance and safety implications in sports where these attributes are competitively significant. These data significantly undermine the delivery of fairness and safety presumed by the criteria set out in transgender inclusion policies, particularly given the stated prioritization of fairness as an overriding objective (for the IOC). If those policies are intended to preserve fairness,

inclusion and the safety of biologically female athletes, sporting organizations may need to reassess their policies regarding inclusion of transgender women.

From a medical-ethical point of view, it may be questioned as to whether a requirement to lower testosterone below a certain level to ensure sporting participation can be justified at all. If the advantage persists to a large degree, as evidence suggests, then a stated objective of targeting a certain testosterone level to be eligible will not achieve its objective and may drive medical practice that an individual may not want or require, without achieving its intended benefit.

The research conducted so far has studied untrained transgender women. Thus, while this research is important to understand the isolated effects of testosterone suppression, it is still uncertain how transgender women athletes, perhaps undergoing advanced training regimens to counteract the muscle loss during the therapy, would respond. It is also important to recognize that performance in most sports may be influenced by factors outside muscle mass and strength, and the balance between inclusion, safety and fairness therefore differs between sports. While there is certainly a need for more focused research on this topic, including more comprehensive performance tests in transgender women athletes and studies on training capacity of transgender women undergoing hormone therapy, it is still important to recognize that the biological factors underpinning athletic performance are unequivocally established. It is, therefore, possible to make strong inferences and discuss potential performance implications despite the lack of direct sport-specific studies in athletes. Finally, since athlete safety could arguably be described as the immediate priority above considerations of fairness and inclusion, proper risk assessment should be conducted within respective sports that continue to include transgender women in the female category.

If transgender women are restricted within or excluded from the female category of sport, the important question is whether or not this exclusion (or conditional exclusion) is necessary and proportionate to the goal of ensuring fair, safe and meaningful competition. Regardless of what the future will bring in terms of revised transgender policies, it is clear that different sports differ vastly in terms of physiological determinants of success, which may create safety considerations and may alter the importance of retained performance advantages. Thus, we argue against universal guidelines for transgender athletes in sport and instead propose that each individual sports federation evaluate their own conditions for inclusivity, fairness and safety.

Compliance with Ethical Standards

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Authorship contributions Both authors (ENH and TRL) were involved in the conception and design of this paper, and both authors drafted, revised and approved the final version of the paper.

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Data availability Available upon request.

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Best Practices in Transgender Health A Clinician's Guide



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KEYWORDS

- Transgender health • LGBTQ health • Organ inventory • Gender affirming care
- Annual examination • Transgender mental health

KEY POINTS

- Transgender patients often look for subtle clues in the office environment to suggest that the practice is transgender friendly; as such, creating a trans-affirming practice is a crucial first step to providing competent care.
- Providers should perform an annual organ inventory and keep this up to date in their electronic medical record system to help guide preventative screenings.
- As a general rule, if an individual has a particular body part or organ and otherwise meets criteria for screening based on risk factors or symptoms, screening should proceed, regardless of hormone use.
- There are standard guidelines for initiation and continuation of hormone replacement therapy; however, it is important to have an open dialogue with your patient regarding their goals of therapy and reasonable expectations.

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INTRODUCTION

Providing culturally competent and medically knowledgeable care to the transgender and the gender nonconforming community is increasingly requested and falls within the realm of primary care practice. This patient population has unique health care needs, is subject to a variety of health care disparities, and is often reticent to seek medical care owing to prior negative experiences.¹ Few medical schools, medical residency programs, or training programs for advanced practice providers provide formal training in this arena.² The purpose of this article is to offer current primary care clinicians an overview of best practices as they relate to health care for transgender individuals. This article is by no means a comprehensive guide, but is intended as a starting point for clinicians so that they may provide high-quality, affirming, and value-based care to their transgender patients.

HEALTH DISPARITIES AND SOCIAL DETERMINANTS OF HEALTH

Social determinants of health often contribute to health disparities among vulnerable populations. In the transgender population, relevant social determinants include chronic stress, higher rates of homelessness, unemployment, frequent victimization, and high Adverse Childhood Events scores.³ One study suggested that 28% of transgender individuals were harassed in medical settings, 19% were denied care, and 2% experienced violence.⁴ Owing to inconsistent access to health care in general, and more specifically gender-affirming care, the transgender population is at increased risk of experiencing retraumatization in medical settings.⁵ Approximately one-fifth of the transgender population has experienced homelessness, 12% of whom have been homeless within the last year.⁶ Income disparities exist with poverty levels twice the nation average and a high rate of people in the lowest income bracket (<\$10,000 per year).⁴ Of those who were out (had disclosed their gender identity and/or sexual orientation) to their immediate family, 10% reported experiencing violence and 8% were kicked out of the house because of their disclosure.⁶

Relevant medical literature supports the premise that the intersection between being a gender minority (ie, transgender) and a racial minority is associated with increased rates of poverty, unemployment, and greater health disparities when compared with the Caucasian transgender population.⁶ Disabled and undocumented people who are transgender experience increased discrimination as well.³ Environmental factors that affect the health of lesbian, gay, bisexual, transgender (LGBT) individuals include legal discrimination, a lack of laws protecting children from bullying in schools, a lack of social programs, and a shortage of health care providers who are knowledgeable and culturally competent.³

Other factors that contribute to this population's health disparity include high uninsured rates and greater reliance on public insurance.⁶ For example, only 40% of transgender individuals had access to employer health insurance compared with 62% of cisgender individuals (one whose gender identity matches their sex assigned at birth).⁶ Another source of disparities in LGBT health care comes from a long history of anti-LGBT bias in health care that has resulted in fewer people from this population seeking care and to an overall decrease in access to care.⁷ Access to knowledgeable providers willing to care for transgender patients is limited. Homophobia and transphobia persist in some health care settings, with limited emphasis during training on cultural empathy or understanding among health care professionals, which presents challenges for the provision of appropriate primary care.^{8–11} Additionally, challenges for aging or disabled patients include finding skilled nursing facilities, rehabilitation units, and/or assisted living facilities that allow rooming in for same sex couples, allow family

of choice to make medical decisions, set appropriate visitation parameters, and respect the gender identity of transgender patients.¹² **Table 1** includes selected key health disparities in the transgender population.

CREATING A TRANS-AFFIRMING PRACTICE

Research suggests that LGBT patients often search for subtle cues in the environment to determine if a practice is friendly.¹³ Because of this, it is crucial for practices to create a gender-affirming environment throughout the clinical practice. Characteristics of such an environment are varied and impact all aspects of the practice. Intake forms should be inclusive of a wide range of gender identities and patients should be addressed by their preferred pronoun(s).¹³ All staff should be trained to refer to patients by their preferred pronouns and their correct gender identity. The physical office space should display LGBT-friendly symbols, stickers, photographs, and posters representing a diverse patient population.¹³ Brochures in the waiting room should include material pertinent to the transgender community. Within the examination room, the clinician should foster a welcoming environment by asking open, nonjudgmental questions. The provider should ask about the patient's gender identity and their preferred pronoun(s), which should be used when addressing the patient throughout the visit.¹³ The provider should feel confident in conducting an organ inventory (described elsewhere in this article), which should guide preventive care for the patient. Ideally, the electronic health record (EHR) should be able to capture sexual orientation and gender identity information accurately for purposes of patient care and appropriate handling of insurance and billing functions.^{14–16}

THE ELECTRONIC HEALTH RECORD

The EHR can become a barrier to care for transgender patients if it does not incorporate appropriate collection of sexual orientation and gender identity data.¹⁵ Key components of appropriate sexual orientation and gender identity data collection include capture of the patient's preferred name, gender at birth, sexual orientation, and gender identity.^{14–16} If the EHR is not built to collect these data appropriately at registration and intake, many difficulties can arise for the patient and the provider entity. Problems can include nonaffirming experiences for patients called by the wrong name, identified by inappropriate pronouns, or treated incorrectly based on provider or staff assumptions about sex, gender identity, and sexual orientation and behaviors. Surgeries appropriate to the patient's situation may be denied or questioned based on incorrect assumptions about gender identity or the presence or absence of organs. Laboratory tests that are appropriate for the patient's gender identity may be reported with the incorrect reference ranges based on gender as reported in the EHR. Patients may also be denied insurance payment for appropriate health care services and provider entities may encounter significant billing and compliance issues because of inaccurate data used in health care documentation.

UNDERSTANDING THE MEANING OF "TRANSITIONING" FOR TRANSGENDER PATIENTS

The process of transitioning one's gender is complex and varies from individual to individual.¹⁷ Individuals may complete some, none, or all of the components of the 3 broad categories of transitioning (social, medical, and surgical) over the course of their lifetimes.¹⁷ Underlying the decision to transition requires identification of the dysphoria brought about through identification with the sex and gender roles assigned at birth

Table 1
Key health disparities in the transgender population

Key Transgender Health Disparities	
Youth ^{6,47–51}	• LGBT youth are 2–3 times as likely to attempt suicide • LGBT youth are more likely to be homeless • Homeless youth who are LGBT are more likely to report victimization, substance abuse, and to have more sexual partners and more psychopathology than their heterosexual comparison • Youth are frequently bullied at school and are more likely to be victims of sexual violence than their peers according to the Youth Risk Behavior Survey in 2016 • At school (K-12) youth who were perceived as transgender were likely to be verbally harassed (54%), physically attacked (24%), and sexually assaulted (13%), resulting in 17% of kids leaving school owing to the environment • HIV prevalence in male-to-female youth varied from 19% to 22%, showing them to be at high risk for infection
Access ^{3,6}	• Transgender individuals are less likely to have health insurance than heterosexual or LGB counterparts • 29% of the transgender population lives in poverty compared with 12% of the US population • One-third of USTS respondents had a negative experience with a health care provider related to being transgender within the last year • 23% of USTS participants did not seek health care owing to fear of being mistreated • 25% of USTS participants had a health insurance problem related to being transgender in the last year • 55% of USTS participants had sought coverage for surgery and were denied • 25% of USTS participants had sought care for hormones and were denied • 33% of USTS participants did not go to a health care provider owing to the expense • The unemployment rate in the transgender population in the USTS survey was 15% compared with 5% in the cisgender population
Infections ^{51–53}	• Some studies suggest a disparity in the availability of HIV treatment services. A recent four-city study found that transgender women were less likely to receive highly active antiretroviral therapy than a control group of MSM, heterosexual women and men, and male intravenous drug users • Hepatitis C prevalence rates between 11% and 24% and hepatitis B rates from 4% to 76% among specific samples of transgender women are estimates based on limited studies • A prevalence rate of tuberculosis of up to 13% among transgender women in San Francisco • HIV infection is highest among transgender women of color, with HIV prevalence rates ranging from ◦ 41% to 63% among African-American transgender women ◦ 4% to 50% among Latina transgender women ◦ 4% to 13% among Asian-Pacific Islander transgender women • HIV prevalence in transgender men (female to males) is estimated to range from 2% to 3%, which is still elevated compared with cisgender men • Some limited research has found elevated rates of sexually transmitted diseases with varying prevalence rates of ◦ Syphilis (3%–79%) ◦ Gonorrhea (4%–14%) ◦ Chlamydia (2%–8%) ◦ Herpes (2%–6%) ◦ Human papillomavirus (3%–7%)

(continued on next page)

Table 1
(continued)

Key Transgender Health Disparities	
Substance abuse ^{21,51,54}	• Adolescents are 2.5 to 5.0 times more likely to use substances (including vaping, smoking, drinking, heavy episodic drinking) than their nontransgender peers • Transgender adolescent youth are at higher risk of recent substance use and earlier onset of substances, which increases risk for long-term addiction • Increased gender and sexuality based harassment is associated with increased substance abuse at every grade • Some studies have shown that marijuana, crack cocaine, and alcohol are the most commonly used drugs by transgender people • Studies have also found alarming rates of methamphetamine use (4%–46%) and injection drug use (2%–40%) • Some studies suggest that tobacco use rates can range from 45% to 74% • Access to substance abuse treatment services can be very difficult for transgender people. Studies have suggested that barriers to treatment services often include: ◦ Discrimination, ◦ Provider hostility and insensitivity, ◦ Strict binary gender (male/female) segregation within programs, and ◦ Lack of acceptance in gender-appropriate recovery groups.
Obesity ⁵⁰	• LGBT youth have higher rates of obesity, which predisposes to metabolic syndrome and diabetes
Cancer ^{55–59}	• Transgender men were more likely to have an inadequate pap than cisgender women and this increased with duration of testosterone therapy • Transgender men were less likely to be up-to-date on pap screenings (AOR, 0.63; $P < .01$) • Although rare, there is an increased risk for vaginal, cervical, and endometrial cancer with hormone therapy • Male to female transgender persons are not at higher risk than biological women for breast cancer and thus not recommended for screening mammography • Association between masculinizing hormone therapies and elevated liver enzymes, loss of bone mineral density, and increased risk for ovarian cancer • Underutilization of health care in general and limited screening owing to gender mismatch
Mental health ^{6,48,60}	• 39% had serious psychological distress in the previous month compared with only 5% of the US population • Higher rates of depression and anxiety • When compared with MSM and bisexually active women, transgender women were most likely to report depressive symptoms and suicidal ideation
Suicide ⁶	• 40% of respondents in the USTS had attempted suicide in their life time compared with 4.6% of the general population • 7% had attempted suicide in the last year compared with 0.6% in the US population
Violence ^{6,37}	• Approximately 66% of transgender people have been sexually assaulted in their lifetime • 50% of undocumented transgender individuals had been homeless in their lifetime and 68% had faced intimate partner violence • 16%–60% of transgender people are victims of physical assault or abuse • Social stigmatization and other factors may additionally lead to an underreporting of acts of violence committed against transgender people

Abbreviations: MSM, men who have sex with men; USTS, US transgender survey.

and acknowledgment of a desire to see oneself and to be seen by others as a different sex and/or gender. Throughout different components of transitioning, sexual orientation can change.¹⁸ This fluctuation tends to occur more commonly with individuals who are attracted to the opposite biological sex before transitioning.

Social transition includes the decision to present publicly as one's gender identity and may include changes in appearance, use of pronouns, preferred name, and sexual behaviors and partnering.¹⁷ Social/behavioral interventions include resocialization efforts to learn the mannerisms, communication, and interactions styles of the preferred gender, tucking of the penis or binding of the breasts, and voice coaching. Support for mental health conditions, screening for depression and anxiety, and assessment of readiness to begin medical transition is important in this phase of transition.

Medical, or endocrine, transition includes the decision to seek medical (typically hormonal) therapy to shift the appearance and function of hormone-producing organs, hair growth patterns, and other outward signs gender.¹⁷ World Professional Association for Transgender Health has developed Standards of Care that include diagnosing gender dysphoria, treating comorbid conditions and making sure mental health conditions are stable, education about the medical treatment under consideration, and the ability to give consent before medical treatment.¹⁹ Ideally, this phase of transition includes mental health support, including management of mood, anxiety, and other conditions. A systemic review of the effects of hormone therapy on psychological functioning showed a statistically significant improvement in mental health conditions during the transition and affirming process.²⁰

Surgical transition includes the surgical augmentation of internal and external hormone and sex-related organs.¹⁷ Options include surgery to remove the Adam's apple (tracheal shave), orchiectomy, vaginoplasty, and breast augmentation for male-to-female individuals. For female-to-male transitioning patients, surgical options include mastectomy, hysterectomy and salpingo-oophorectomy, metoidioplasty, phalloplasty, and sexual reassignment surgery.

THE HISTORY AND PHYSICAL EXAMINATION

General Considerations

When taking a patient's history and conducting a physical examination, it is crucial to do so in a gender-affirming way. History taking should be done in an open, nonjudgmental fashion, considering individualized changes and characteristics in the setting of hormone administration and/or surgical interventions that have taken place. The clinician should be sensitive to potential prior negative experiences and trauma, especially within the health care environment.⁴ Physical examination should be relevant to the anatomy that is present, regardless of gender presentation. Providers should have an understanding that secondary sexual characteristics may present on a spectrum of development in patients transitioning with hormone therapy and somewhat depend on the durations of use and age at initiation.

The Organ Inventory

An organ inventory is an anatomic survey that allows providers to record the organs each patient has at any given point in time.²¹ Such an inventory should be conducted annually for all transgender patients. Once someone has transitioned socially, medically, and/or surgically, they may change their gender marker in the medical record. It then becomes important to know sex assigned at birth, current hormone-producing organs, and current exogenous hormones. An organ inventory allows

providers to maintain a record of the patient's medical transition history and current anatomy. In turn, this inventory drives routine health care screenings that a patient requires. A sample organ inventory is displayed in **Box 1**.

The Physical Examination

There are likely to be special considerations with regard to the pelvic examination in both male-to-female and female-to-male patients. In transgender females who have undergone gender reassignment surgery, the anatomy of the neovagina differs from a natal vagina.²¹ It is a blind cuff, without a cervix or surrounding fornices and could have a more posterior orientation. Because of this, an anoscope should be used when visual inspection is necessary.²¹ For the transgender male, the clinician should have an understanding that the pelvic examination may be traumatic or induce anxiety.²¹ Transgender men are less likely to be up to date on cervical cancer screenings and have a higher rate of inadequate cytologic sampling.²¹ Additionally, it is imperative to make clear to the laboratory that the sample provided is a cervical pap smear even, if the gender listed is male to avoid incorrect handling of the specimen.²¹

Other special considerations include chest binding and tucking of the testicles and penis. Chest binding is done to create a more masculine appearance of the chest; however, it may lead to skin breakdown or other complications of the skin.²² Patients may be hesitant to remove the binder during an examination.²³ Safe binding education is recommended for all trans male patients who have not undergone mastectomy. Tucking of the testicles and penis may lead to hernias or other complications at the external inguinal ring or the potential for skin breakdown at the perineum.²² Thorough

Box 1

Sample organ inventory

Organ inventory

Cervix

Uterus

Natal vagina

Neophallus

Penis

Prostate

Testes

Neovagina

Organ inventory with laterality

Left breast

Left fallopian tube

Left ovary

Left testis

Right breast

Right fallopian tube

Right ovary

Right testis

and sensitive history taking, examination, and education are recommended for all transgender patients.²²

Hormonal Therapy: Consideration of Risks

When caring for transgender patients, the clinician should counsel on risks of cross-sex hormone therapy, particularly before the initiation of therapy and at each subsequent visit, weighing the risks and benefits to guide therapeutic decision making. It is critical to consider risks in the context of family history and medical comorbidities. Unsupervised hormone therapy is not advised²⁴ and physicians should ask patients about any history of previous hormone use not under the supervision of a medical provider.

For transgender females using estrogen therapy, high-risk adverse outcomes include thromboembolic disease, and moderate risk adverse outcomes includes hyperprolactinemia, breast cancer, coronary artery disease, cerebrovascular disease, cholelithiasis, and hypertriglyceridemia.²⁵ Given these risks, it is strongly recommended for clinicians to encourage tobacco cessation, although smoking is not an absolute contraindication to estrogen. If a transgender female has a prior history of a sex hormone-responsive cancer (breast or pituitary), consultation with an oncologist before initiating therapy is critical.²¹ Antiandrogen therapy is typically used in prostate cancer therapy; however, there is less clear of a role of estrogen on the development of prostate cancer.²⁶ For those with family history or personal history of venous thromboembolism, an anticoagulative workup should take place to guide decision making in antiplatelet or anticoagulation therapy.²¹ Routine prophylaxis with antiplatelet therapy is not recommended based on current evidence. In patients with a high risk of venous thromboembolism, the preferred route of administration of estrogen is transdermal to minimize risk because it avoids first-pass liver metabolism and induction of clotting factor production.²¹ Although no evidence exists to strongly support the use of 81 mg/d aspirin in smokers, it can be considered as an additional preventive measure while using informed assessment of the risk versus benefit between venous thromboembolism prevention and gastrointestinal hemorrhage. As with cisgender women, avoidance of synthetic estrogens other than 17 beta estradiol and conjugated estrogens decreases the risk of venous thromboembolism by nearly one-half.²¹

In transgender males, the use of testosterone carries a very high risk of erythrocytosis (hematocrit >50%) and moderate risk of severe liver dysfunction (transaminases >3 times the upper limit of normal). The risk for coronary artery disease, cerebrovascular disease, and hypertension increases to that of a cisgender male. There may also be an increased risk for breast and/or uterine cancer.²⁵

For both transgender males and females, it is important to avoid supraphysiologic dosing of sex steroids because the associated risks are more likely to arise and are worsened in this scenario.²⁷ The most recent Endocrine Society guidelines recommend regular clinical evaluation for physical changes and potential adverse outcomes after initiation of sex hormones and laboratory evaluation of sex steroids hormone levels every 3 months during the first year of therapy for both male and female transgender patients, then once or twice yearly.²⁵

Monitoring of Hormonal Therapy

The endocrine transition provides an important opportunity for appropriate regular medical monitoring. Clinicians should monitor weight and blood pressure and conduct appropriate physical examinations. They should assess various health questions, including tobacco use, symptoms of depression, adverse effects of sex steroids, and symptoms concerning for deep vein thrombosis or pulmonary embolism.²⁸

For transgender males, the goal of therapy is to maintain testosterone in the physiologic normal male range while avoiding adverse events resulting from excess testosterone therapy such as erythrocytosis, sleep apnea, hypertension, excessive weight gain, salt retention, lipid changes, and excessive or cystic acne.²⁹ In contrast with the Endocrine Society guidelines, the University of California San Francisco (UCSF) guidelines recommend against routine screening for lipids and hemoglobin A1c and recommend following the United States Preventative Services Task Force guidelines to drive decision making.²¹ The UCSF guidelines also recognize that serum total testosterone has limitations owing to fluctuations in gonadotropins and recommend calculating the bioavailable testosterone using the total testosterone, albumin and sex hormone-binding globulin with a general reference range of greater than 72 ng/dL.²¹ **Box 2** illustrates the current monitoring plan for transgender males as per the Endocrine Society guidelines²⁵ and **Table 2** provides the UCSF recommended guidelines.²¹

For transgender females either on estrogens, gonadotropin suppression, or antiandrogens, key issues include avoiding supraphysiologic doses or blood levels of estrogen that put the patient at a greater risk of thromboembolic disease, liver dysfunction, or elevations in blood pressure. Clinicians should choose a quality controlled assay for measuring serum estradiol levels to avoid measurement challenges.³⁰ In a study examining a large Dutch cohort, the risk of venous thromboembolism was shown to be 20-fold increased in Dutch transgender patients using estrogen.³¹ This increase may have been associated with the use of the synthetic estrogen, ethinyl estradiol.³² Given this finding, the use of synthetic estrogens and conjugated estrogens is not recommended because of the inability to monitor and dose based on serum levels in the setting of venous thromboembolism risk.²⁵ Additionally, in transgender females, periodic prolactin assessment is recommended by the Endocrine Society,²⁵ because estrogen therapy may increase the growth of pituitary lactotroph cells. Several reports

Box 2

Monitoring of transgender males on gender affirming hormone therapy as recommended by the Endocrine Society guidelines

- Clinical evaluation and monitoring every 3 months in the first year and then every 6 to 12 months appropriate signs of virilization and for development of adverse events.
- Measure serum testosterone every 3 months until levels are in the physiologic male range.
 - For intramuscular preparations, measure midway. The target is 400 to 700 ng/dL.
 - Transdermal testosterone can be measured following 1 week of daily application at least 2 hours after application.
- Measure hematocrit or hemoglobin at baseline and then every 3 months in the first year of therapy. Monitor weight, blood pressure, and lipids at regular intervals.
- Screening for osteoporosis should be undertaken in those who stop testosterone therapy, who develop risks for bone loss, or are nonadherent with therapy.
- If cervical tissue is present, regular screening as recommended by the American College of Obstetricians and Gynecologists.
- Ovariectomy can be considered after completion of hormone transition.
- Conduct annual breast examinations if mastectomy is performed and, if not, then consider mammograms as recommended by the American Cancer Society.

From Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2017;102(11):3890; with permission.

Table 2 Monitoring of therapy for transgender males: University of California San Francisco guidelines		
Parameter	Baseline	Additional Monitoring
Lipids	No evidence supporting, use discretion. Monitor as per USPSTF guidelines	PRN
Hemoglobin A1C or fasting glucose	No evidence supporting, use discretion. Monitor as per USPSTF guidelines	PRN
Estradiol	Not indicated	PRN
Total testosterone	Not indicated	3, 6 and 12 ^a months then PRN
Sex hormone-binding globulin ^b	Not indicated	3, 6 and 12 ^a months then PRN
Albumin ^b	Not indicated	3, 6 and 12 ^a months then PRN
Hematocrit and hemoglobin	Measure	3, 6, 12 ^a months, yearly and PRN

Abbreviations: PRN, pro re nata (as needed); USPSTF, US Preventative Services Task Force.

^a In first year of therapy only.

^b Used to calculate bioavailable testosterone; monitoring bioavailable testosterone is optional and may be helpful in complex cases.

Adapted from Deutsch MB. Guidelines for the primary and gender-affirming care of transgender and gender nonbinary people. 2nd edition. Available at: <http://transhealth.ucsf.edu/pdf/Transgender-PGACG-6-17-16.pdf>. Accessed November 12, 2017; with permission.

have demonstrated the development of prolactinomas occurring after long-term, high-dose estrogen therapy, and up to 20% of transgender females treated with estrogens may have elevations in prolactin levels.³³ In contrast, the UCSF guidelines recommend against routine prolactin screening unless there is evidence of visual disturbances, excessive galactorrhea, or new onset of headaches.²¹ Last, in general, reference ranges for laboratory values used in monitoring hormonal therapy should take into consideration the identified gender, not the physiologic gender.²¹ **Box 3** displays recommended monitoring in transgender females per the Endocrine Society²⁵ and **Table 3** per the UCSF guidelines.²¹

MENTAL HEALTH AND THE TRANSGENDER PATIENT

Current medical, psychological, and social research has increasingly shown that, while being transgender is not a mental disorder or medical condition, gender dysphoria, the manifestation of psychological distress brought on by the dissonance between assigned gender and felt gender, is a condition that can be treated.³⁴ The treatments discussed above are affirming of patients' gender identity and can help transgender youth and adults facilitate a successful gender transition. There is increasing evidence that this approach leads to improved health and mental health outcomes.^{35–37} To be clear, the treatment of gender dysphoria does nothing to resolve the social stigma, discrimination, oppression, and health disparities that contribute to the high rates of unemployment (double the national average), harassment (78%), physical (61%) or sexual assault (64%), homelessness (double the national average), depression (35%–58%), anxiety (25%), eating disorders (7%), and suicide ideation (51%) and suicide attempts (41%) within the transgender population.^{4,38–42} These concerns can be easily screened for during medical visits.

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Box 3**Monitoring of transgender females on gender affirming hormone therapy as recommended by the Endocrine Society guidelines**

- Evaluate patient every 3 months in the first year and then 6 to 12 months to monitor for appropriate signs of feminization and for development of adverse reactions.
- Measure serum testosterone and estradiol levels every 3 months.
 - Goal serum testosterone level is less than 50 ng/dL.
 - Serum estradiol should not exceed the peak physiologic range: 100 to 200 pg/mL.
- For patients taking spironolactone, serum electrolytes including potassium should be monitored every 3 months in the first year and annually thereafter.
- Routine cancer screening is recommended as in nontransgender individuals (all tissues present).
- Consider bone mineral density testing at baseline. In patients at low risk, screening for osteoporosis should be conducted at 60 years of age or in those who are not compliant with hormone therapy.

From Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2017;102(11):3890; with permission.

Transgender or gender diverse adolescents are especially vulnerable, because they are experiencing gender identity development at the same time that they may be exploring their sexual orientation, while also going through puberty and navigating high school. Coming out to friends and family, managing school policy around using

Table 3**Monitoring of therapy for transgender females: University of California San Francisco guidelines**

Parameter	Baseline	Additional Monitoring
Lipids	No evidence supporting, use discretion. Monitor as per USPSTF guidelines.	PRN
A1C or fasting glucose	No evidence supporting, use discretion. Monitor as per USPSTF guidelines.	
Estradiol	Not indicated.	3, and 6 ^a months, PRN
Total testosterone	Not indicated.	3, 6 and 12 ^a months then PRN
Sex hormone-binding globulin ^b	Not indicated.	3, 6 and 12 ^a months then PRN
Albumin ^b	Not indicated.	3, 6 and 12 ^a months then PRN
Prolactin	Only if symptoms of prolactinoma.	PRN
Bun/Cr/K ^c	Measure.	3, 6, 12 ^a months, yearly and PRN

Abbreviations: BUN/Cr/K, blood urea nitrogen, creatinine, potassium; PRN, pro re nata (as needed); USPSTF, US Preventative Services Task Force.

^a In first year of therapy only.

^b Used to calculate bioavailable testosterone; monitoring bioavailable testosterone is optional and may be helpful in complex cases.

^c For patients on spironolactone only.

Adapted from Deutsch MB. Guidelines for the primary and gender-affirming care of transgender and gender nonbinary people. 2nd edition. Available at: <http://transhealth.ucsf.edu/pdf/Transgender-PGACG-6-17-16.pdf>. Accessed November 12, 2017; with permission.

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the bathroom or locker room, and having preferred name and pronouns used appropriately by others are just a few experiences unique to transgender youth. The amount of psychosocial stress that is endured by these youth cannot be overstated. In just 1 clinic, the Transgender Health Clinic at Cincinnati Children's, 30% of the transgender youth that they served reported at least 1 suicide attempt; a history of self-injury was reported by 42% of the youth they served.⁴³

Clinicians in a primary care setting are often in an optimal position to provide support to transgender individuals. Understanding the risks and recognizing that transgender patient's access to medical or mental health care may be limited is key in maximizing the work that can be done during their visit.

CONSIDERATIONS FOR SPECIAL POPULATIONS

Pediatric and Adolescent Patients

There is no universal treatment path that can, or should, be applied to all transgender children and youth. Often, treatment includes 1 or more of the following: psychotherapy, social transition, use of puberty blockers to delay the onset of puberty, hormone replacement therapy, and surgical options for young adults, 18 or older. All of these treatments can be used in an effort to relieve gender dysphoria by helping to align one's body with one's gender identity, allowing the individual to live and present in the world as the gender they authentically feel themselves to be.

In minor children presenting with gender dysphoria for a period of over 6 months who have not yet started puberty or who have not yet progressed beyond Tanner stage II of puberty, the suggested treatment includes supportive efforts to help the child explore their gender identity.²⁵ This process may include support from a mental health provider trained in working with gender diverse children, efforts toward social transition, and the possible use of puberty blockers (leuprolide or histrelin). Puberty blockers are medications that suppress the increase of testosterone and estrogen in the body, delaying puberty until the blockers are discontinued. Because puberty blockers have been used for decades in children with precocious puberty,⁴⁴ they are considered a safe alternative to having a child with gender dysphoria progress through a puberty that they feel is incorrect and therefore exacerbates gender dysphoria and increases the risk of self-harm, including suicide.²⁵ This treatment option buys the patient some time to continue gender identity development and exploration until they are older and can make a more informed decision about what puberty would be most appropriate for them. The Endocrine Society guidelines recommend clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation before initiating puberty suppression in adolescents and before treating with hormonal therapy of the affirmed gender in both adolescents and adults.²⁵

In youth with gender dysphoria who have already started puberty, are beyond Tanner stage II, and have reached 16 years of age, the suggested medical treatment includes the use of hormone replacement therapy or gender-affirming hormones.^{21,25} Gender-affirming hormones effectively cause the transgender youth to go through a second puberty, which brings about either the masculinization or feminization of their bodies and features. Because the sex hormones, estrogen and testosterone, are found in both natal males and natal females, providing hormone replacement therapy acts to rebalance the dominant hormone in the patient to match the patient's gender identity.

Because the transgender youth who are seeking treatment are minors, it is recommended that informed consent be obtained by a legal guardian, as well as assent (for

adolescents) from the patient. Guardians and patients should be provided the information, education and resources to help them make informed decisions about the treatment options available to alleviate gender dysphoria and improve long-term health and mental health outcomes.

Aging and Elderly Patients

Like cisgender individuals, transgender people are subject to the vagaries of aging, and the potential conditions related to it. In general, screening and treatment of age-related illnesses in this population should be no different than in cisgender patients, with the exception of the use of appropriate organ inventories to guide screening. However, it is important to note that, for some transgender patients, it is only in later ages and stages of life that they feel safe to approach health care providers and others about their symptoms of gender dysphoria. Health care providers should be sensitive to, and have comfort with, discussing sexual orientation and gender identity issues with all aging patients. For transgender people who are aging, it is particularly important that primary care providers be familiar with the diagnosis of gender dysphoria and available treatments, including hormone therapy, mental health care, and surgical procedures. It is also important to address the potential for isolation and violence in the home as potential threats to aging transgender people.⁴⁵ A high index of suspicion for substance abuse, particularly alcohol use and misuse, is important. The combination of isolation, substance abuse, and depression can be particularly lethal for both cisgender and transgender elderly people, but the addition of stigma and the potential for violence and physical and mental abuse is particularly high among transgender individuals compared with their cisgender counterparts.⁴⁶ Overall, a high degree of compassion and sensitivity, combined with knowledge on the provider's part of current available therapies and best practices in medical record-keeping will help to ensure affirming care of aging transgender patients.

SUMMARY

As a growing number of transgender individuals become empowered to seek primary care, it is imperative that providers are prepared to meet their health care needs. This requires providers to approach these patient encounters with cultural humility and sound medical knowledge based on current guidelines. As new research emerges in the field of trans health clinicians will need to stay abreast of current best practices. In the meantime, clinicians could enhance care by creating a transgender-friendly office environment, conducting an annual organ inventory, updating their EHR system to incorporate transgender-friendly data collection, and taking into consideration current guidelines for gender affirmation, transition, screening, and prevention in this population.

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Individuals Treated for Gender Dysphoria with Medical and/or Surgical Transition Who Subsequently Detransitioned: A Survey of 100 Detransitioners

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Abstract

The study's purpose was to describe a population of individuals who experienced gender dysphoria, chose to undergo medical and/or surgical transition and then detransitioned by discontinuing medications, having surgery to reverse the effects of transition, or both. Recruitment information with a link to an anonymous survey was shared on social media, professional listservs, and via snowball sampling. Sixty-nine percent of the 100 participants were natal female and 31.0% were natal male. Reasons for detransitioning were varied and included: experiencing discrimination (23.0%); becoming more comfortable identifying as their natal sex (60.0%); having concerns about potential medical complications from transitioning (49.0%); and coming to the view that their gender dysphoria was caused by something specific such as trauma, abuse, or a mental health condition (38.0%). Homophobia or difficulty accepting themselves as lesbian, gay, or bisexual was expressed by 23.0% as a reason for transition and subsequent detransition. The majority (55.0%) felt that they did not receive an adequate evaluation from a doctor or mental health professional before starting transition and only 24.0% of respondents informed their clinicians that they had detransitioned. There are many different reasons and experiences leading to detransition. More research is needed to understand this population, determine the prevalence of detransition as an outcome of transition, meet the medical and psychological needs of this population, and better inform the process of evaluation and counseling prior to transition.

Keywords Gender dysphoria · Detransition · Transgender

Introduction

Detransition is the act of stopping or reversing a gender transition. The visibility of individuals who have detransitioned is new and may be rapidly growing. As recently as 2014, it was challenging for an individual who detransitioned to find another person who similarly detransitioned (Callahan, 2018). Between 2015 and 2017, a handful of blogs written by individual detransitioners started to appear online, private support groups for detransitioners formed, and interviews with detransitioners began to appear in news articles, magazines, and

blogs (Anonymous, 2017; 4thwavenow, 2016; Herzog, 2017; McCann, 2017). Although few YouTube videos about detransition existed prior to 2016, multiple detransitioners started to post videos documenting their experiences in 2016 and the numbers of these videos continues to increase.¹ In late 2017, the subreddit r/detrans (r/detrans, 2020) was revitalized and in four years has grown from 100 members to more than 21,000 members. A member poll of r/detrans conducted in 2019 estimated that approximately one-third of the members responding to the survey were desisters or detransitioners (r/detrans, 2019). The Pique Resilience Project, a group of four detransitioned or desisted young women, was founded in 2018 as a way to share the experiences of detransitioners with the public (Pique Resilience Project, 2019). In late 2019, the Detransition Advocacy Network, a nonprofit organization to “improve the well-being of detransitioned people everywhere” was launched (The

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¹ A search of the word “detransition” in YouTube can be filtered by date of upload. https://www.youtube.com/results?search_query=%22detransition%22&sp=CAI%253D22.

Detransition Advocacy Network, 2020) and the first formal, in-person conference for detransitioned people was held (Bridge, 2020). In the face of this massive change, clinicians have called for more research into the experiences of detransitioners (Butler & Hutchinson, 2020; Entwistle, 2021; Marchiano, 2020).

Although there were rare published reports about detransitioners prior to 2016, most of the published literature about detransition is recent (Callahan, 2018; D'Angelo, 2018; Djordjevic et al., 2016; Kuiper & Cohen-Kettenis, 1998; Levine, 2018; Marchiano, 2017; Pazos Guerra et al., 2020; Stella, 2016; Turban & Keuroghlian, 2018; Turban et al., 2021; Vandenbussche, 2021). The prevailing cultural narratives about detransition are that most individuals who detransition will retransition and that the reasons for detransition are discrimination, pressures from others, and nonbinary identification (Turban et al., 2021). However, case reports are shedding light on a broader and more complex range of experiences that include trauma, worsened mental health with transition, re-identification with natal sex, and difficulty separating sexual orientation from gender identity (D'Angelo, 2018; Levine, 2018; Pazos Guerra et al., 2020).² Detransitioners and desisters, in their own words, have provided additional depth to the discussion, describing that:

- (1) Trauma (including sexual trauma) and mental health conditions contributed to their transgender identification and transition (Callahan, 2018; Herzog, 2017; twitter.com/fmdetransed & twitter.com/radfemjourney, 2019)
- (2) Their dysphoria and transition were due to homophobia and difficulty accepting themselves as homosexual (Bridge, 2020; Callahan, 2018; upperhandMARS, 2020)
- (3) Peers, social media, and online communities were influential in the development of transgender identification and desire to transition (Pique Resilience Project, 2019; Tracey, 2020; upperhandMARS, 2020)
- (4) Their dysphoria was rooted in misogyny (Herzog, 2017)

Two recently published convenience sample reports provide additional context about the topic of detransition. First, Turban

et al. (2021) analyzed data from the United States Trans Survey (USTS) (James et al., 2016). The USTS contains data from 27,715 transgender and gender diverse adults from the U.S. who were recruited through lesbian, gay, bisexual, transgender, queer (LGBTQ), and allied organization outreach. The USTS included the question, "Have you ever detransitioned? In other words, have you ever gone back to living as your sex assigned at birth, at least for a while?" with the multiple choice options of "yes," "no," and "I have never transitioned." For the 2,242 participants who answered "yes," Turban et al. analyzed the responses to the multiple choice question, "Why did you detransition? In other words, why did you go back to living as your sex assigned at birth? (Mark all that apply)." Although most of the offered answer options were about external pressures to detransition (pressure from spouse or partner, pressure from family, pressure from friends, pressure from employer, discrimination, etc.), participants could write in additional reasons that were not listed. Turban et al.'s sample included more natal males (55.1%) than natal females (44.9%). Roughly half (50.2%) had taken cross-sex hormones and 16.5% had obtained surgery. The findings revealed that most (82.5%) of the sample expressed at least one external factor for detransitioning and 15.9% expressed at least one internal factor (factors originating from self).

The second study by Vandenbussche (2021) recruited detransitioners from online communities of detransitioners and analyzed data for the participants who answered affirmatively to the question, "Did you transition medically and/or socially and then stopped?" The sample of 237 participants was predominantly natal female (92%), and from the U.S. (51%) and Europe (32%). Most (65%) had transitioned both medically and socially. Participants selected from multiple choice options to indicate why they detransitioned with options covering a range of experiences. Respondents also had the option to write in additional reasons. Frequently endorsed reasons for detransition included realizing that their gender dysphoria was related to other issues (70%); health concerns (62%); observing that transition did not help their dysphoria (50%); and that they found alternatives to deal with their dysphoria (45%). In contrast to Turban et al. (2021), external factors such as lack of support, financial concerns, and discrimination were less common (13%, 12%, and 10%, respectively). Many in the sample described that when they detransitioned they lost support or were ostracized from lesbian, gay, bisexual, and transgender (LGBT) communities, suggesting that many of the participants in Vandenbussche (2021) would not have been reached by the recruitment efforts of the USTS (James et al., 2016).

The objective of the current study was to describe a population of individuals who experienced gender dysphoria, chose to undergo medical and/or surgical transition and then detransitioned by discontinuing medications, having surgery to reverse the effects of transition, or both. In contrast to Turban et al. (2021) and Vandenbussche (2021), this study focused only on

² The debate about the terminologies used to describe an individual's sex (including "assigned sex at birth," "biological sex," "natal sex," "birth sex," "sex," etc.) is far from settled. Although some professionals have argued for the use of "assigned sex at birth," others argue that this terminology is misleading and not consistent with the events that occur at birth and prior to birth (Bouman et al., 2017; Byng et al., 2018; Dahlen, 2020; Griffin et al., 2020). Supporting the unsettled nature of the discussion, I received conflicting comments from the reviewers of this manuscript about my selection of natal sex terms—one reviewer asked that I justify my preference for natal sex over the other terminologies; another reviewer expressed support for my use of natal sex. I prefer to use "natal sex" and "birth sex" because they are accurate and objective. Further, I propose that "natal sex" and "birth sex" might be seen as reasonable, polite compromise terms between "biological sex" and "assigned sex at birth."

individuals who transitioned and detransitioned medically, surgically, or both. For the purpose of this study, medical transition refers to the use of puberty blockers, cross-sex hormones, or anti-androgens and surgical transition refers to any of a variety of surgical procedures (common surgical procedures include mastectomy, genital surgery, and breast augmentation). This study does not describe the population of individuals who undergo medical or surgical transition without issue nor is it designed to assess the prevalence of detransition as an outcome of transition. Instead, the goal was to identify detransition reasons and narratives in order to inform clinical care and future research.

Method

Participants and Procedure

During the recruitment period, 101 individuals who met the study criteria completed online surveys. Inclusion criteria were (1) completion of a survey via Survey Monkey; (2) answering that they had taken or had one or more of the following for the purpose of gender transition: cross-sex hormones, anti-androgens, puberty blockers, breast surgery, genital surgery, other surgery; and (3) answering that they had done any of the following for the purpose of detransitioning: stopped taking cross-sex hormones, stopped taking anti-androgens, stopped taking puberty blockers, had any surgery to reverse transition. One survey was excluded for nonsense answers leaving 100 surveys for analysis. The sample included more natal females (69.0%) than natal males (31.0%) with respondents who were predominantly White (90.0%), non-Hispanic (98.0%), resided in the U.S. (66.0%); had no religious affiliation (63.0%), and support the rights of gay and lesbian couples to marry legally (92.9%) (see Table 1). At the time of survey completion, the mean age of respondents was 29.2 years ($SD=9.1$) though natal females were significantly younger ($M=25.8$; $SD=5.0$) than natal males ($M=36.7$; $SD=11.4$), $t(98)=-6.56$, $p<.001$. Prior to transitioning, natal females were more likely to report an exclusively homosexual sexual orientation and natal males were more likely to report an exclusively heterosexual sexual orientation.

A 115-question survey instrument with multiple choice, Likert-type, and open-ended questions was created by the author and two individuals who had personally detransitioned. The author had met both detransitioners by way of introductions from colleagues. The author and both individuals who had detransitioned created questions for the survey, provided feedback, and revised the survey questions collaboratively with a focus on content, clarity, and relevance to a variety of transition and detransition experiences. The survey instrument included two questions that were adapted from an online survey of female detransitioners (Stella, 2016). Once completed, the

survey was uploaded onto Survey Monkey (SurveyMonkey, Palo Alto, CA) via an account that was HIPAA-enabled.

Recruitment information with a link to the survey was posted on blogs that covered detransition topics and shared in a private online detransition forum, in a closed detransition Facebook group, and on Tumblr, Twitter, and Reddit. Recruitment information was also shared on the professional listservs for the World Professional Association for Transgender Health, the American Psychological Association Section 44, and the SEXNET listserv (which is a listserv of sex researchers and clinicians) and the professionals on the listservs were asked to share recruitment information with anyone they knew who might be eligible. Efforts were made to reach out to communities with varied views about the use of medical and surgical transition and recruitment information stated that participation was sought from individuals regardless of whether their transition experiences were positive, negative or neutral. Potential participants were invited to share recruitment information with any potentially eligible person or community with potentially eligible people. The survey was active from December 15, 2016 to April 30, 2017 (4.5 months). The median time to complete a survey was 49 min; 50% of the surveys were completed between 32 and 71 min. There were no incentives offered for participating. Data were collected anonymously, without IP addresses, and stored securely with Survey Monkey.

Participation in this study was voluntary. Electronic consent was obtained from all participants in the following manner. The first page of the online survey informed respondents about the research purpose, potential risks and benefits, that participation was voluntary, and provided contact information for the researcher. Survey questions were only displayed if the participant clicked “agree” which indicated that they read the information, voluntarily agreed to participate and were at least 18 years of age.

Measures

Demographic and Baseline Characteristics

Information was collected about participant age, natal sex, race/ethnicity, country of residence, educational attainment, socioeconomic status, religion, attitudes about legal marriage for gay and lesbian couples, and where they first heard about the study. The term sexual orientation in this article is intended to refer to the natal sex of the participant and the natal sex of the individuals with whom they are sexually attracted. Participants were asked to select one or more labels for how they identified their sexual orientation prior to transition with options inclusive of participant sex (e.g., asexual female, bisexual female, heterosexual female, etc.). These responses were coded to be consistent with participant natal sex and were categorized into homosexual, heterosexual, bisexual, pansexual, asexual, and multiple. The multiple category included respondents who

Table 1 Demographic and baseline characteristics

	Natal female <i>N</i> (%) <i>N</i> = 69	Natal male <i>N</i> (%) <i>N</i> = 31
<i>Race/ethnicity*</i>		
White	62 (89.9%)	28 (90.3%)
Multiracial	6 (8.7%)	3 (9.7%)
Other	4 (5.8%)	0 (0%)
Asian	1 (1.4%)	1 (3.2%)
Hispanic	1 (1.4%)	1 (3.2%)
Black	0 (0%)	0 (0%)
<i>Country of residence</i>		
USA	46 (66.7%)	20 (64.5%)
UK	8 (11.6%)	1 (3.2%)
Canada	5 (7.2%)	4 (12.9%)
Australia	2 (2.9%)	2 (6.5%)
Other	8 (11.6%)	4 (12.9%)
<i>Education</i>		
Bachelor's or graduate degree	29 (42.0%)	18 (58.1%)
Associates degree	3 (4.3%)	1 (3.2%)
Some college but no degree	28 (40.6%)	9 (29.0%)
High school graduate or GED	8 (11.6%)	2 (6.5%)
<High school	1 (1.4%)	0 (0%)
Other	0 (0%)	1 (3.2%)
<i>Socioeconomic status compared to others in country of residence</i>		
Above average (somewhat or very much)	19 (27.5%)	12 (38.7%)
About average	20 (29.0%)	7 (22.6%)
Below average (somewhat or very much)	27 (39.1%)	12 (38.7%)
Prefer not to say	3 (4.3%)	0 (0%)
<i>Categorized sexual orientation (by natal sex) prior to transition^a</i>		
Homosexual	18 (26.1%)	2 (6.5%)
Heterosexual	6 (8.7%)	12 (38.7%)
Bisexual	15 (21.7%)	8 (25.8%)
Pansexual	4 (5.8%)	1 (3.2%)
Multiple	20 (29.0%)	5 (16.1%)
Asexual	6 (8.7%)	3 (9.7%)
<i>Religious affiliation</i>		
No religious affiliation	41 (59.4%)	22 (73.3%)
Liberal Christian	5 (7.2%)	3 (10.0%)
Liberal Jewish	5 (7.2%)	0 (0%)
Conservative Christian	1 (1.4%)	2 (6.7%)
Liberal Muslim	1 (1.4%)	0 (0%)
Conservative Jewish	0 (0%)	0 (0%)
Conservative Muslim	0 (0%)	0 (0%)
Other	16 (23.2%)	3 (10.0%)
<i>Legal marriage for gay and lesbian couples</i>		
Favor	65 (97.0%)	26 (83.9%)
Oppose	1 (1.5%)	5 (16.1%)
Don't know	1 (1.5%)	0 (0%)
<i>Source where participant first heard about study</i>		
Detransition blogs	26 (37.7%)	15 (48.4%)
Other social media	37 (53.6%)	11 (35.5%)
A person they know	3 (4.3%)	3 (9.7%)
Other	3 (4.3%)	2 (6.5%)

*May select more than one answer

^aNatal females were more likely to express an exclusively homosexual sexual orientation prior to transition ($\chi^2 = 5.15$. The *p*-value is .023). Natal males were more likely to express an exclusively heterosexual sexual

Table 1 (continued)

orientation prior to transition ($\chi^2 = 13.05$. The p value is $< .001$). Natal sex differences were not significant for individuals expressing pre-transition sexual orientations of bisexual, pansexual, multiple, and asexual. For bisexual sexual orientation, $\chi^2 = 0.20$. For pansexual sexual orientation, $\chi^2 = 0.29$. For multiple sexual orientations reported, $\chi^2 = 1.88$. For asexual sexual orientation, $\chi^2 = 0.02$

selected more than one response where responses indicated more than one pattern of sexual attraction (e.g., lesbian female and heterosexual female). Other questions about baseline characteristics included questions about diagnosed psychiatric disorders and neurodevelopmental disabilities, trauma, and non-suicidal self-injury (NSSI) before the onset of gender dysphoria.

Gender Dysphoria Onset and Typologies

Participants were asked how old they were when they first experienced gender dysphoria and whether this was during childhood, at the onset of puberty, during puberty, or later. Respondents were categorized as having early-onset gender dysphoria if they indicated that their gender dysphoria began “during childhood” and late-onset gender dysphoria if their gender dysphoria began “at the onset of puberty” or later. To evaluate typologies, participants were characterized by Blanchard’s (1985, 1989) typology as homosexual (if the sexual orientations listed prior to transition were exclusively homosexual) or non-homosexual which includes heterosexual, asexual, bisexual, pansexual, and multiple responses.

Transition

Participants were asked for their age and the year that they first sought care to transition, sources that encouraged them to believe that transition would be helpful to them, and whether they felt pressured to transition. The friendship group dynamics that were identified in previous work were assessed by asking respondents whether their friendship group mocked people who were not transgender, whether people in their pre-existing friend group transitioned before the participant decided to transition, and how participant popularity changed after announcing that they would transition (Littman, 2018). Questions were asked about participant experiences with clinicians, the social, medical, and surgical steps they took to transition, and the duration of time spent taking each medication.

Detransition

Participants were asked for their age and the year that they decided to detransition, how long they were transitioned before deciding to detransition, their reasons for wanting to detransition, what sources encouraged them to believe that detransition would be helpful to them, and whether they felt pressured to detransition. Participants were also asked which

social, medical, and surgical steps they took to detransition and whether they contacted the doctor or clinic that they used for their transition to tell them that they detransitioned.

Transition and Detransition Narratives

In this article, “narratives” denote participant interpretations of their experiences and rationales surrounding their decisions to transition and detransition. To associate each participant survey with a set of relevant narratives, the data were reviewed with horizontal (beginning to end) passes and vertical passes for selected questions (these questions are listed in the supplemental materials). Surveys were coded as belonging to zero or more of the following narrative categories: discrimination, nonbinary, retransition, trauma and mental health, internalized homophobia, social influence, and misogyny. Each narrative and the responses that were associated with them are detailed below. Example quotes were selected with care taken to avoid quoting a participant more than once per narrative. Narratives are ordered and reported with the more commonly accepted narratives first and the newer narratives next.

The *discrimination* narrative was defined as when someone detransitioned due to experiencing discrimination or external social pressures. The *nonbinary* narrative consisted of answering that their current identification was “nonbinary/genderqueer” or providing open-text responses that described aspects of discovering or maintaining a nonbinary identification. Although there were no questions in the survey specifically asking about retransition, the *retransition* narrative was identified if participants expressed that they had retransitioned or resumed transition in any of the open-text responses in the survey. The *gender dysphoria was caused by trauma or a mental health condition* narrative was identified by selection for the answers, “what I thought were feelings of being transgender were actually the result of trauma,” “what I thought were feelings of being transgender were actually the result of a mental health condition,” “I discovered that my gender dysphoria was caused by something specific (ex. trauma, abuse, mental health condition)” or open-text responses consistent with these reasons. The *internalized homophobia/difficulty accepting oneself as a lesbian female, gay male, or bisexual person* narrative consisted of descriptions that the respondents’ discomfort and distress about being lesbian, gay, or bisexual was related to their gender dysphoria, transition, or detransition, or that they assumed they were transgender because they did not yet understand themselves to be lesbian, gay or bisexual. The *social pressure to transition* narrative was identified with an affirmative

answer to whether they felt pressured to transition with an open-text response indicating that the pressure came from a person or group of people. The *misogyny* narrative was identified for natal female respondents with open-text responses using the word “misogyny” or expressing a hatred of femaleness.

Gender Identification at Start of Transition and at Survey Completion

Participants were asked how they identified their gender when they started their transition and at the time of survey completion. They were given options of female, male, nonbinary/genderqueer, trans man/FTM, trans woman/MTF, none of the above, and other. Responses were coded by natal sex and categorized as transgender, birth sex, nonbinary, and other. Answers that were combinations of the above categories were reported as combinations such as “birth sex and nonbinary.”

Self-Appraisal of Transition and Detransition

One question asked if participants believe they were helped and another if they were harmed by their transition with options of “very much,” “a little,” or “not at all.” These results were categorized into exclusively helped, exclusively harmed, and both helped and harmed. Participants were asked which of the following reflected their feelings about their transition: “I am glad that I transitioned,” “I wish I had never transitioned,” “Transitioning distracted me from what I should have been doing,” “Transition was a necessary part of my journey.” Participants were asked to rate their regret about their transition (“no regrets,” “mild regrets,” “strong regrets,” and “very strong regrets”) and were asked to indicate their satisfaction with their decisions to transition and detransition (“extremely satisfied,” “very satisfied,” “somewhat satisfied,” “somewhat dissatisfied,” “very dissatisfied,” and “extremely dissatisfied”). Satisfaction options were collapsed into “satisfied” and “dissatisfied.” In addition, participants were asked if they knew then what they know now, would they have chosen to transition.

Data Analysis

After data were cleaned, statistical analyses were performed using google sheets. Results are presented as frequencies, percentages, medians, means and standard deviations. *t* tests and chi-square tests were performed for selected variables and were considered significant for $p < .05$. Qualitative data were obtained from the open-text answers to questions that allowed participants to provide additional information. Selected open-text responses were categorized, tallied, and reported numerically. Salient respondent quotes and summaries from the qualitative data were selected to illustrate the quantitative results and to provide relevant examples.

Results

Before Transition

Mental health diagnoses and traumatic experiences before the onset of gender dysphoria. Table 2 shows data about psychiatric disorders, neurodevelopmental disabilities, NSSI, and trauma that were reported as occurring prior to the onset of gender dysphoria. Because these conditions and events occurred before participants began to feel gender dysphoric, they cannot be considered to be secondary to gender incongruence or transphobia.

Gender dysphoria onset and typology. Most participants (82.0%) were living with one or both parents when they first experienced gender dysphoria at a mean age of 11.2 years ($SD = 5.6$). The mean age of gender dysphoria onset was not statistically different between natal females ($M = 11.3$; $SD = 5.4$) and natal males ($M = 11.0$; $SD = 5.9$), $t(96) = 0.25$. By Blanchard typologies, 26.1% of natal females were exclusively homosexual and 73.9% non-homosexual while 6.5% of natal males were exclusively homosexual and 93.5% non-homosexual (Blanchard, 1985, 1989). Slightly more than half of the respondents (56.0%) experienced early-onset gender dysphoria and slightly less than half (44.0%) experienced late-onset gender dysphoria. Although late-onset gender dysphoria in natal females was largely absent from the scientific literature prior to 2012 (Steensma et al., 2013; Zucker & Bradley, 1995; Zucker et al., 2012a), 55.1% of the natal female participants reported that their gender dysphoria began with puberty or later. Because the information about the timing of gender dysphoria onset was obtained from participants reporting on their own experiences, it can be assumed that these cases were indeed late-onset rather than early-onset gender dysphoria that was concealed from parents and other people.

Transition reasons. Table 3 shows data about the reasons that individuals wanted to transition and the most frequently endorsed were: wanting to be perceived as the target gender (77.0%); believing that transitioning was their only option to feel better (71.0%); the sensation that their body felt wrong the way it was (71.0%), and not wanting to be associated with their natal sex (70.0%). Most participants believed that transitioning would eliminate (65.0%) or decrease (63.0%) their gender dysphoria and that with transitioning they would become their true selves (64.0%).

Sources of transition encouragement and friend group dynamics. Participants identified sources that encouraged them to believe transitioning would help them. Social media and online communities were the most frequently reported, including YouTube transition videos (48.0%), blogs (46.0%), Tumblr (45.0%), and online communities (43.0%) (see supplemental materials). Also common were people who the respondents knew offline such as therapists (37.0%); someone (28.0%) or a group of friends (27.0%) that they knew in-person. A subset of

Table 2 Mental health diagnoses and traumatic experiences prior to the onset of gender dysphoria

	Natal female <i>N</i> (%) <i>N</i> = 69	Natal male <i>N</i> (%) <i>N</i> = 31
<i>Diagnosed with a mental illness or neurodevelopmental disability</i> ^{*a}		
Depression	27 (39.1%)	5 (16.1%)
Anxiety	22 (31.9%)	5 (16.1%)
Attention deficit hyperactivity disorder (ADHD)	10 (14.5%)	2 (6.5%)
Post-traumatic stress disorder (PTSD)	10 (14.5%)	1 (3.2%)
Eating disorders	10 (14.5%)	0 (0%)
Autism spectrum disorders	9 (13.0%)	1 (3.2%)
Bipolar disorder	9 (13.0%)	0 (0%)
Obsessive compulsive disorder	6 (8.7%)	3 (9.7%)
Borderline personality disorder	5 (7.2%)	0 (0%)
Schizophrenia or other psychotic disorders	1 (1.4%)	0 (0%)
None of the above	28 (40.6%)	17 (54.8%)
Other	7 (10.1%)	2 (6.5%)
<i>Non-suicidal self-injury (NSSI)</i> ^b		
Engaged in NSSI before the onset of gender dysphoria	19 (27.5%)	5 (16.1%)
<i>Trauma</i> ^c		
Experienced a trauma less than one year before the start of gender dysphoria	33 (47.8%)	4 (12.9%)

*May select more than one answer

^aNatal sex difference for one or more pre-existing diagnoses (100-none of the above) was not significant [$\chi^2(1, 100) = 1.76$]

^bNatal sex differences for NSSI before the onset of gender dysphoria was not significant ($\chi^2 = 1.52$)

^cExperiencing a trauma less than one year before the start of gender dysphoria was statistically different [$\chi^2(1, 100) = 11.19, p < .001$] with natal females > natal males

Table 3 Transition reasons

	Natal female <i>N</i> (%) <i>N</i> = 69	Natal male <i>N</i> (%) <i>N</i> = 31
<i>Reasons for transition</i> [*]		
I wanted others to perceive me as the target gender	53 (76.8%)	24 (77.4%)
I thought transitioning was my only option to feel better	50 (72.5%)	21 (67.7%)
My body felt wrong to me the way it was	50 (72.5%)	21 (67.7%)
I didn't want to be associated with my natal sex/natal gender	51 (73.9%)	19 (61.3%)
It made me uncomfortable to be perceived romantically/sexually as a member of my natal sex/natal gender	49 (71.0%)	18 (58.1%)
I thought transitioning would eliminate my gender dysphoria	43 (62.3%)	22 (71.0%)
I felt I would become my true self	42 (60.9%)	22 (71.0%)
I identified with the target gender	40 (58.0%)	24 (77.4%)
I thought transitioning would lessen my gender dysphoria	45 (65.2%)	18 (58.1%)
I felt I would fit in better with the target gender	36 (56.5%)	20 (64.5%)
I felt I would be more socially acceptable as a member of the target gender	38 (55.1%)	11 (35.5%)
I felt I would be treated better if I was perceived as the target gender	35 (50.7%)	14 (45.2%)
I saw myself as a member of the target gender	31 (44.9%)	18 (58.1%)
I thought transitioning would reduce gender-related harassment or trauma I was experiencing	35 (50.7%)	5 (16.1%)
I had erotic reasons for wanting to transition	9 (13.0%)	12 (38.7%)
Other	9 (13.0%)	3 (9.7%)

*May select more than one answer

participants experienced the friendship group dynamics identified in previous work, including belonging to a friendship group that mocked people who were not transgender (22.2%), having one or more friend from the pre-existing friend group transition before the participant decided to transition (36.4%), and experiencing an increase in popularity after announcing plans to transition (19.6%) (Littman, 2018). Most did not have this experience (68.7%, 61.6%, and 62.9%, respectively).

Pressure to transition. More than a third of the participants (37.4%) felt pressured to transition. Natal sex differences in feeling pressured to transition were significant by chi-square test with natal females > natal males $\chi^2(1, 99) = 4.22, p = .04$. Twenty-eight participants provided open-text responses of which 24 described sources of pressure (17 described social pressures and 7 described sources that were not associated with other people). Clinicians, partners, friends, and society were named as sources that applied pressure to transition, as seen in the following quotes: “My gender therapist acted like it [transition] was a panacea for everything;” “[My] [d]octor pushed drugs and surgery at every visit;” “I was dating a trans woman and she framed our relationship in a way that was contingent on my being trans;” “A couple of later trans friends kept insisting that I needed to stop delaying things;” “[My] best friend told me repeatedly that it [transition] was best for me;” “The forums and communities and internet friends;” “By the whole of society telling me I was wrong as a lesbian;” and “Everyone says that if you feel like a different gender... then you just are that gender and you should transition.” Participants also felt pressure to transition that did not involve other people as illustrated by the following: “I felt pressured by my inability to function with dysphoria” and “Not by people. By my life circumstances.”

Experiences with clinicians. When participants first sought care for their gender dysphoria or desire to transition, more than half of the participants (53.0%) saw a psychiatrist or psychologist; about a third saw a primary care doctor (34.0%) or a counselor (including licensed clinician social worker, licensed professional counselor, or marriage and family therapist) (32.0%); and 17.0% saw an endocrinologist. For transition, 45.0% of participants went to a gender clinic (44.4% of those attending a gender clinic specified that the gender clinic used the informed consent model of care); 28.0% went to a private doctor’s office; 26.0% went to a group practice; and 13.0% went to a mental health clinic (see supplemental materials).

The majority (56.7%) of participants felt that the evaluation they received by a doctor or mental health professional prior to transition was not adequate and 65.3% reported that their clinicians did not evaluate whether their desire to transition was secondary to trauma or a mental health condition. Although 27.0% believed that the counseling and information they received prior to transition was accurate about benefits and risks, nearly half reported that the counseling was overly positive about the benefits of transition (46.0%) and not negative enough about the risks (26.0%). In contrast, only a small

minority found the counseling not positive enough about benefits (5.0%) or too negative about risks (6.0%) suggesting a bias toward encouraging transition.

Transition

Participants were on average 21.9 years old ($SD = 6.1$) when they sought medical care to transition with natal females seeking care at younger ages ($M = 20.0$; $SD = 4.2$) than natal males ($M = 26.0$; $SD = 7.5$), $t(97) = -5.07, p < .001$. Given that the majority of natal males were categorized as Blanchard typology non-homosexual, the finding that natal males sought medical care to transition at older ages than natal females is concordant with previous research (Blanchard et al., 1987). The average year for seeking care was more recent for natal females ($M = 2011$; $SD = 3.8$) than natal males ($M = 2007$; $SD = 6.9$), $t(96) = 2.78, p = .007$, and thus, there may have been differences in the care they received due to differences in the culture surrounding transition and the prevailing medical approaches to gender dysphoria for the time.

At the start of transitioning, nearly all (98.0%) of the participants identified as either transgender (80.0%), nonbinary (15.0%), or both transgender and nonbinary (3.0%). Participants identified which social, medical, and surgical steps they had taken to transition. Table 4 shows these steps, separated by natal sex where appropriate. Most respondents adopted new pronouns (91.0%) and names (88.0%), and the vast majority (97.1%) of natal females wore a binder. Most participants took cross-sex hormones (96.0%) and most natal males took anti-androgens (87.1%). The most frequent transition surgery was breast or chest surgery for natal females (33.3%). Genital surgery was less common (1.4% of natal females and 16.1% of natal males). Natal females took testosterone for a mean duration of 2.0 years ($SD = 1.6$). Natal males took estrogen for a mean duration of 5.1 years ($SD = 5.9$) and anti-androgens for 2.8 years ($SD = 2.6$). The minority of patients who took puberty blockers took them for a mean duration of less than a year ($M = 0.9$ years; $SD = 0.6$).

Detransition

Before deciding to detransition, participants remained transitioned for a mean duration of 3.9 years ($SD = 4.1$) with natal females remaining transitioned for a shorter period of time ($M = 3.2$ years; $SD = 2.7$) than natal males ($M = 5.4$ years; $SD = 6.1$), $t(96) = -2.40, p = .018$. When participants decided to detransition they were a mean age of 26.4 years old ($SD = 7.4$) though natal females were significantly younger ($M = 23.6$; $SD = 4.5$) than natal males ($M = 32.7$; $SD = 8.8$), $t(97) = -6.75, p < .001$. The mean calendar year when participants decided to detransition was 2014 ($M = 2014$; $SD = 3.3$), but the difference

Table 4 Steps taken for social, medical, and surgical transition

	<i>N</i> (%)
<i>Social transition*</i>	
Pronouns	91 (91.0%)
Different name	88 (88.0%)
Clothes/hair/makeup	90 (90.0%)
Legal name change	49 (49.0%)
Gender/sex changed on government documents	36 (36.0%)
Voice training	20 (20.0%)
Natal female	
Wore a binder	67 (97.1%)
<i>Medical transition*</i>	
Cross-sex hormones	96 (96.0%)
Puberty blockers	7 (7.0%)
Natal male	
Anti-androgens	27 (87.1%)
<i>Surgical transition*</i>	
Face/neck surgery	5 (5.0%)
Natal female	
Breast/chest surgery	23 (33.3%)
Genital surgery (to create a penis)	1 (1.4%)
Natal male	
Breast implants	5 (16.1%)
Genital surgery (to create a vagina)	5 (16.1%)

*May select more than one answer

between natal females and natal males was not significant ($M=2014$, $SD=3.3$; $M=2014$, $SD=3.5$), $t(95)=0.52$.

Respondents detransitioned for a variety of reasons and most (87.0%) selected more than one reason. The most frequently endorsed reason for detransitioning was that the respondent's personal definition of male and female changed and they became comfortable identifying with their natal sex (60.0%) (see Table 5). Other commonly endorsed reasons were concerns about potential medical complications (49.0%); transition did not improve their mental health (42.0%); dissatisfaction with the physical results of transition (40.0%); and discovering that something specific like trauma or a mental health condition caused their gender dysphoria (38.0%). External pressures to detransition such as experiencing discrimination (23.0%) or worrying about paying for treatments (17.0%) were less common.

Encouragement and pressure to detransition. Participants were asked to select sources that encouraged them to believe that detransitioning would help them. These included blogs (37.0%), Tumblr (35.0%), and YouTube detransition videos (23.0%) (see supplemental materials). At some point in their process, 23.2% felt pressured to detransition. There was no significant difference between natal females and natal males for feeling pressured to detransition, $\chi^2(1, 99)=1.11$. Of the 21 open-text responses provided, 14 respondents expressed social pressure to detransition; three expressed internal pressure to detransition and four provided responses that were neither

Table 5 Reasons for detransitioning

	Natal female <i>N</i> (%) <i>N</i> =69	Natal male <i>N</i> (%) <i>N</i> =31
<i>Reasons for detransitioning*</i>		
My personal definition of female or male changed and I became more comfortable identifying as my natal sex	45 (65.2%)	15 (48.4%)
I was concerned about potential medical complications from transitioning	40 (58.0%)	9 (29.0%)
My mental health did not improve while transitioning	31 (44.9%)	11 (35.5%)
I was dissatisfied by the physical results of the transition/felt the change was too much	35 (50.7%)	5 (16.1%)
I discovered that my gender dysphoria was caused by something specific (ex, trauma, abuse, mental health condition)	28 (40.6%)	10 (32.3%)
My mental health was worse while transitioning	27 (39.1%)	9 (29.0%)
I was dissatisfied by the physical results of the transition/felt the change was not enough	22 (31.9%)	11 (35.5%)
I found more effective ways to help my gender dysphoria	25 (36.2%)	7 (22.6%)
My physical health was worse while transitioning	21 (30.4%)	11 (35.5%)
I felt discriminated against	12 (17.4%)	11 (35.5%)
I had medical complications from transitioning	12 (17.4%)	7 (22.6%)
Financial concerns about paying for transition care	11 (15.9%)	6 (19.4%)
My gender dysphoria resolved	10 (14.5%)	5 (16.1%)
My physical health did not improve while transitioning	9 (13.0%)	2 (6.5%)
I resolved the specific issue that was the cause of my gender dysphoria	6 (8.7%)	4 (12.9%)
I realized that my desire to transition was erotically motivated	1 (1.4%)	5 (16.1%)
Other	19 (27.5%)	6 (19.4%)

*May select more than one answer

or unclear. Regarding social pressure to detransition, seven participants expressed that the pressure came from partners, parents, or other family members as shown in the following example quotes: “I was threatened that if I did not immediately detransition I would NEVER see my [...] children again,” “My father very much wanted me to desist,” and “Parents constantly encouraging me to detransition.” Five participants expressed societal pressure to detransition as expressed in the following quotes: “I did not pass, I was mocked in public, I could not get a job. It was not ok to be trans” and “Well, I mean basically the entire world was against me transitioning, so yeah.” One participant felt pressured by doctors and another one from a blog.

Detransition steps. Table 6 shows data about the social, medical, and surgical steps participants took to detransition. Nearly all participants medically detransitioned by ceasing cross-sex hormones (95.0%). Social detransition steps were also common and included returning to the use of previously used pronouns (63.0%) and birth names (33.0%) and changing one’s clothes and hair presentations (48.0%). Surgical detransition steps were less common (9.0%).

Finding better ways of coping with gender dysphoria. Participants were asked to select responses that they considered to have been better ways for them to cope with their gender dysphoria. Responses included community (44.0%), mindfulness/meditation (41.0%), exercise (39.0%), therapy (24.0%), trauma work (24.0%), medication to treat a mental health condition (18.0%), and yoga (14.0%).

Transition and Detransition Narratives

Several transition and detransition narratives emerged from the data. A sizable minority of participants (41.0%) expressed more than one narrative in their responses.

The *discrimination and external pressures to detransition* narrative was described by 29.0% of participants. Examples include: “I had to detransition in order to get a job”; “I was afraid of being homeless and unable to support myself”; “I felt much happier with myself but I couldn’t go anywhere without being afraid. I passed okay but not perfectly. I was stared down and sneered at in the women’s clothes section, I wouldn’t dare use a public toilet because I’d find either violent men or women who wished an encounter with a violent man on me.”

A *nonbinary* narrative was expressed by 16.0% of participants. Some described that they discovered their nonbinary gender identity during their transition, as in the following quotes: “I still was uncomfortable with my body and figured I should stop and make sure I really wanted to keep going. I didn’t and I decided I must be nonbinary, not FTM”; “Transitioning didn’t do what I thought I wanted it to. I had transitioned to the wrong gender. I still felt wrong. Then, I realized I was not male, but genderqueer. I detransitioned to suit my true identity.” And others described a consistent nonbinary identification, as in the following quote, “I identified the same way that I did before.

Table 6 Social, medical, and surgical detransition steps

	N (%)
<i>Social detransition*</i>	
Previous pronouns	63 (63.0%)
Clothes/hair/makeup	48 (48.0%)
Birth name	33 (33.0%)
New name (not birth name)	24 (24.0%)
None of the above	2 (2.0%)
<i>Medical detransition*</i>	
Stopped cross-sex hormones	95 (95.0%)
Stopped puberty blockers	4 (4.0%)
Started hormones consistent with natal sex	14 (14.0%)
Natal male	
Stopped anti-androgens	17 (54.8%)
<i>Surgical detransition*</i>	
Surgery to reverse changes from transition	9 (9.0%)

*May select more than one answer

I had gotten what I wanted out of HRT and was ready to stop taking it.” (Cross-sex hormones are sometimes referred to as “hormone replacement therapy” and abbreviated as HRT).

Three participants (3.0%) expressed the *retransition* narrative in open-text answers indicating that they had retransitioned, including the following quotes: “I am now transitioning for a second time”; “I retransitioned after 5 years of detransitioning”; and “Anyway, I retransitioned over 10 years after detransitioning.”

Most participants (58.0%) expressed the *gender dysphoria was caused by trauma or a mental health condition* narrative which included endorsing the response options indicating that their gender dysphoria was caused by something specific, such as a trauma or a mental health condition. More than half of the participants (51.2%) responded that they believe that the process of transitioning delayed or prevented them from dealing with or being treated for trauma or a mental health condition. The following are example quotes that were in response to why participants chose to detransition: “I slowly began addressing the mental health conditions and traumatic experiences that caused such a severe disconnect between myself and my body...”; “I was starting to become critical of transition because I felt that many people were doing it out of self-hatred and started to realize that applied to me as well”; “I was deeply uncomfortable with my secondary sex characteristics, which I now understand was a result of childhood trauma and associating my secondary sex characteristics with those events.”

Despite the absence of any questions about this topic in the survey, nearly a quarter (23.0%) of the participants expressed the *internalized homophobia and difficulty accepting oneself as lesbian, gay, or bisexual* narrative by spontaneously describing that these experiences were instrumental to their gender dysphoria, their desire to transition, and their detransition. All

of the participants in this category indicated that they were either same-sex attracted exclusively or were same-sex attracted in combination with opposite-sex attraction (such as bisexual, pansexual, etc.). The following responses were written in as “other” for the question about why participants transitioned: “Transitioning to male would mean my attraction to girls would be ‘normal’”; “being a ‘gay trans man’ (female dating other females) felt better than being a lesbian, less shameful”; “I felt being the opposite gender would make my repressed same-sex attraction less scary”; “I didn’t want to be a gay man.” Some participants described that it took time for them to gain an understanding of themselves as lesbian, gay, or bisexual as seen in the following: “At the time I was trying to figure out my identity and felt very male and thought I was transgender. I later discovered that I was a lesbian...”; and “Well, after deep discovery, I realized I was a gay man and realized that a sexual trauma after puberty might [have] confused my thought. I wanted to live as a gay man again.” Several natal female respondents expressed that seeing other butch lesbians would have been helpful to them as shown by the following: “What would have helped me is being able to access women’s community, specifically lesbian community. I needed access to diverse female role-models and mentors, especially other butch women.”

The *social influence* narrative was identified where participants added information to the question about if they had felt pressured to transition and the response described pressure from a person or people. One-fifth (20.0%) of participants expressed that they felt pressured by a person or people to transition. Example quotes for social influence were described in a previous section.

Of the natal females, 7.2% expressed the *misogyny* narrative. Example quotes include: “...I realized how much of it [dysphoria] may have been caused by internalized misogyny and homophobia”; “Finally realizing there’s nothing wrong or disgusting or weak about being female”; and “My transition was a desperate attempt to distance myself from womanhood and femaleness due to internalized lesbophobia and misogyny combined with a history of sexual trauma.”

After Detransition

Disposition. At the time of survey completion, most participants had returned to identifying solely as their birth sex (61.0%) with an additional 10.0% identifying as their birth sex plus another identification. Fourteen percent of the participants identified solely as nonbinary with an additional 11.0% identifying as nonbinary plus a second identification. Eight percent of the participants identified solely as transgender with an additional 5.0% identifying as transgender plus another identification. Four percent of the responses did not fit into the above categories and were coded as “other.” Figure 1 illustrates the distribution of participants’ current gender identification (post-detransition). Only 24.0% of participants had informed

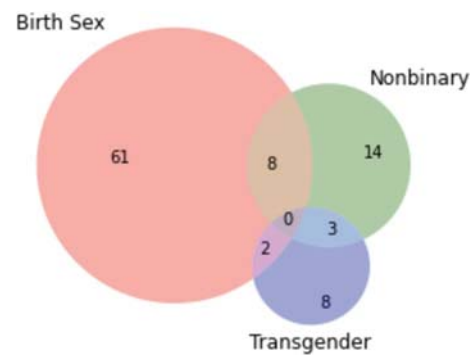


Fig. 1 Distribution of participants’ current gender identification (after detransition) (n=100). *Notes:* The sum of the numbers appearing in the “Birth Sex” circle indicates the number of participants who returned to identifying with their birth sex (71)—either as birth sex alone (61) or birth sex in addition to a second identification (10) represented in the overlap between two circles. For example, eight participants identify as their birth sex and as nonbinary. The sum of the numbers appearing in the “Nonbinary” circle indicates the number of participants who identify as nonbinary (25)—either as nonbinary alone (14) or nonbinary in addition to a second identification (11). The sum of the numbers appearing in the “Transgender” circle indicates the number of participants who identify as transgender (13)—either as transgender alone (8) or transgender in addition to a second identification (5). Four participants had responses that did not fit the categories above and were coded as “other”

the doctor or clinic that facilitated their transitions that they had detransitioned.

Self-appraisal of past transgender identification. Table 7 presents the data for responses endorsed by participants to reflect how they feel currently about having identified as transgender in the past. The statements most frequently selected included: “I thought gender dysphoria was the best explanation for what I was feeling” (57.0%), “My gender dysphoria was similar to the gender dysphoria of those who remain transitioned” (42.0%), “What I thought were feelings of being transgender actually were the result of trauma” (36.0%), “What I thought were feelings of being transgender actually were the result of a mental health condition” (36.0%).

Self-appraisal of transition and detransition. When asked to select which statement best reflects their feelings about their transition, nearly a third (30.0%) indicated that they wish they had never transitioned while 11.0% indicated they were glad they transitioned. Some (34.0%) selected the statement that transition “was a necessary part of [their] journey” but others (21.0%) indicated that the process of transitioning distracted them from what they should have been doing. Responses about whether transition helped or harmed them were also complicated. While 50.5% selected answers consistent with being both helped and harmed, 32.3% indicated that they were only harmed and 17.2% indicated that they were only helped. The majority of respondents were dissatisfied with their decision to transition (69.7%) and satisfied with their decision to detransition (84.7%). At least some amount of transition regret was

Table 7 Self-appraisal of past transgender identification

	Natal female <i>N</i> (%) <i>N</i> = 69	Natal male <i>N</i> (%) <i>N</i> = 31
<i>Self-appraisal about identifying as transgender in the past*</i>		
I thought gender dysphoria was the best explanation for what I was feeling	39 (56.5%)	18 (58.1%)
My gender dysphoria was similar to the gender dysphoria of those who remain transitioned	32 (46.4%)	10 (32.3%)
What I thought were feelings of being transgender actually were the result of trauma	31 (44.9%)	5 (16.1%)
What I thought were feelings of being transgender actually were the result of a mental health condition	28 (40.6%)	8 (25.8%)
Someone else told me that the feelings I was having meant that I was transgender and I believed them	25 (36.2%)	10 (32.3%)
I still identify as transgender	20 (29.0%)	10 (32.3%)
I believed I was transgender then, but I was mistaken	16 (23.2%)	6 (19.4%)
I was transgender then but I am not transgender now	15 (21.7%)	7 (22.6%)
I formerly identified as transgender and now identify as genderqueer/nonbinary	12 (17.4%)	5 (16.1%)
My gender dysphoria was different from the gender dysphoria of those who remain transitioned	11 (15.9%)	4 (12.9%)
I was never transgender	8 (11.6%)	3 (9.7%)
I thought I had gender dysphoria but I was mistaken	4 (5.8%)	4 (12.9%)
I never had gender dysphoria	1 (1.4%)	2 (6.5%)
N/A as I did not identify as transgender in the past	0 (0%)	1 (3.2%)
Other	18 (26.1%)	5 (16.1%)

*May select more than one answer

common (79.8%) and nearly half (49.5%) reported strong or very strong regret. Most respondents (64.6%) indicated that if they knew then what they know now, they would not have chosen to transition.

Discussion

This study was designed to explore the experiences of individuals who obtained medical and surgical treatment for gender dysphoria and then detransitioned by discontinuing the medications or having surgery to reverse the changes from transition. The findings of this study, however, should not be assumed to be representative of all individuals who detransition. Although this study further documents that detransitioners exist, the prevalence of detransition as an outcome of transition is unknown. Only a small percentage of detransitioners (24.0%) informed the clinicians and clinics that facilitated their transitions that they had detransitioned. Therefore, clinic rates of detransition are likely to be underestimated and gender transition specialists may be unaware of how many of their own patients have detransitioned, particularly for patients who are no longer under their care.

This research demonstrates that the experiences of individuals who detransition are varied and the reasons for detransition are complex. Nearly all participants identified as transgender or nonbinary at the start of their transition and most sought transition because they did not want to be associated with their natal

sex, their bodies felt wrong the way they were, and they believed that transition was the only option to relieve their distress. Some were helped by transition and only detransitioned because they were pressured to do so by people in their lives, society, or because they had medical complications. Some were harmed by transition and detransitioned because they concluded that their gender dysphoria was caused by trauma, a mental health condition, internalized homophobia, or misogyny—conditions that are not likely to be resolved with transition. These findings highlight the complexity of gender dysphoria and suggest that, in some cases, failure to explore co-morbidities and the context in which the gender dysphoria emerged can lead to misdiagnosis, missed diagnoses, and inappropriate gender transition. Some individuals detransitioned because their gender dysphoria resolved, because they found better ways to address their symptoms, or because their personal definitions of male and female changed and they became comfortable identifying as their natal sex.

The study sample was predominantly young natal females, many of whom experienced late-onset gender dysphoria which mirrors the recent, striking changes in the demographics of gender dysphoric youth seeking care as well as the youth described by their parents in Littman (2018) (see also Aitken et al., 2015; de Graaf et al., 2018; Zucker, 2019). Concerns have been raised that this new cohort of gender dysphoric individuals is unlike previous cohorts. Professionals have started to call for caution before treating this cohort with interventions with permanent effects because the etiologies, desistance and persistence rates,

expected duration of symptoms, and whether this new population is helped or harmed by gender transition is still unknown (D'Angelo et al., 2021; Kaltiala-Heino et al., 2018). The natal females and natal males in this sample differed on several dimensions, including that natal females were younger than natal males when they sought transition, when they decided to detransition, and at the time of survey completion. Natal females were more likely than natal males to have experienced a trauma less than one year before the onset of their gender dysphoria and were more likely to have felt pressured to transition. Compared to natal males, natal females remained transitioned for a shorter duration of time before deciding to detransition. Additionally, natal females transitioned more recently than natal males, so their experiences may vary due to changing trends in the clinical management of gender dysphoria and the cultural settings in which they became gender dysphoric.

The study findings covered a wide range of detransition experiences that are consistent with the diversity of experiences described in previously published clinical case reports and case series. Overlap of findings include: transition regret; absence of transition regret; re-identification with birth sex; continued identification as transgender; improvement or worsening of well-being with transition; retransitioning; detransitioning due to external social pressures; nonbinary identification; and recognizing and accepting oneself as homosexual or bisexual (D'Angelo, 2018; Djordjevic et al., 2016; Levine, 2018; Pazos Guerra et al., 2020; Turban & Keuroghlian, 2018; Turban et al., 2021; Vandenbussche, 2021). The population in this study is similar to the population in Vandenbussche in that both were predominantly natal females in their mid-20s. Because the current study recruited in 2016–2017 and Vandenbussche recruited in 2019, the similar mean age of participants may reflect the age of individuals who can be reached in online detransitioner communities. Several findings in this study were consistent with Vandenbussche's findings, including similar reasons for detransition (realizing that their gender dysphoria was related to other issues, finding alternatives to address gender dysphoria, gender dysphoria resolved, etc.). Although these two studies were recruited in different years, had different eligibility criteria, and included participants from several countries, it is possible that there may be some overlap of study populations.

The current study findings provide additional insight into the complex relationships between internalized homophobia, gender dysphoria, and desire to transition. Contrary to arguments against the potential role of homophobia in gender transitions (Ashley, 2020), participants reported that their own gender dysphoria and desire to transition stemmed from the discomfort they felt about being same-sex attracted, their desire to not be gay, and the difficulties that they had accepting themselves as lesbian, gay or bisexual. For these individuals, exploring their distress and discomfort around sexual orientation issues may have been more helpful to them than medical and surgical transition or at least an important part of exploration before making

the decision to transition. This research adds to the existing evidence that gender dysphoria can be temporary (Ristori & Steensma, 2016; Singh et al., 2021; Zucker, 2018). It has been established that the most likely outcome for prepubertal youth with gender dysphoria is to develop into lesbian, gay, bisexual (LGB) (non-transgender) adults (Ristori & Steensma, 2016; Singh et al., 2021; Wallien & Cohen-Kettenis, 2008; Zucker, 2018). And, temporary gender dysphoria may be a common part of LGB identity development (Korte et al., 2008; Patterson, 2018). Therefore, intervening too soon to medicalize gender dysphoric youth risks iatrogenically derailing the development of youth who would otherwise grow up to be LGB non-transgender adults. Participants who detransitioned because they became comfortable identifying as their natal sex and because their gender dysphoria resolved further support that gender dysphoria is not always permanent.

The data in this study strengthen, with first-hand accounts, the rapid-onset gender dysphoria (ROGD) hypotheses which, briefly stated, are that psychosocial factors (such as trauma, mental health conditions, maladaptive coping mechanisms, internalized homophobia, and social influence) can cause or contribute to the development of gender dysphoria in some individuals (Littman, 2018). Littman also postulated that certain beliefs could be spread by peer contagion, including the belief that a wide range of symptoms should be interpreted as gender dysphoria (and proof of being transgender) and the belief that transition is the only solution to relieve distress. The current study supports the potential role of psychosocial factors in the development of gender dysphoria and further suggests, by participant responses that transitioning prevented or delayed them from addressing their underlying conditions, that maladaptive coping mechanisms may be relevant for some individuals. The potential role of social influence is demonstrated as well. First, when respondents were asked to describe how they currently feel about having identified as transgender in the past, more than a third endorsed the option, "Someone told me that the feelings I was having meant that I was transgender, and I believed them." Second, a subset of participants experienced the unique friendship group dynamics reported in Littman where peer groups mocked people who were not transgender and popularity within the friend group increased when respondents announced their plan to transition. Additionally, respondents identified several social sources that encouraged them to believe that transitioning would help them including: YouTube transition videos, blogs, Tumblr, and online communities. And finally, 20.0% of participants felt pressured to transition by social sources that included friends, partners, and society. More research is needed to further explore these hypotheses.

The current study and the Turban et al. (2021) analysis of the USTS data share some similarities and differences. Similarities include the use of convenience samples, targeted recruitment, and anonymous data collection. The findings of Turban et al. (including external pressures to detransition and transgender

identification after detransition) are a subset of the array of experiences described in the current study. The current study differed from James et al. (2016) and Turban et al. in that it enrolled participants based on the criterion of detransition after medical or surgical transition regardless of how they currently identified, recruited from communities with diverse perspectives about transition and detransition, used a precise definition for detransition that specifies the use of medication or surgery, and included answer options that were relevant to many different types of detransition experiences. In contrast, the USTS only enrolled transgender-identifying individuals regardless of whether they medically or surgically transitioned, recruited from communities likely to have similar perspectives about transition and detransition, and provided multiple choice answer options that were relevant to a narrower range of detransition experiences (James et al., 2016). Further, the definition used by the USTS for “detransitioned” (having “gone back to living as [their] sex assigned at birth, at least for a while”) is quite vague. Although Turban et al. provide valuable information about the subset of transgender-identifying people who may have detransitioned, the current study provides a more comprehensive view of individuals who detransition after medical or surgical transition.

Over the past 15 years, there have been substantial changes in the clinical approach to gender dysphoric patients notable for a shift from approaches that employ thorough evaluations and judicious use of medical and surgical transition (the watchful waiting or Dutch approach, the developmentally informed approach, and the medical model of care) to approaches with minimized or eliminated evaluation and liberal use of transition interventions (the affirmative approach and the informed consent model of care) (Cavanaugh et al., 2016; de Vries & Cohen-Kettenis, 2012; Meyer et al., 2002; Rafferty et al., 2018; Schulz, 2018; Zucker et al., 2012b). This trend is prominent in the U.S. where the American Academy of Pediatrics endorsed the affirmative approach in 2018 and Planned Parenthood currently uses the informed consent model to provide medical transition in more than 200 clinics in 35 states (Planned Parenthood, 2021; Rafferty et al., 2018). It is plausible that an unintended consequence of these clinical shifts may be an increase in people who detransition. Many participants in this study believe that they did not receive an adequate evaluation by a clinician before transition. The definition of “adequate evaluation” was not provided in the survey and may be open to respondent interpretation. But given the complexities of the gender dysphoria described in the current study, one might consider a low bar of “adequate” to be the exploration of factors that could be misinterpreted as non-temporary gender dysphoria as well as factors that could be underlying causes for gender dysphoria. The most recently emerging approach to gender dysphoria is called the “exploratory approach” which is a neutral psychotherapeutic approach to help individuals gain a deeper understanding of their gender distress and the factors contributing to

their dysphoria (Churcher Clarke & Spiliadis, 2019; Spiliadis, 2019). The study’s findings suggest that an exploratory type of approach may have been beneficial to some of the respondents. Future research is needed to determine which patients are best treated by which approaches long term.

Patients considering medical and surgical interventions deserve accurate information about the risks, benefits, and alternatives to that treatment. In this sample, nearly half of the participants reported that the counseling they received about transition was overly positive about the benefits of transition and more than a quarter reported that the counseling was not negative enough about the risks. Several participants felt pressured to transition by their doctors and therapists. If these types of clinical interactions are verified, exploration is needed to determine the extent to which this situation occurs and what measures might be taken to ensure that clinicians provide patients with their options accurately and dispassionately.

There are several obstacles to obtaining accurate rates of detransition and desistance, including stigma and the low numbers of detransitioners who inform their clinicians that they detransitioned. One approach to bypass some of these barriers would be to incorporate non-judgmental questions about detransition and desistance into nationally representative surveys that collect health data. For example, the Behavioral Risk Factor Surveillance System contains an optional module about sexual orientation and gender identity that includes two questions to explore gender issues (Downing & Przedworski, 2018). By changing one existing question, “Do you consider yourself to be transgender?” into two questions, “Have you ever, at any point in your life, considered yourself to be transgender?” and “Do you currently consider yourself to be transgender?” and by adding a follow-up question if answers indicate past but not current transgender identification, “Did you ever take puberty blockers, cross-sex hormones, anti-androgens, or have any surgery as part of your transition?”, valuable information about desistance, detransition, and current transgender identification could be obtained. These types of questions may also be of use in clinical practice and electronic medical records. The information gained about rates of detransition and desistance would enhance transgender healthcare by aiding informed consent processes at the start of any medical or surgical transition.

One of the strengths of this study is that it is one of the largest samples of detransitioners to date. Other strengths include the use of a precise definition for detransition, enrollment of detransitioners regardless of their post-detransition gender identification, recruitment from communities with likely divergent views about transition and detransition, and collaboration with two individuals who had detransitioned which helped to create a survey instrument with questions relevant to a variety of detransition experiences and enhanced the recruitment efforts.

There are several limitations to this study that should be considered when interpreting the findings. Like Vandembussche (2021), James et al. (2016), and Turban et al. (2021), this study

used a cross-sectional design, anonymous surveying, and a convenience sample and therefore shares the same limitations that are inherent to these methodologies. These limitations include that conclusions about causation cannot be determined, identities of participants cannot be verified, and the findings of this study may not be generalizable to the entire population of people who detransition or to people outside of the countries where participants were from. Although this study reached out to communities with differing perspectives about transition and detransition, targeted recruitment and convenience samples always introduce the limitations associated with selection biases which should be addressed in future research. Finally, many of the participants in this study had less than ideal outcomes to their medical and surgical transitions, and it is possible that these experiences may have colored some of the responses.

Additional research is needed to determine the prevalence of detransition as an outcome of transition and to identify and meet the psychological and medical needs of the emerging detransitioned population. Because many individuals who detransition re-identify with their birth sex, are no longer connected to LGBT communities, and don't return to gender clinics, future research about detransition needs to expand recruitment efforts beyond gender clinics and transgender communities. The development and testing of non-medical interventions for gender dysphoria could provide valuable options to be used as alternatives or in conjunction with medical and surgical treatments. Because of the potential for some to experience trauma, mental health conditions, internalized homophobia, and misogyny as gender dysphoria, research needs to be conducted on the evaluation process before transition to find approaches that respectfully and collaboratively explore factors that might contribute to gender-related distress. There continues to be an absence of long-term outcomes evidence for youth treated with medical and surgical transition and a lack of information about the trajectories of youth experiencing late-onset gender dysphoria—research is needed to address these gaps. Continued work is needed to reduce rigid gender roles, increase representation of gender stereotype nonconformity, and to address discrimination and social pressures exerted against people who are transgender, lesbian, gay, bisexual, and gender stereotype non-conforming.

Conclusion

This study described individuals who, after transitioning with medications or surgery, have detransitioned. The prevalence of detransitioning after transition is unknown but is likely underestimated because most of the participants did not inform the doctors who facilitated their transitions that they had detransitioned. There is no single narrative to explain the experiences of all individuals who detransition and we should take care to avoid painting this population with a broad brush. Some detransitioners return to identifying with their birth sex, some assume

(or maintain) a nonbinary identification, and some continue to identify as transgender. Some detransitioners regret transitioning and some do not. Some of the detransitioners reported experiences that support the ROGD hypotheses, including that their gender dysphoria began during or after puberty and that mental health issues, trauma, peers, social media, online communities, and difficulty accepting themselves as lesbian, gay, or bisexual were related to their gender dysphoria and desire to transition. Natal female and natal male detransitioners appear to have differences in their baseline characteristics and experiences and these differences should be further delineated. Future research about gender dysphoria and the outcomes of transition should consider the diversity of experiences and trajectories. More research is needed to determine how best to provide support and treatment for the long-term medical and psychological well-being of individuals who detransition. Findings about detransition should be used to improve our understanding of gender dysphoria and to better inform the processes of evaluation, counseling, and informed consent for individuals who are contemplating transition.

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Declarations

Conflict of interest The author has no relevant financial or non-financial conflicts of interest to disclose.

Consent to Participate Electronic consent was obtained from all participants included in the study. On the first page of the online survey, participants were informed of the research purpose and potential risks and benefits of participating, that their participation was voluntary, and were presented with a way to contact the researcher. The research survey questions were displayed only if the participant clicked “agree” which indicated that the participant read the information, voluntarily agreed to participate, and were at least 18 years of age.

Ethical Approval The research was determined to be Exempt Human Research by the Program for the Protection of Human Subjects of the Icahn School of Medicine at Mount Sinai in New York, NY. All procedures were performed in accordance with the ethical standards of the Program for the Protection of Human Subjects at the Icahn School of Medicine at Mount Sinai and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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The Role of Enjoyment and Motivational Climate in Relation to the Personal Development of Team Sport Athletes

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Sport has been identified as a context in which youth encounter positive and negative experiences. However, relatively little is known about the factors that lead to positive and negative personal development among sport participants. The purpose of this study was to investigate the role of enjoyment and motivational climate on positive and negative personal development of team sport participants. A sample of 510 athletes between the ages of 9 and 19 completed questionnaires on positive and negative personal development, enjoyment, and motivational climate. Stepwise multiple regression analyses examined the effects of enjoyment and motivational climate on the personal development of the athletes. Results demonstrated that positive experiences in sport were most strongly predicted by affiliation with peers, self-referenced competency, effort expenditure, and a task climate. Negative experiences were most strongly predicted by an ego climate and other-referenced competency. Results suggest that creating an environment that encourages peer affiliation and personal achievement can result in the positive personal development of youth sport participants.

Sport has been identified as the most popular structured activity for youth participation (Mahoney, Larson, Eccles, & Lord, 2005). Recently, Guèvremont, Findlay, and Kohen (2008) reported that approximately 76% of Canadian youth between the ages of 6 and 17 years participated in at least one structured sport activity in the past year. In the United States, it is estimated that approximately 62% of high school students participated on at least one school or nonschool sport team in the

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previous year (Pate, Trost, Levin, & Dowda, 2000). These data demonstrate that the majority of North American youth have some experience with organized sport.

Weiss and Williams (2004) summarized the reasons why youth participate in sport. They suggested that youth participate for reasons of physical competence/adequacy (i.e., improve skills, achieve goals), social acceptance (i.e., make new friends, team atmosphere), and enjoyment (i.e., energy release, excitement). These reasons point to the complexity of youth sport involvement, and demonstrate that individual (i.e., enjoyment) and environmental (i.e., team atmosphere) factors are important for understanding participation. Weiss and Williams concluded that participation in youth sport can be enhanced by (a) making sure the sport is enjoyable, (b) creating a task-oriented motivational climate, (c) providing social support, and (d) helping children help themselves. These recommendations highlight enjoyment and motivational climate as critical factors for prolonged participation of youth in sport. The following paragraphs elaborate on the relationship between enjoyment, motivational climate and youth sport.

Enjoyment is consistently associated with continued sport participation (Scanlan, Carpenter, Schmidt, Simons, & Keeler, 1993; Scanlan, Stein, & Ravizza, 1989; Weiss, Kimmel, & Smith, 2001; Wiersma, 2001). To explain why youth commit to sport, Scanlan and colleagues (Scanlan et al., 1989; 1993) developed the sport commitment model. They argued that sport commitment is influenced by five constructs. Four of these constructs—enjoyment, personal investment, social constraints, and involvement opportunities—were positively associated with commitment, while involvement alternatives were negatively related to sport commitment. Results of their analyses pointed to enjoyment as the most important component linked to youth's commitment to sports. Subsequent work by Weiss et al. (2001) extended the sport commitment model (Scanlan et al., 1993) by including enjoyment as a mediating variable rather than a direct predictor of sport commitment. Although not statistically more predictive than the model developed by Scanlan et al. (1993), Weiss and colleagues (2001) suggested that enjoyment could be conceived as a partial mediator in conceptualizing sport commitment. Both models support the contention that enjoyment plays an important role in youth's decision to participate in sport for an extended period of time. What is less clear is how an individual's enjoyment levels influence youth experience in sports.

Motivational climate is another important factor that is known to influence participation in sport (Balaguer, Duda, & Crespo, 1999; Duda & Balaguer, 2007; Smith, Smoll, & Cumming, 2007). Operationalized as either task or ego, motivational climate reflects an individual's perception of the sport setting. A task climate is created when the focus is on personal skill development regardless of how others perform. Conditions where coaches and/or peers encourage athletes to give their best effort in attaining challenging but realistic goals facilitate a task oriented climate. Alternatively, an ego climate is formed when the focus is on demonstrating superior ability over others (Smith et al., 2007). In general, research on motivational climate suggests that a task climate has a positive effect on athletes while an ego climate results in negative sport experiences (Duda & Balaguer, 2007). In a study investigating the effects of a motivational climate intervention with coaches on athlete anxiety levels, Smith et al. (2007) found that athletes who played for coaches who received task climate training decreased in anxiety throughout the season. Athletes who played for coaches who did not receive any training increased

in anxiety as the season progressed. Balaguer et al. (1999) investigated perceptions of motivational climate on satisfaction and coach ratings in a group of 219 tennis players and found that task climate was linked to increased perceptions of ability to use psychological skills, satisfaction with level of play, and match results. Their results were corroborated by Cumming, Smoll, Smith, and Grossbard (2007) who found that a task climate was significantly related to an athlete's satisfaction with the coach. Cumming et al. also found that a task climate was related to win-loss records and enjoyment. Alternatively, perceptions of an ego climate are associated with negative experiences such as peer conflict (Ommundsen, Roberts, Lemyre, & Miller, 2005), negative perceptions of the coach (Smith, Fry, Ethington, & Li, 2005), and increased anxiety (Pensgaard & Roberts, 2002). Overall, these studies suggest that a task oriented motivational climate is beneficial for sport participation while an ego climate can reduce participation in youth.

While the above research studies pertaining to enjoyment and motivational climate are largely framed around sport participation, it has been suggested that another primary goal of youth sport programs should be personal development (Côté & Fraser-Thomas, 2007). Authors argue that a properly structured youth sport program is an ideal setting in which youth can learn valuable skills that can be applied to other facets of their lives (Fraser-Thomas, Côté, & Deakin, 2005; Petitpas, Cornelius, Van Raalte, & Jones, 2005). Hansen and colleagues (Hansen & Larson, 2007; Hansen, Larson, & Dworkin, 2003; Larson, Hansen, & Moneta, 2006) tested this assumption with a series of studies that examined the experiences of youth in different structured activities (i.e., sports, arts, faith groups, academic programs, community groups). Hansen et al. (2003) found that sport participants and faith groups developed higher emotional regulation than academic groups. They also found that sport participants reported higher rates of negative peer interactions than faith, academic, and arts groups and that inappropriate adult behaviors were higher in sports than in faith groups. In another study of 2280 11th grade youth who participated in the same activities outlined above, Larson et al. (2006) found that sport participants reported higher rates of goal setting and effort; however athletes also reported higher levels of the negative experiences of stress and social exclusion compared with other activities.

A more recent study by Strachan, Côté, and Deakin (2009) assessed positive and negative personal development between groups of athletes aged 12–16 years who *sample* (athletes who participate in multiple sports) or *specialize* (athletes heavily invested in only one sport). They found that athletes in the sampling group reported stronger links to their sport, family, and community, whereas specialists reported higher rates of diverse peer groups, but also higher rates of physical and emotional exhaustion. These results demonstrate that participation in sport is related to a range of positive and negative developmental experiences.

Given that enjoyment and motivational climate are established predictors of sport participation, they may also be useful in predicting other youth sport outcomes such as positive and negative personal development. However, these relationships have yet to be investigated. One possible explanation for the lack of research on this topic is the shortage of tools available to measure personal development in sport participants. Until recently, a personal development measure designed specifically for sport participants had yet to be developed. MacDonald, Deakin, Eys, and Côté (2009) created the Youth Experiences Survey for Sport (YES-S) by modifying the

more general Youth Experience Survey (YES; Hansen & Larson, 2002; 2005). The YES-S is a 37-item scale that measures positive and negative personal development of sport participants on the five dimensions of personal and social skills, cognitive skills, goal setting, initiative, and negative experiences. As a result, the purpose of the current study was to examine the effects of enjoyment and motivational climate on the personal development of youth sport participants. Hypotheses were that higher reports of enjoyment and task climate would be associated with positive personal development experiences and that higher reports of an ego climate would be associated with greater negative experiences.

Method

Participants

The participants in the study were 510 male (47.5%) and female (52.5%) athletes between the ages of 9 and 19 years ($M = 14.88$, $SD = 1.58$). Athletes participated in school sports or nonelite community programs across the sports of baseball (9), basketball (68), curling (6), dance (29), football (55), hockey (132), lacrosse (13), ringette (11), rowing (2), soccer (99), softball (20), synchronized swimming (10), and volleyball (56). A diverse sample of team sports was used to provide a wide range of possible experiences. The sample was limited to team sports given that motivational climate reflects individual perceptions of group atmosphere. The operational definition used in the current study to represent team sports was that athletes practice and compete as a group.

Measures

Youth Experience Survey for Sport. Positive and negative personal development experiences were assessed using the Youth Experience Survey for Sport (YES-S; MacDonald et al., 2009). The YES-S was developed from a modified version of the Youth Experience Survey 2.0 (YES; Hansen & Larson, 2005) in a group of 637 youth sport participants. The YES-S is a 37-item questionnaire that measures personal development experiences of youth sport participants on the five dimensions of personal and social skills (14 items; i.e., “I became better at giving feedback”), cognitive skills (5 items; i.e., “this activity increased my desire to stay in school”), goal setting (4 items; i.e., “I set goals for myself in this activity”), initiative (4 items; i.e., “I put all my energy into this activity”), and negative experiences (10 items; i.e., “I got stuck doing more than my fair share”). Athletes reflect on their current or recent sport involvement in a given setting and respond to each statement using a 4-point Likert-type scale anchored by ‘Not at all’ to ‘Yes definitely’ as representing experiences that occurred during their sport involvement. The instrument has shown acceptable psychometric properties with values of $Q = 2.32$, $CFI = .91$, and $RMSEA = .06$ (MacDonald et al., 2009). Reliability analyses of the subscales in the current study produced Cronbach alpha values between .79 and .90.

Sources of Enjoyment in Youth Sport Questionnaire. The second measure used was the Sources of Enjoyment in Youth Sport Questionnaire (SEYSQ; Wiersma,

2001). The SEYSQ is a 28-item scale that measures enjoyment on the six dimensions of self-referenced competency (4 items; i.e., “playing well compared to how I’ve played in the past”), other-referenced competency and recognition (6 items; i.e., “being better in my sport than other athletes my age or in my league”), effort expenditure (5 items; i.e., “playing hard during competition”), competitive excitement (4 items; i.e., “the excitement of competition”), affiliation with peers (5 items; i.e., “being with friends on my team”), and positive parental involvement (4 items; i.e., “getting support from my parent(s) for playing my sport”). Each statement is preceded by the stem “During the times when I most enjoy sport, I usually experience that enjoyment from . . .”. Responses on the SEYSQ are given using a 5-point Likert-type scale that ranges from ‘Not at all’ to ‘Very much’. The six-factor structure of the SEYSQ has been validated by Wiersma (2001) with a sample of 896 young athletes between the ages of 12 and 18 years. Results of the confirmatory factor analysis demonstrated good fit parameters with a RMSEA = .05 and a CFI = .97. Reliability analyses demonstrated acceptable values ranging between .65 and .85. In the current study, reliability coefficients for the different subscales of the SEYSQ were between .74 and .84.

Motivational Climate Scale for Youth Sport. The final measure used was the Motivational Climate Scale for Youth Sport (MCSYS; Smith, Cumming, & Smoll, 2008). The instrument was developed with 992 young athletes between the ages of 9 and 16 years and measures two dimensions of motivational climate (task and ego) present in the youth sport domain. The two factor model tested by Smith et al. (2008) demonstrated strong psychometric properties with values of $Q = 1.52$, CFI = .97, GFI = .97, and RMSEA = .04. Specifically, the MCSYS asks athletes to rate 12 statements related to the sport climate on a 1 (Not at all true) to 5 (Very true) Likert-type scale. Six statements are linked to a task climate while six are related to an ego climate. In the current study, task and ego subscales showed reliability coefficients of .82 and .79 respectively.

Procedure

Data were collected from community sport programs and high schools located in the province of Ontario, Canada. Following university ethics approval, sport programs and high schools were contacted for participation in the study. When a school or program agreed to participate, arrangements were made to secure a time during which data collection could occur.

For the athletes in the schools, data collection occurred during a designated class time. Before data collection, letters of information and consent were sent home with students. A research assistant then proceeded with the data collection phase with students who agreed to participate. Athletes were given the opportunity to withdraw from the study on the day of data collection if they did not want to participate. The students who agreed to participate were given instructions about the purpose of the study and asked to fill out each questionnaire with their primary sport in mind. These instructions allowed athlete’s to choose the sport in which they were most involved and reflect on the experiences that occurred in that environment. Any questions that came up during data collection were addressed immediately. All questionnaires were completed during the designated time and collected by the

research assistant. The time needed for participants to complete the questionnaires was approximately 30–40 min.

Once sport teams agreed to participate, a meeting time was arranged to explain the purpose of the study and provide athletes the opportunity to complete the questionnaires. This meeting typically occurred at the end of a practice or game. During this meeting, the purpose was explained and appropriate documentation was provided to the participants. Participation was voluntary and athletes could withdraw at any moment without consequence. A copy of each questionnaire, letter of information, and consent/assent forms were distributed to athletes who agreed to participate. Each participant was encouraged to complete the questionnaires on location however some could not commit the 30–40 min required to complete the forms and completed the questionnaires at home. When athletes completed the questionnaire at home, the primary researcher returned after a subsequent practice or game to collect the completed documents. Athletes returned the completed questionnaires to the primary researcher in a sealed envelope. Only a small number of athletes were unable to commit the time required to complete the questionnaires and chose to not participate in the study.

Data Analysis

Data were entered into a spreadsheet and cleaned to contain only valid cases. In some instances participants did not complete all the questionnaires; these individuals were subsequently removed from the analysis due to large amounts of missing data. For other missing data, a pairwise deletion method was employed. This method removes individual cases in the variable of interest. A research assistant double checked the data for entry errors. With incomplete cases removed, normality and homoscedasticity were assessed across variables of interest. No variables had to be recoded due to nonnormal or heteroscedastic patterns.

Stepwise multiple regression analysis was used to assess the relationships between subscales of the SEYSQ and MCSYS on personal development as outlined by the YES-S. Stepwise regression was selected over other approaches because the relationships between experiences, enjoyment, and motivational climate have yet to be established. Therefore, a method which builds a model was preferred over a method that tests a model (Tabachnick & Fidell, 2007). Five separate models using each subscale of the YES-S as the dependent variable tested the relationships.

Results

Mean and standard deviation values for each subscale with corresponding reliability coefficients are presented in Table 1. Mean values of the YES-S demonstrate that youth experiences were quite positive but that athletes also faced negative experiences. The climate in which these activities took place were mainly task oriented and athletes reported high levels of enjoyment on all subscales. Reliability analyses of the YES-S, MCSYS and SEYSQ showed acceptable values for each of the subscales. Inspection of correlations between subscales of the SEYSQ and MCSYS showed low to moderate relationships with Pearson coefficients between $-.30$ and $.63$ (Table 2).

Table 1 Descriptive Statistics and Cronbach Reliability Coefficients of the YES-S, MCSYS, and SEYSQ Subscales

	M	SD	α
Youth Experience Survey for Sport ^a			
Personal and social skills	2.98	.63	.90
Cognitive skills	2.26	.87	.84
Goal setting	3.06	.69	.81
Initiative	3.47	.56	.79
Negative experiences	1.71	.79	.93
Motivational Climate Scale for Youth Sport ^b			
Task climate	4.11	.71	.82
Ego climate	2.24	.86	.79
Sources of Enjoyment in Youth Sport Questionnaire ^b			
Self-referenced competency	4.24	.65	.74
Other-referenced competency	3.52	.94	.85
Effort expenditure	4.03	.75	.79
Competitive excitement	4.30	.71	.78
Affiliation with peers	4.05	.71	.77
Positive parental involvement	4.08	.86	.84

^aLikert scale anchors between 1–4^bLikert scale anchors between 1–5

The personal development of athletes was investigated using stepwise multiple regressions. Five models, using each subscale of the YES-S as a dependent variable, were tested with two subscales of the MCSYS and six subscales of the SEYSQ as independent variables to determine which predicted positive and negative personal development. Results of the models are presented in Table 3.

Personal and Social Skills

Five variables significantly predicted personal and social skills. The strongest predictor, which explained approximately 27% of the variance, was affiliation with peers. The variables of effort expenditure, task climate, competitive excitement, and ego climate also predicted personal and social skills and accounted for an additional

Table 2 Correlation Matrix of Subscales

	Self-Referenced Competency	Other Self-Referenced Competency	Effort Expenditure	Competitive Excitement	Affiliation with Peers	Positive Parental Involvement	Ego Climate	Task Climate
Self-Referenced Competency	—	.42**	.63**	.62**	.51**	.44**	.01	.31**
Other Self-Referenced Competency		—	.36**	.36**	.27**	.23**	.32**	.09
Effort Expenditure			—	.59**	.50**	.50**	.04	.29**
Competitive Excitement				—	.50**	.49**	.01	.33**
Affiliation with Peers					—	.50**	-.03	.33**
Positive Parental Involvement						—	-.10*	.34**
Ego Climate							—	-.30**
Task Climate								—

** Correlation is significant at .001; * Correlation is significant at .05

Table 3 Stepwise Multiple Regression Analyses Predicting the YES-S Subscales

YES-S subscales	Significant predictors	<i>MS</i>	<i>B</i>	<i>r</i> ²
Personal and social skills	Affiliation with peers	54.61	.27	.27
	Effort expenditure	33.84	.18	.34
	Task climate	23.93	.15	.36
	Competitive excitement	18.37	.10	.37
	Ego climate	14.92	.06	.37
Cognitive skills	Other-referenced competency	34.43	.25	.09
	Effort expenditure	23.14	.33	.12
	Self-referenced competency	17.63	-.23	.14
Goal setting	Self-referenced competency	46.96	.23	.19
	Affiliation with peers	29.21	.18	.24
	Task climate	20.80	.13	.25
	Effort expenditure	16.31	.13	.27
Initiative	Competitive excitement	35.43	.19	.22
	Effort expenditure	20.60	.12	.26
	Task climate	14.86	.11	.28
	Self-referenced competency	11.56	.12	.29
Negative experiences	Ego climate	28.84	.20	.09
	Other-referenced competency	19.25	.21	.12
	Self-referenced competency	15.91	-.33	.15
	Effort expenditure	12.92	.15	.16

10% of the variance. The relationship between the predictors and dependent variable were positive meaning that high scores on these scales led to higher reports of personal and social skills.

Cognitive Skills

Three variables significantly contributed to the explanation of cognitive skill development and accounted for approximately 14% of the variance. Other-referenced competency was the strongest predictor and accounted for approximately 9% of the variance in cognitive skills. Conceptualized as comparing one's ability to others,

this result suggests that comparison between athletes is beneficial to the development of cognitive skills. Similarly, the construct of self-referenced competency, which is manifested through an individual's attainment of personal performance goals, was negatively related to the development of cognitive skills. Finally, high effort expenditure was positively related to the development of cognitive skills.

Goal Setting

Approximately 27% of the variability in goal setting was explained by four variables. Self-referenced competency, affiliation with peers, task climate, and effort expenditure were found to be positively related to goal setting behaviors. Self-referenced competency and task climate are complimentary concepts and deal with reaching one's potential by achieving personal performance benchmarks. Affiliation with peers and effort expenditure are two constructs that relate to goal setting. Team sport participants need to function as a unit and invest similar amounts of effort to reach their goals. The results of this model suggest that high levels of connectedness with peers and higher effort during an activity leads to more opportunities for goal setting.

Initiative

Four variables (competitive excitement, effort expenditure, task climate, and self-referenced competency) combined to explain approximately 29% of the variance in initiative. Experiencing enjoyment from upcoming competitions explained the most variance in initiative with 22%. Similar to goal setting, effort expenditure, a task climate, and self-referenced competency combined to explain part of the variability in initiative.

Negative Experiences

Four variables predicted 16% of the variance in negative experiences. The strongest predictor of negative experiences was an ego climate. This result suggests that climates which place emphasis on evaluating ability based on outperforming others (i.e., winning) promote negative experiences in young athletes. Related to an ego climate, results indicate that having high scores on other-referenced competency also predict negative experiences. Considering that both these constructs are similar in nature, this result was not entirely surprising. Athletes who reported high levels of self-referenced competency showed lower rates of negative experiences.

Discussion

Across the positive domains of the YES-S, results identified affiliation with peers, effort expenditure, self-referenced competency, and task climate as the important predictors of personal development in youth sport participants. This supports the first hypothesis of this study by linking high rates of enjoyment and a task climate to positive personal development. Conversely an ego climate was found to be the strongest predictor of negative personal development, which supports the second hypothesis of the study.

Positive Personal Development

The strongest predictor of personal and social skills was affiliation with peers. This suggests that creating opportunities for positive peer interactions in the sport domain is beneficial for the development of personal and social skills. This finding adds to our understanding of peer relationships in sport by demonstrating that positive relationships with peers are not only important for participation purposes (Smith, 2007; Weiss & Williams, 2004) but can also lead to positive personal development in youth.

The benefit of establishing positive and strong relationships with peers may well be responsible for the finding of task and ego climates as positive contributors to the development of personal and social skills. This finding differs from previous work (Cumming et al. 2007; Duda & Balaguer 2007) that links task climates with positive emotional and cognitive development in athletes and ego climates with negative development (for a review, see Duda & Balaguer, 2007). Results also suggest that peer relationships within the sport setting play a larger role (Holt, Black, Tamminen, Fox, & Mandigo, 2008) than the perceived climate, which would explain why personal and social skills developed across both task and ego climates. However, further investigations of the relationship between affiliation with peers and motivational climates are necessary to substantiate this claim.

Eccles and Barber (1999) linked sport participation with increased grade-point average and subsequent college enrolment. The relationship between sport and school success suggests that processes within the sport environment help athletes develop cognitive abilities. The present study found that other-referenced competency and effort expenditure were positively related to cognitive skills while self-referenced competency was negatively related. These findings imply that comparison with others and effort relates to greater cognitive skill development than other aspects of enjoyment and motivational climate. Although it is unclear why this is the case, it is possible that other-referenced competency and effort serve as moderating variables between participation in sport and a child's cognitive development. In addition, it is unclear if the findings of this study would be supported for youth who participate in different structured activities such as arts or faith-based programs. It would be worthwhile for future studies to examine the relationship between comparisons to others and cognitive development across different domains to further understand the role of structured activities on cognitive development.

Approximately 25% of the variance in goal setting was explained by positive reports of self-referenced competency, affiliation with peers, and task climate. It is believed that the predictors of goal setting identified in this study reflect how athletes use individual and team goals in the sport environment (Dawson, Bray, & Widmeyer, 2002). Individual goals reflect self-referenced competency and can be used to set personal standards of performance or desired outcomes of sport participation (Burton & Weiss, 2008). Team goals, which are related to affiliation with peers, are important for team success (Prapavessis, Carron, & Spink, 1996) and should be used by coaches and teams to set performance standards. The present results suggest that goal setting behaviors can be enhanced by creating a task-oriented environment that stresses positive affiliation with peers and self-referenced competency.

Applications of goal setting behaviors in youth sport programs were related to the personal development of children. Danish and colleagues (Danish, Forneris,

Hodge, & Heke, 2004; Danish, Forneris, & Wallace, 2005) developed Sports United to Promote Education and Recreation (SUPER; see Danish, Fazio, Nellen, & Owen, 2002); a program which teaches youth sport participants a number of life skills within the sport setting by providing workshops to participants. Of the 18 workshops that makeup the SUPER program, seven deal with goal setting and discuss how goals are created/reached in sport and in other aspects of life (Danish et al., 2005). Brunelle, Danish, and Forneris (2007) assessed the impact of the SUPER program on adolescent development and found that the program had a positive effect on youth's prosocial behavior and social responsibility. Although the impact of goal setting modules was not teased out, their results support the findings of this study and identify goal setting as a component of personal development.

Competitive excitement, effort expenditure, task climate, and self-referenced competency were positively related to the construct of initiative. This demonstrates that initiative can be developed in sport by creating an environment that promotes excitement, effort expenditure, and self-referenced competency within a task climate. Coaches and sport programs interested in the development of initiative in youth should consider these factors if they want to create an environment consistent with principles of positive youth development through sport. Larson (2000) argues that youth will develop initiative if they are intrinsically motivated, invest high amount of effort in the activity, and participate over time. The strongest predictor of initiative, which is competitive excitement, shares similarities with intrinsic motivation. Scanlan and Lewthwaite (1986) argue that enjoyment and intrinsic motivation are related and require athletes to develop positive perceptions of competence before an activity is deemed enjoyable and intrinsically motivating. Given the connection between enjoyment and intrinsic motivation, the present results suggest that increased enjoyment may have a role in the development of initiative. Another predictor of initiative is effort expenditure. This construct reflects Larson's (2000) notion of investing high amounts of energy in the activity. Given that athletes typically participate in sport for an extended period of time (i.e., at least one season), the current predictive model supports the three conditions identified by Larson (2000) for the development of initiative.

Negative Personal Development

The strongest predictors of negative personal development were an ego climate and other-referenced competency. This result suggests that focusing one's attention on comparison with others rather than personal achievement will increase negative experiences in the sport domain. The link between ego climates and negative sport experiences is well documented (Balaguer et al., 1999; Cumming et al., 2007; Smith et al., 2008; Vazou, Ntoumanis, & Duda, 2006) and implies that an environment emphasizing comparisons with others leads to higher rates of negative experiences. Although an ego climate was found to be a positive predictor of personal and social skill development, it is recommended that ego climates be implemented with caution as results point to negative experiences as an additional outcome of ego climates. In contrast, self-referenced competency was negatively related to negative experiences meaning that environments which focus on mastery of skills and personal achievement can reduce negative experiences in youth.

Summary and Conclusion

The results of this study are important for understanding the positive and negative personal development of young athletes; however limitations exist. The relationships were found in team sport athletes and may not necessarily reflect the personal development of individual sport athletes. For example, it is possible that affiliation with peers is not a significant predictor of goal setting in individual sports. Future research is needed to understand how motivational climate and enjoyment affect personal development across individual and team sports. A second limitation is that total weekly involvement in sport programs was not taken into account. It is possible that differences exist between athletes who invest more time in their program compared with athletes who spend less time. Analyses of how much time spent in the sport affects personal development is an interesting avenue of future investigation. A third limitation deals with the age of the participants in the sample. Although a wide age range was collected, it is unclear if athletes of different ages had differing personal development experiences. Investigations of how personal development differs across athletes of different ages would be important to investigate in future studies. Finally, due to a lack of statistical power, the analyses used in this study did not account for individuals being nested within teams. Future studies that collect data from teams should collect a sufficiently large sample size to use multilevel modeling techniques and account for individual and program level variables (Tabachnick & Fidell, 2007).

The findings of the current study identify affiliation with peers, effort expenditure, self-referenced competency, and task climate as the most important predictors of personal development in young athletes. Research on motivational climate and enjoyment has linked these constructs to sport participation (Duda & Balaguer, 2007; Weiss & Williams, 2004); however their impact on the personal development of youth was unknown. The findings strengthen the understanding of how personal development can be increased within the youth sport domain and suggest that sport programs and coaches who wish to increase the personal development of athletes consider these factors and incorporate them into their sport environment. This can be achieved by fostering an environment of personal success by promoting the use of personal achievement goals within the sport setting. Creating an environment that focuses on the child reflects the factors of task climate and self-referenced competency. In addition, if athletes are encouraged to share their goals with others and support each other in achieving them, stronger peer relationships and increased motivation to participate may ensue, which are important factors identified as predictors of the personal development of young athletes.

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Hormonal Tx of Youth With Gender Dysphoria Stops in Sweden

[Lisa Nainggolan](#)

May 12, 2021

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Karolinska Hospital in Sweden, plus a number of the other centers in the country that treat youth with gender dysphoria, has become the latest clinic to stop the routine hormonal treatment of youth under 18.

The [new policy](#), affecting Karolinska's pediatric gender services at Astrid Lindgren Children's Hospital (ALB), in Stockholm, has ended the practice of prescribing puberty blockers and cross-sex hormones to minors with gender dysphoria.

Hormonal treatments will now only be prescribed to patients under the age of 18, and treatment may only occur within the setting of a clinical trial approved by the EPM (Ethical Review Agency/Swedish Institutional Review Board).

Other centers in Sweden that treat gender dysphoria youth — in Lund and Linköping — will follow the lead of the ALB. Other centers in Umeå, Alingsås in Gothenburg, and a center in Uppsala have not yet decided whether they will do the same, Olle Söder, MD, PhD, a pediatric endocrinologist who retired from Karolinska Hospital 2 years ago, told *Medscape Medical News*.

This decision comes amid growing unease in some quarters regarding the speed at which hormonal treatment of children with gender dysphoria has become accepted as the norm in many countries, despite what critics say is a lack of evidence of any benefit, plus known harms, of treatment.

The Swedish hospital cited the Keira Bell ruling in the UK as having an impact on its decision. As [detailed](#) in a recent *Medscape Medical News* feature, the December 2020 ruling by the High Court in London effectively stopped the initiation of puberty blockers in children under 16 with gender dysphoria, and recommended that those between the ages of 16-18 seek court approval for any hormonal treatment.

"The UK ruling, from an endocrinology point of view, is that these interventions are experimental, that young people can't understand the implications of initiating puberty blockers, cross-sex hormones, and surgeries — and that makes sense based on our understanding of brain development, endocrinologist Will Malone, MD, of Twin Falls, Idaho, told *Medscape Medical News* when interviewed for the feature.

Malone is one of several clinicians and researchers who formed the Society for Evidence-Based Gender Medicine (SEGM), a not-for-profit organization that now has at least 100 physician members, and which calls into question the medical transition of youth with gender dysphoria.

In a [statement](#) on its website, following the Swedish announcement, SEGM said: "This is a watershed moment, with one of world's most renowned hospitals calling the 'Dutch Protocol' experimental and discontinuing its routine use outside of research settings."

A number of US states are also attempting to outlaw the medical, and surgical, treatment of youth with gender dysphoria under 18; the first being Arkansas which [passed](#) such a law last month which — if not overturned — will come into effect in July. The bill bans doctors from prescribing puberty blockers, hormone therapies, or genital-altering surgeries for anyone under 18. Even referring a youth for such treatment from another doctor is prohibited.

The Endocrine Society has [condemned](#) such laws, and in June it will join in and appear against the UK High Court ruling in the Keira Bell case.

"The treatment of transgender and gender diverse youth should be governed by the best available medical evidence, not politics," said Joshua D. Safer, MD, coauthor of the Society's [Clinical Practice Guideline](#) and [position statement](#) on transgender medicine.

Sweden is continuing to fully review its guidance on the issue.

In December 2019, its SBU (Swedish Agency for Health Technology Assessment and Assessment of Social Services) published an overview of the knowledge base, which was partly instigated by a three-part [Swedish documentary](#) entitled, "Trans Train." This chronicled several interviews with detransitioners — individuals who medically transitioned to the opposite gender, and in most cases had surgery too, but who came to regret the decision — and stated that medical transition of minors is not evidence-based.

The final guidelines will appear in print and online at the beginning of 2022, Söder told *Medscape Medical News*.

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How SEX and GENDER Influence Health and Disease

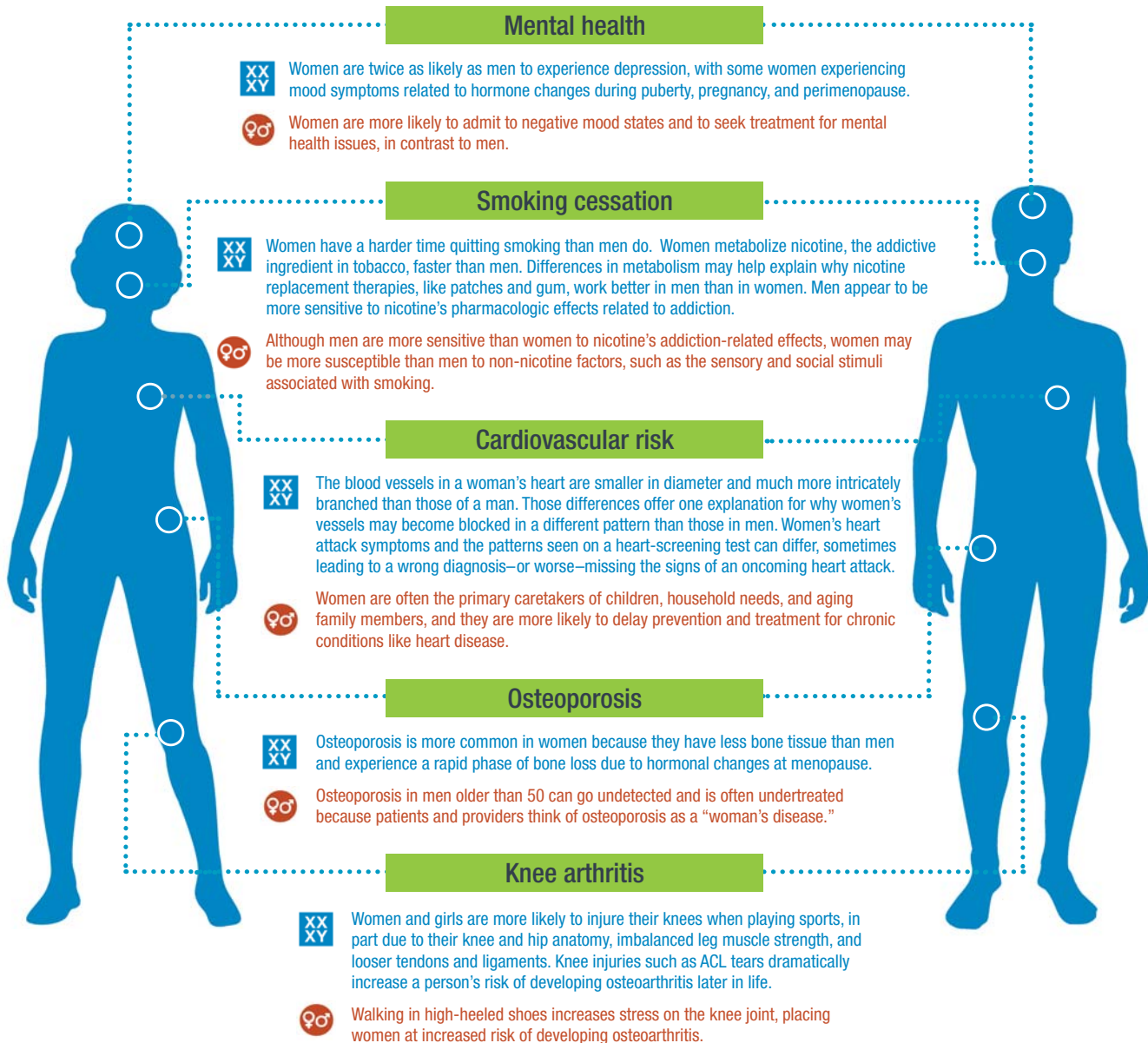
Sex and gender can influence health in important ways. While sex and gender are distinct concepts, their influence is often inextricably linked. The scientific studies that generate the most complete data consider sex and/or gender influences in study design, data collection and analysis, and reporting of findings.

Sex is a biological classification, encoded in our DNA. Males have XY chromosomes, and females have XX chromosomes. Sex makes us male or female. Every cell in your body has a sex—making up tissues and organs, like your skin, brain, heart, and stomach. Each cell is either male or female depending on whether you are a man or a woman.

Gender refers to the socially constructed roles, behaviors, expressions, and identities of girls, women, boys, men, and gender diverse people. It influences how people perceive themselves and each other, and how they act and interact. Gender is usually conceptualized as binary (girl/woman and boy/man), yet there is considerable diversity in how individuals and groups understand, experience, and express it.

Visit [NIH.gov/women](https://www.nih.gov/women) to learn how studying sex and gender strengthens science.

Examples of SEX and GENDER influences



Sources: Institute of Medicine. Canadian Institutes of Health Research. World Health Organization. National Institute on Drug Abuse. NIH Osteoporosis and Related Bone Diseases National Resource Center. National Institute of Arthritis and Musculoskeletal and Skin Diseases. Kerrigan, D.C.; Johansson, J.L.; Bryant, M.G.; Boxer, J.A.; Della Croce, U.; & Riley, P.O. (2005). Moderate-heeled shoes and knee joint torques relevant to the development and progression of knee osteoarthritis. *Archives of Physical Medicine and Rehabilitation*, 86(5), 871-875.



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PSYCHOMETRIC PROPERTIES OF THE CARING CLIMATE SCALE IN A PHYSICAL ACTIVITY SETTING

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Mi-Sook Kim,⁴ Michelle Magyar,⁵ y Marta Guivernau⁶

PSYCHOMETRIC PROPERTIES OF THE CARING CLIMATE SCALE IN A PHYSICAL ACTIVITY SETTING

KEYWORDS: Measurement, Youth programming, Multiethnic, Caring climate.

ABSTRACT: Scholars have emphasized the importance of creating a caring environment in physical activity settings. Given that there is currently no measure of a caring environment in the physical domain, the purpose of these two studies was to develop the *Caring Climate Scale* (CCS) and examine its psychometric properties. A caring climate is defined in this paper as the extent to which individuals perceive a particular setting to be interpersonally inviting, safe, supportive and capable of providing the experience of being valued and respected. In Study 1, 353 children in a sport camp completed the CCS. Exploratory factor analyses revealed an internally consistent single factor, labelled caring climate, and supported the validity of the measure. In Study 2, 395 sport campers completed the CCS and assessments of the programme's future involvement and reported value. Confirmatory factor analysis revealed support for a 13-item version of the CCS.

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Introduction

Research is providing increasingly more evidence that positive youth development is dependent on offering *intentional* programming. Participation alone does not result in growth and in fact may contribute to negative outcomes (Ewing, Gano-Overway, Branta, and Seefeldt, 2002; McLaughlin, 2000). Of particular importance are the characteristics of the settings in which programming occurs. The quality of relationships and social interactions that exist between and among youth and adults was identified in a National Research Council and the Institute of Medicine report on community programs and youth development as critical to fostering numerous social, academic, and psychological outcomes. Effective programs incorporate supportive relationships wherein social interactions are characterized by warmth, closeness, caring, support, guidance, good communication, secure attachment and responsiveness (Eccles and Gootman, 2002). These qualities are quite diverse but collectively they capture the psychological climate fundamental to positive development. An umbrella term that captures the essence of the qualities is 'caring'.

Caring has been identified as an important feature in the contextual life of young people (Noblit, 1993). Rhodes (2004) suggests that "caring youth-staff relationships" may be the most important factor determining the success of youth programs. Caring has also been identified as a key requisite in physical activity settings. Hellison (2003) regards caring as fundamental to engaging students in physical activity. Ennis (1999) suggests that establishing caring relationships are critical to "catch and hold the attention and interest of urban adolescents" to physical education (p. 165).

Larson (2006) suggests that physical education settings offer unique opportunities for caring to occur given the high level of interpersonal interaction. Despite the conceptual and philosophical importance of caring, researchers, particularly in sport and physical education settings, have tended to focus on achievement-related characteristics of the context (e.g., task-involving and ego-involving motivational climates). The ability to assess caring and explore its links with positive development would provide researchers, theorists, and practitioners a more complete understanding of the optimal environment to create in physical activity settings. Therefore, the purpose of the current investigation was to develop and validate a measure of participants' perceptions of a caring climate in the physical activity domain.

Delimiting the concept of caring is essential to adequate assessment and understanding. Noddings (1984, 1992, 1995) has written extensively on caring and the ethic of care in educational settings. She identifies caring as "stepping out of one's personal frame of reference and into the other's" (Noddings, 1984 p. 24). Essentially caring is a relation, something that one is engaged in, involving verbal and nonverbal cues as well as recognition of the motivation and intentions of individuals involved (Noddings, 1992). Noddings conceptualizes caring as containing two interrelated dimensions. First, caring for someone requires engrossment or attention. Engrossment and attention refer to the acts of fully attending to another, being open and receiving another in a bias free manner, or in more lay terms, *really* seeing, feeling, and caring for another. Engrossment also suggests that a caring person is nonjudgmental, does not attempt to shape another, and allows for a significant

amount of choice by the receiver of caring. Second, caring embodies motivational displacement. Motivational displacement refers to being empathetic, having concern for and giving priority to the needs of another. The needs of the care-receiver are given focused unyielding attention (Noddings, 1984, 1992, 1995). As an educational philosopher Noddings provides a strong rationale and foundation from which to consider the process and value of caring, but she does not address the very complex issue of measurement. With regard to the physical domain, having a tool to assess participants' perceptions of the degree to which the environment is caring is an important next step in furthering this line of inquiry.

The education literature reveals that quantitative assessments of caring are very limited. Bulach, Brown, and Potter (1998) developed a 26-item Likert-type instrument to measure behaviors used by teachers to create a caring learning community. The instrument was created to identify caring behaviors and provide direction to teachers in the field wishing to create a caring environment. Based on a factor analysis conducted on the measure, five broad categories of caring behaviors emerged. These dimensions included the ability to reduce anxiety, willingness to listen, rewarding good behavior, being a friend, and appropriate use of criticism. Total instrument internal reliability was reported to be .80; however, consistency of the subcategories of caring behaviors was not reported. In addition, the theoretical or conceptual grounding of item creation was not clearly articulated. Lastly, the instrument focuses solely on teacher behaviors (e.g., "My teacher displays my work") and failed to capture other classroom generated contextual demonstrations of caring or perceptions of feeling cared-for by the care-giver.

Battistich and colleagues (Battistich, Solomon, Watson, and Schaps, 1997) utilize a self-report, Likert-type questionnaire to assess student autonomy and influence in the classroom (e.g., "In my class the teacher and students decide together what the rules will be") as well as caring and supportive interpersonal relationships in the classroom (e.g., "People care about each other in this school," "My class is like a family"). The researchers typically average the two subscales together to create a single indicator of students' sense of community within the academic setting (Battistich and Hom, 1997).

Battistich and colleagues' assessment of sense of community is broad, encompassing both autonomy focused items as well as interpersonal support and caring items. Additionally, the measure assesses community in two different contexts (in the classroom and in the school) and incorporates both personal and contextual aspects in the measure. For example, the personally focused item "The teacher lets *me* [italics added] choose what I will work on" and the contextually focused item "People care about *each other* [italics added] in this school" both appear in the measure. Including both types of items in one measure makes it very difficult to understand if variation in responses are due to feeling personally cared for and/or perceiving a context to be caring. Furthermore, the concept of school as community appears to be broader and inclusive of a more diverse range of constructs than is the focus of the present research.

In physical education Larson (2006) utilized a critical incident form to elicit students' descriptions of caring teachers. Content analysis revealed 11 categories of behaviors that were grouped into three subcategories. The subcategories were called

recognize me, help me learn, and trust/respect me. The main or collective category, referred to as paying attention to me, best characterized the range of responses. Larson's (2006) findings support Noddings (1984, 1992, 1995) contention that attention or engrossment are central in caring relationships. Furthermore her findings reveal that students do perceive caring acts within the physical education setting, suggesting the creation of a quantitative assessment of caring in the physical domain is quite relevant.

While limited research has been conducted examining a caring climate in a physical activity context, a strong body of work has assessed individuals' perceptions of the motivational climate in the physical domain utilizing Nicholls' theory of achievement motivation. The motivational climate represents an individual's appraisal of the salient motivational goal structure and characteristics of a particular context, and variations in the motivational climate stem from the manner in which effort and ability are valued, recognized, and rewarded, (Ames, 1992; Newton, Duda and Yin, 2000). In a task-involving motivational climate effort and personal mastery are endorsed, cooperation among participants is encouraged, and everyone is made to feel that he/she plays an important role in the group. In an ego-involving motivational climate the demonstration of superior ability is rewarded, rivalry is encouraged, and mistakes are punished. Extensive research has revealed the benefits of creating a task-involving climate with regard to promoting adaptive motivational responses (Duda and Whitehead, 1999).

While one may argue that creating a task-involving climate reflects caring behaviors, (e.g., encouraging individuals to work hard to reach their personal potential), work in this area has focused on the achievement related aspects of the climate, and not directly

considered the caring nature of the climate which is based on perceptions of interpersonal warmth and support. Though the constructs of the motivational climate and a caring climate are distinct, conceptually logical relationships should emerge. A task-involving climate involves emphasizing individual improvement and should positively relate to a caring climate where the individual is prioritized, attended to, and valued. Endorsement of an ego-involving climate, on the other hand, requires that individual recognition be based on a hierarchical notion of ability and outcome and is contradictory to a caring climate. Thus, a caring climate should negatively relate to perceptions of an ego-involving motivational climate.

In sum, while scholars and researchers have emphasized the need for intentional programming as well as the importance of warm and supportive relationships in creating optimal settings and fostering positive youth development, little research on a caring climate has been conducted in the physical domain. Caring climate measures have been developed for use in an educational context, but they are limited in their applicability to the physical domain. To address these needs and limitations, the purpose of this project was to develop a self-report assessment of participants' perceptions of a caring climate in the physical domain, and examine its psychometric properties across two samples. The term *caring climate* was operationally defined as the extent to which individuals perceive a particular setting to be interpersonally inviting, safe, supportive, and able to provide the experience of being valued and respected. In Study One the *Caring Climate Scale* (CCS) was developed and its factor structure, validity, and internal reliability were examined. It was hypothesized that the measure would exhibit adequate face

validity and a single internally reliable factor characterizing perceptions of a caring climate would emerge. Additionally, convergent and discriminant validity were examined by correlating the new scale with the task- and ego-involving scales of the *Perceived Motivational Climate in Sport Questionnaire*. Specifically, a task-involving climate was hypothesized to be positively associated to the caring climate, supporting convergent validity, while an ego-involving climate was expected to negatively correspond with a caring climate, supporting discriminant validity. However, the magnitude of these relationships was expected to be small, indicating that the measure would be distinct from the motivational climate scales.

In Study Two, the factor structure identified in Study One was confirmed and additional evidence for the convergent validity of the measure was examined. Given the importance of maximizing attendance in after school and out-of-school programs such as the National Youth Sport Program (NYSP) this study examined the link between perceptions of a caring climate and future anticipated participation as well as the reported personal value given to NYSP. The notion that individuals may be more likely to engage in a caring environment is not without precedent. Ennis (1999) reported that urban adolescents were more likely to be engaged in physical activity in contexts that were trusting and caring. Watson, Newton, and Kim (2003) found a positive link between caring for others and sport interest, enjoyment, and future anticipated involvement in a physical activity program. Therefore, it was hypothesized that perceptions of a caring climate would be related to a greater desire to participate in the NYSP in the future and value the NYSP. Both findings would support the convergent validity of the CCS.

Study One

Method

Participants

Youth enrolled in the National Youth Sport Program (NYSP) participated in this study. Participants were from two NYSP programs. Some youngsters participated in an NYSP in the western region of the U.S. and others were from an NYSP in the mid-southern region of the U.S. Both NYSP sites have offered programming for over 10 years.

353 participants included boys ($n = 214$) and girls ($n = 138$) aged 9 to 17 years ($M_{\text{age}} = 12.18$, $SD = 1.55$). One participant did not report gender information. A majority of the campers (82%) were born in the United States and their race/ethnicity included Black/African American (69%), Hispanic/Chicano (12%), White/Caucasian (1%), Asian (1%), Venezuelan (.2%), Samoan (.2%), Other/Mixed (5%), and 12% who chose not to identify their race.

The NYSP is a federally funded summer program that has offered physical activity opportunities for underserved youngsters for over 30 years. Program funding eligibility stipulates that 90% of camp participants be from underserved or low-income families. The free five-week summer program includes a minimum of 50 instructional hours in sport/physical activity and drug and alcohol awareness programming.

Procedures

The investigators met with all campers and invited them to participate in the study. For those campers who desired to participate, parental consent was obtained prior to the data collection. Given that the questions were intended to tap the campers' perceptions of the environment within their NYSP program data were collected during

the fifth and final week of camp. Participants were gathered in small groups and given a questionnaire packet including demographic information, the *Caring Climate Scale*, and a modified version of the *Perceived Motivational Climate in Sport Questionnaire*. It should be noted that two versions of the questionnaire packet were created by counterbalancing the measures in order to reduce response bias. The head researcher read aloud each item while research assistants circulated in order to answer any questions. The questionnaire required approximately 25 minutes to complete. Due to the nature of the questions on the survey (i.e., asking specifically about the environment created by the NYSP leaders), no NYSP personnel remained in the room during the data collection.

Measures

Demographic Information. Campers were asked to report their age, gender, and ethnicity.

Caring Climate. The *Caring Climate Scale* (CCS) was developed to measure the extent to which youngsters perceive the social and interpersonal context to be caring. More specifically, the CCS assesses the extent to which individuals consistently perceive a particular setting to be interpersonally inviting, safe, supportive, and able to provide the experience of being valued and respected. Stemming from the conceptual frameworks and literature related to caring in youth contexts (Cohen, 2001; Hellison, 1995; Noddings, 1984, 1992, 1995) as well as the researchers' practical experience working with youth, items were developed to reflect a sense of caring. Caring stems not only from the leader but also emanates from others within the group setting. Therefore, the initial items referred specifically to the leader as well as more general items that referred to feeling

cared for within the group. A total of 30 initial items were generated to assess a sense of caring among youth participants in physical activity settings, and particular attention was paid to insure that the items were appropriate for use in the physical domain. Individuals with expertise in sport psychology, pedagogy, and social psychology examined 1) the extent to which each item reflected and was consistent with the conceptual framework and the operational definition; and 2) the quality of each item in terms of clarity and simplicity. Based upon the experts' evaluations and comments on the initial items, 10 items were removed resulting in the retention of 20 items. Given that the data were to be collected in a summer camp setting, a stem specific to the setting (NYSP) was added to each item (e.g., "In NYSP, the leaders accept kids for who they are."). Youth were asked to respond to each item using a five point Likert-type scale (1 = strongly disagree, 3 = not sure, 5 = strongly agree). A mean scale score was computed.

Perceived Motivational Climate. The *Perceived Motivational Climate in Sport Questionnaire* (PMCSQ; Seifriz, Duda, and Chi, 1992) was used to assess the extent to which the campers perceived a task or ego-involving climate in NYSP. The 21-item measure was slightly adapted for use in the NYSP program; the stem was changed from "On this team" to "In my group" and references to "coach" were changed to "leader." A sample-item from the task-involving scale (eight items) read "In my group, the group leader wants us to try new skills." and a sample ego-involving item (13 items) is "In my group, only the most athletic kids get noticed". Participants responded using a 5-point scale ranging from 1 (strongly disagree) to 5 (strongly agree). Mean scale scores were calculated for the perception of a task-

involving motivational climate as well as an ego-involving motivational climate. Previous research has supported the validity and reliability of this measure (Seifriz et al., 1992; Walling, Duda, and Chi, 1993). In the current investigation the task-involving and ego-involving subscales were found to have adequate internal reliability (α 's = .72 and .75, respectively).

Results

Factor Validity and Internal Reliability of the Caring Climate Scale

An exploratory factor analysis (EFA) with maximum likelihood (ML) method was conducted to identify the underlying factor structure of the caring climate scale as well as the number of items that best represented this underlying structure (Berbing and Hamilton, 1996). The researchers developed the caring climate measure with a single factor in mind. However, if any additional factors emerged an oblique rotation would be used to interpret the factors given the researchers' belief that any additional factors, although distinct, would be correlated to some degree. The number of factors was determined by examination of the eigenvalues (> 1.0), the scree test, and the theoretical logic of the emerged factors. Once the potential factors were identified, interpretation of the factor was based on those items that achieved a factor loading of .55 or greater. This cutoff criterion is considered a good indicator (indicating 30% overlapping variance) of the concept being measured (Tabachnick and Fidell, 2001).

Prior to conducting the EFA the suitability of the correlation matrix was examined. The Kaiser-Meyer-Olkin measure of sampling adequacy was .94 and the Bartlett test of sphericity was significant (2981.4, $p < .0001$) indicating the suitability of the data. In conducting the EFA three factors emerged

with eigenvalues above 1.0. However, examination of the scree plot demonstrated that one strong factor emerged from the data. Therefore, a second EFA was conducted forcing a single factor solution. This single factor represented a general notion of caring in the climate and accounted for 37% of the variance. However, examination of the factor loadings indicated that six items were below the .55 criterion (see Table 1). Based on reevaluation of each item's communality (i.e., its unique contribution to the single factor scale), and item-to-item correlations, these six items were removed in the subsequent analyses (Pett, Lackey, and Sullivan, 2003). A final EFA with ML method forcing a single factor solution was conducted and revealed a single factor accounting for 44% of the variance which is considered moderately acceptable (Fabrigar, Wegener, MacCallum, and Strahan, 1999) (see Table 1).

To determine the internal reliability of this revised 14-item measure an item analysis was conducted. The measure would be considered reliable if a) the inter-item correlations were between $r = .20$ and $r = .70$; b) the item-total correlations were above $r = .40$; and c) Cronbach's alpha coefficient was above $\alpha = .70$ (Kidder and Judd, 1986). The scale was found to be internally reliable with a Cronbach alpha coefficient $\alpha = .92$, inter-item correlations ranging from $r = .24$ to $r = .66$, and corrected item-total correlations ranging from $r = .56$ to $r = .72$.

Descriptive Statistics

Descriptive statistics revealed that youth did perceive the climate created in the NYSP to be moderately caring. Additionally, according to the NYSP campers, a high task-involving climate and moderate ego-involving climate characterized the NYSP (see Table 2).

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Caring Climate Scale...

Caring Climate Scale Number and Item	Initial Analysis		Final Analysis	
	Factor		Factor	
	Loadings	<i>h2</i>	Loadings	<i>h2</i>
1. Kids are treated with respect.	.75	.57	.76	.57
2. The leaders respect kids.	.74	.55	.74	.55
3. The leaders are kind to kids.	.71	.50	.70	.49
4. The leaders care about kids.	.68	.46	.69	.47
5. Everyone is treated with kindness.	.67	.44	.65	.43
6. Kids feel that they are treated fairly.	.66	.44	.66	.43
7. The leaders try to help kids.	.66	.44	.68	.46
8. The leaders want to get to know all the kids.	.66	.43	.66	.43
9. Everyone likes kids for who they are.	.65	.42	.64	.41
10. The leaders listen to kids.	.65	.42	.65	.43
11. The leaders accept kids for who they are.	.65	.42	.65	.42
12. Kids feel safe.	.61	.37	.60	.37
13. Kids feel comfortable.	.60	.36	.60	.36
14. Kids feel welcomed every day.	.58	.33	.58	.34
15. The leaders want kids to be successful.	.54	.29	—	—
16. Kids know everyone will be nice to them.	.53	.28	—	—
17. The leaders disrespect kids.	.48	.22	—	—
18. People miss them when kids are absent.	.47	.22	—	—
19. Kids feel like other kids care about them.	.43	.19	—	—
20. People make fun of each other.	.34	.12	—	—
Variance (%)	.37		.44	
Alpha Coefficient	.		.92	

Table 1. Factor Analysis of the Caring Climate Scale.

Variables	Means (SD)	Simple Correlations		
		1	2	3
1. Caring Climate Scale	3.80 (0.76)	1.00	.56**	-.36**
2. Task-involving Climate	3.98 (0.64)	1.00	-.19**	
3. Ego-involving Climate	3.12 (0.67)	1.00		

Note: ** $p < .01$

Table 2. Descriptive Statistics and Convergent Validity of Observed Variables

Convergent and Discriminant Validity

To examine convergent and discriminant validity of the CCS correlations were calculated between caring and task- and ego-involving climates. It was hypothesized that the caring climate would be distinct but positively related to a task-involving motivational climate (i.e., convergent validity) and negatively related to an ego-involving climate (i.e., discriminant validity). The correlational analysis demonstrated support for both convergent and discriminant validity; that is, the caring climate was positively correlated with the task-involving climate while being negatively related to the ego-involving climate (see Table 2). Therefore, those who perceived a caring climate were also more likely to perceive the environment as task-involving. However, it should be noted that the shared variance between these measures only ranged from 15% to 34% suggesting that the caring climate was distinct from the motivational climate, albeit moderately associated.

Discussion

The purpose of the first study was to develop a self-report questionnaire, the *Caring Climate Scale* (CCS), to assess the extent to which participants perceived a physical activity setting to be interpersonally inviting, safe, supportive, and able to provide an experience of being valued and respected. The CCS was designed based on the writings of Noddings (1984, 1992, 1995), Cohen (2001), and Hellison (1995). The initial items were validated by experts from multiple fields of study suggesting the items developed captured the notion of caring defined in the current study. This face validity was further supported by the exploratory factor analysis resulting in one single factor solution. The relatively robust internal reliability of the resulting single factor suggests that the participants responded to these items in a highly consistent manner lending support to the psychometric strength of the measure.

In addition to factorial validity, support was revealed for the convergent and discriminant validity of the CCS. The relationships between a perceived caring climate to perceptions of a task-involving and ego-involving motivational climate were significant, not particularly robust, and in the hypothesized directions. Thus, the CCS was related to perceptions of the motivational climate but was also distinct suggesting the CCS appears to measure a unique characteristic of the psychological climate. In summary, the findings from Study One supported preliminary psychometric properties for the CCS. Study 1 also contributes to the literature in sport and educational psychology by presenting a measure of the caring climate that is appropriate for use in physical activity settings. The CCS provides an alternative to the current measures that assess the caring environment in classroom and schoolwide contexts (Bulach et al., 1998; Battistich et al., 1997).

Based on the findings from Study One, Study Two had two primary purposes. The first purpose was to confirm the factor structure that was reported in the first study. It was hypothesized that adequate fit indices would result from the confirmatory factor analysis. The second purpose was to examine the convergent validity of the CCS in regard to two motivational variables, the campers' future anticipated involvement in the program and their reported value of participation in the program.

Study Two

Method

Participants

Youth in the National Youth Sport Program (NYSP) were invited to participate in this study. A total of 395 girls ($n = 198$)

and boys ($n = 197$) from two NYSPs were involved in this study. The majority of youth involved in NYSP were from low-income families given that NYSP program funding eligibility stipulates that 90% of participants be from underserved populations. The campers ranged in age from 9 to 16 years old ($M_{age} = 11.80$, $SD = 1.54$) and represented a variety of ethnic/racial groups (61% African American, 26% Hispanic Americans, 4% White Americans, .5% Asian American, .5% Vietnamese, .5% Samoan, .5% Native American, and 8% who did not identify their ethnic/racial group). A majority of the young people were born in the United States.

Procedures

The procedures used in Study One were utilized in this study. The questionnaire included demographic information, the *Caring Climate Scale*, and measures of campers' anticipated future involvement in NYSP, and the extent to which they value the NYSP experience. Although the questionnaire contained additional measures that were part of a larger research project, only those pertinent to this study are discussed.

Measures

Demographic information. To accurately describe the sample of young people who engaged in this study several demographic variables were measured including age, gender, ethnicity/race, and birthplace.

Caring Climate Scale (CCS). The revised 14-item questionnaire described in detail in Study One was utilized to assess perceptions of a caring context.

Future Involvement. A 3-item measure was constructed to discover whether youth involved in the NYSP anticipated wanting to participate in NYSP next summer (i.e., "I want to do NYSP again next year." "I am looking forward to NYSP next year." and "I

don't want to do NYSP next year.”). Participants were asked to think about whether they wanted to be in NYSP next summer, read each statement, and then indicate on a 5-point Likert scale (1 = strongly disagree to 5 = strongly agree) how much they agreed with each statement. A mean scale score was computed with the third item noted above being reverse scored. Examination of the internal consistency of this measure revealed an acceptable level ($\alpha = .83$).

Reported Value of NYSP program. To assess the value participants placed on their engagement in NYSP three items were created to tap this construct (i.e., “Being part of NYSP is important to me”, “It means a lot to me to be part of NYSP.”, and “I really value being involved in NYSP.”). When completing the items, campers were asked to reflect on how important NYSP has been to them and then read each item and indicate how much they agreed with the statement on a 5-point Likert scale (1 = strongly disagree to 5 = strongly agree). This measure was found to have high reliability in this study ($\alpha = .87$).

Results

Confirmatory Factor Analyses Results of CCS

A confirmatory factory analysis (CFA) using AMOS 6.0 was conducted to confirm the factor structure of the 14-item CCS obtained in Study One. A number of fit indices were utilized to determine the fit of the factor structure of the CCS to the data (Hu and Bentler, 1999; Marsh, Hau, and Wen, 2004). The standardized root mean squared residual (SRMR) and the root mean square error of approximation (RMSEA) were employed to examine the extent of unaccounted variance in the model. In addition, the proportionate improvement in fit of the

target model against a more restricted, nested baseline model was determined by Tucker-Lewis index (TLI) and comparative fit index (CFI). According to the structural equation modeling (SEM) literature, obtaining a resultant SRMR near .08, RMSEA of .06 with 90% confidence interval, and a TLI and CFI close to .95 are recommended to establish the acceptable fit of the hypothesized model (Hu and Bentler, 1999; Marsh, Hau, and Wen, 2004).

The normality of the data was tested using Mardia's coefficient of multivariate kurtosis (Arbuckle, 1999). Mardia's coefficient of multivariate kurtosis was statistically significant (multivariate kurtosis = 124.83, critical ratio = 54.93, $p < .05$) indicating that the data violated the normality assumption. To remedy non-normality of the data, a bootstrapping approach was conducted. This method is a well recognized strategy in the SEM literature for dealing with non-normally distributed data (Byrne, 2001).

The initial CFA supported the single factor structure. Although all 14 items significantly loaded on the single factor and the fit indices indicated an adequate fit of the data, SRMR = .04, CFI = .93, TLI = .92, and RMSEA = .07 (90% confidence interval = .06 - .08), this measure was inspected for any possible misspecifications in the model. Examination of the modification indices revealed one item (“In NYSP, everyone is treated with kindness.”) shared a fair amount of variance (error variance = 1.04) with other manifest indicators. When this item was carefully reviewed, it seemed to reflect a general caring climate, which could be echoed in many other items causing lack of uniqueness among indicators. Particularly, this item

shared a fair amount of variance with one item ("Kids feel that they are treated fairly."). Due to the apparent interdependence of this item with other manifest indicators, the item was eliminated from the model.

With the one item removed a second confirmatory factor analysis was conducted. Goodness of fit indices for the revised CCS revealed that eliminating the one general item from the model enhanced the model fit. Observed fit indices with the revised model met the cut-off criteria specified in the SEM literature, SRMR = .037, CFI = .96, TLI =

.95, and RMSEA = .06 (90% confidence interval = .05 - .07), providing support for the proposed factor structure of the CCS. All standardized and unstandardized factor loadings for the indicators were statistically significant ($p < .05$) with all unstandardized coefficient/standard error ratios above 1.96. In sum, the final version of the CCS contained a total of 13 items measuring the perceived caring climate in a physical activity setting. The 13-item CCS is presented in Table 3 along with the standardized factor loadings and error variances.

Items	Standardized Factor Loadings	Error Variance
1. Kids are treated with respect.	.71	.67
2. The leaders respect kids.	.62	.75
3. The leaders are kind to kids.	.69	.70
4. The leaders care about kids.	.74	.55
5. Kids feel that they are treated fairly.	.62	.73
6. The leaders try to help kids.	.68	.53
7. The leaders want to get to know all the kids.	.66	.75
8. Everyone likes kids for who they are.	.65	.77
9. The leaders listen to kids.	.70	.68
10. The leaders accept kids for who they are.	.64	.72
11. Kids feel safe.	.67	.52
12. Kids feel comfortable.	.63	.70
13. Kids feel welcomed every day.	.67	.67

Note: All factor loadings were significant at $p < .01$. The item numbers are same as Table 1.

Table 3. CFA Factor Loadings and Error Variances of the Final Version of CCS.

Descriptive Statistics

The responses to the newly developed CCS exhibited adequate variability ($M = 3.86$, $SD = .77$) with a range of 4.0 and internal reliability ($\alpha = .92$). Simple correlation

coefficients revealed a significant relationship between the caring climate and reported future involvement whereas reported value of the NYSP program was not significantly related to the CCS (see Table 4).

Variables	Means (SD)	Simple Correlations		
		1	2	3
1. Caring Climate Scale	3.86 (0.77)	1.00	.40**	.08
2. Expected Future Involvement	3.97 (1.04)		1.00	.05
3. Value of Program	3.85 (1.05)			1.00

Note. ** $p < .01$; All variables ranged from 1 to 5.

Table 4. *Descriptive Statistics and Simple Correlation Coefficients of Observed Variables.*

Convergent Validity of CCS

The second purpose of Study Two was to examine the convergent validity of the CCS to motivational indicators including anticipated future involvement and perceived value of the program. To overcome the shortcomings of simple correlational tests, Borshboom and colleagues have recommended using a more robust method to examine the validity of a measure, namely SEM (Borsboom, Mellenbergh, and Heerden, 2004). Utilizing SEM, it was hypothesized that the perceived caring climate would positively predict these motivational indicators.

The results of the SEM showed acceptable model fit indices, SRMR = .035, CFI = .97, TLI = .97, and RMSEA = .04 (90% confidence interval = .03 - .05). More specifically, the caring climate was positively linked to the children's intention to participate in the program in the future. Although

there was a positive link from the caring climate to reported value of the NYSP program, this relationship was not statistically significant (see Figure 1).

Discussion

The purpose of Study Two was to further explore the validity and reliability of the *Climate Caring Scale* by conducting a confirmatory factor analysis and examining the convergent validity of the measure. The CFA on the 14 item measure identified in Study One revealed a reasonable fit. After removing one general item from the measure, the scale was found to demonstrate a good fit of the data. The maximum likelihood estimates suggested that each item in the measure was correctly assigned to the notion of a setting being perceived as caring. These findings further refined the measure and lend support

to the conceptual viewpoint of the current study that the multiple characteristics of a caring climate (Noddings, 1984, 1992, 1995) can be viewed as a single general notion of the construct.

The internal reliability of the resultant 13 item Caring Climate Scale was strongly supported suggesting that participants responded extremely consistently to the items. Using structural equation modeling, convergent validity was partially supported, in line with predictions. The *Caring Climate Scale* was positively and significantly associated with desire for future involvement in the camp but not with valuing the program. In line with previous research linking a sense of belonging

and levels of participation (Anderson-Butcher and Conroy, 2002) as well as motivation (Goodenow, 1993), perceiving the climate to be caring was affiliated with continued plans to be involved in the program.

The lack of a significant link between perceptions of a caring climate and value might be explained by the role of NYSP in the lives of the youth that attend. NYSP is truly an oasis for many of the youth. They are given the opportunity to travel daily to a college campus, their meals/snacks are provided, and they play sports and swim for five weeks during the summer. It is a valued respite, whether it is perceived as caring or not, from their sometimes tumultuous lives.

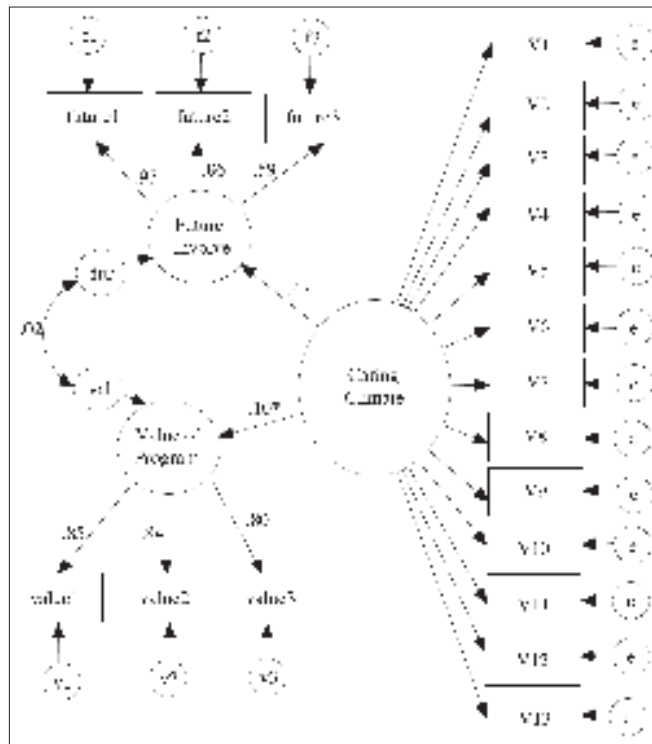


Figure 1. SEM results of Caring Climate Scale and motivational indicators.

Note: (*) indicated statistically insignificant links.

Conclusions

These two studies reflect an initial attempt to quantitatively measure the concept of a perceived caring climate in the physical activity domain and test the psychometric properties of the newly developed *Caring Climate Scale*. The findings support the initial validity and reliability of the scale.

Scholars, researchers, and practitioners have advocated for the importance of a warm and supportive context when attempting to foster optimal development in youth (Eccles and Gootman, 2002; Rhodes, 2004). While the CCS can be used to assess the caring climate in various youth activity contexts (i. e., the items are not specific to physical activity), it was developed to provide an appropriate tool for sport psychology researchers to explore to a greater degree the social emotional impact of physical education, physical activity, and sport on youth.

While the psychometric findings for the CCS are promising, it is critical that further study is pursued. The development of this caring measure drew on Noddings' theoretical work, research conducted within the education setting, and researchers' experience working in youth sport settings, it may be that other aspects of caring salient to individuals participating in physical activity settings may emerge in future research. The inclusion of qualitative methods to explore the concept of caring could address this issue and provide important insight into youngsters' experiences in the physical domain.

In addition, although the initial analysis using EFA of the CCS helped identify a

single factor that accounted for significant variance in the data, the CFA procedures further identified additional variance that remained after the factor was taken into account. Thus, the measurement model was slightly modified during confirmatory factory analyses, which warrants further investigation of the factor structure of the CCS utilizing additional samples.

Finally, conducting additional structural analyses (e.g., measurement invariance) of the CCS with a variety of samples would be informative relative to the psychometrics of the instrument. The youth in this study were involved in recreational physical activity. It would be useful to examine the factor structure, the validity and reliability of the measures in different settings (e.g., physical education, competitive sport, and exercise settings), with participants of different skills levels (e.g., novice, skilled, and elite athletes), and with different groups (e.g., gender, ethnicity, SES, the impact of caring in leadership settings).

Noddings (1995) reflected on the nation's ardent push for solely focusing on academic standards in middle school by stating that, "... we will not achieve even that meager success [academic success] unless our children believe they themselves are cared for and learn to care" (p. 675). A similar dynamic might be occurring in physical activity settings. It may equally be unlikely that we are able to increase our youngster's physical activity status and foster their development *unless* we learn to care and our youngsters feel cared for. The development of the *Caring Climate Scale* may serve as a useful tool in understanding and maximizing the experience of youngsters in physical activity settings.

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Caring Climate Scale...

PROPIEDADES PSICOMÉTRICAS DE LA ESCALA DE CLIMA DE CUIDADOS EN ACTIVIDAD FÍSICA

PALABRAS CLAVE: Cuestionario, Planificación de entornos juveniles, Multirracial, Clima de apoyo y afecto.

RESUMEN: Los académicos subrayan la importancia de crear entornos de apoyo y afecto en ámbitos de educación física. Dado que no existe un instrumento de medida de este tipo de clima en dichos entornos, el principal objetivo de esta investigación consistió en desarrollar una escala de medida de esta variable (*Caring Climate Scale*; CCS) así como en examinar sus propiedades psicométricas. La variable clima de afecto y apoyo fue definida como el grado en el que un entorno específico se percibe como atrayente, de apoyo y capaz de posibilitar el sentirse valorado y respetado. En el estudio 1, 353 participantes en un campamento deportivo completaron el cuestionario. Análisis factoriales exploratorios demostraron la existencia de un factor único (clima de afecto y apoyo) y apoyaron la validez de la escala. En el estudio 2, 395 jóvenes completaron la escala así como medidas de participación futura y el valor percibido del programa. Análisis factoriales confirmatorios apoyaron la versión de 13 ítems del CCS.

PROPIEDADES PSICOMÉTRICAS DA ESCALA DE CLIMA DE SUPORTE EM CONTEXTOS DE ACTIVIDADE FÍSICA

PALAVRAS-CHAVE: Questionário, Planificação de contextos juvenis, Multi-étnico, Clima de suporte, Actividade física.

RESUMO: Os académicos realçaram a importância de criar climas de suporte nos contextos de Actividade Física. Visto não existir um instrumento de medida apropriado para avaliação neste domínio, o objectivo destes dois estudos consistiu no desenvolvimento de uma escala de medida desta variável (*Caring Climate Scale*; CCS) e na análise das suas propriedades psicométricas. A variável clima de suporte foi definida neste trabalho como o grau em que os indivíduos percebem um determinado contexto como sendo seguro, apelativo do ponto de vista interpessoal e capaz de proporcionar percepções pessoais de valorização e respeito. No estudo 1 completaram o questionário 1353 crianças de um acampamento desportivo. As análises factoriais exploratórias demonstraram a existência de um factor único (clima de afecto e de apoio) e apoiaram a validade da escala. No estudo 2, 395 jovens completaram a escala, indicaram a sua intenção de participação futura e o valor percebido do programa. As análises factoriais confirmatórias apoiaram a versão de 13 itens do CCS.

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Mental Health of Transgender Children Who Are Supported in Their Identities

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abstract

OBJECTIVE: Transgender children who have socially transitioned, that is, who identify as the gender “opposite” their natal sex and are supported to live openly as that gender, are increasingly visible in society, yet we know nothing about their mental health. Previous work with children with gender identity disorder (GID; now termed gender dysphoria) has found remarkably high rates of anxiety and depression in these children. Here we examine, for the first time, mental health in a sample of socially transitioned transgender children.

METHODS: A community-based national sample of transgender, prepubescent children ($n = 73$, aged 3–12 years), along with control groups of nontransgender children in the same age range ($n = 73$ age- and gender-matched community controls; $n = 49$ sibling of transgender participants), were recruited as part of the TransYouth Project. Parents completed anxiety and depression measures.

RESULTS: Transgender children showed no elevations in depression and slightly elevated anxiety relative to population averages. They did not differ from the control groups on depression symptoms and had only marginally higher anxiety symptoms.

CONCLUSIONS: Socially transitioned transgender children who are supported in their gender identity have developmentally normative levels of depression and only minimal elevations in anxiety, suggesting that psychopathology is not inevitable within this group. Especially striking is the comparison with reports of children with GID; socially transitioned transgender children have notably lower rates of internalizing psychopathology than previously reported among children with GID living as their natal sex.



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Dr Olson conceptualized and designed the study, assisted in data collection, carried out the initial analyses, and drafted the initial manuscript; Ms Durwood and Ms DeMeules collected the data, supervised data entry, and reviewed the manuscript; Dr McLaughlin conceptualized the study and substantially reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Transgender individuals have been found to have highly elevated rates of anxiety and depression, but little is known about the mental health of transgender children whose identities are affirmed and supported by their families.

WHAT THIS STUDY ADDS: More families are allowing their transgender children to live and present to others as their gender identity. This is the first study to examine mental health in these children, finding that they have low levels of anxiety and depression.

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National media are increasingly presenting stories of a subset of prepubescent transgender children (those who persistently, insistently, and consistently identify as the gender identity that is the “opposite” of their natal sex). More striking to many, a large number of these children have “socially transitioned”: they are being raised and are presenting to others as their gender identity rather than their natal sex,¹⁻⁴ a reversible nonmedical intervention that involves changing the pronouns used to describe a child, as well as his or her name and (typically) hair length and clothing. These stories have sparked an international debate about whether parents of young transgender children should support their children’s desire to live presenting as their gender identity.⁵⁻⁹ Despite considerable and heated discussion on the topic, and despite these children’s increasing appearance at gender clinics,⁶ there have been no reports to date on the mental health of transgender children who have socially transitioned, forcing clinicians to make recommendations to parents without any systematic, empirical investigations of mental health among socially transitioned children.

Most studies of mental health among transgender people have examined adolescents and adults. These studies consistently report dramatically elevated rates of anxiety, depression, and suicidality among transgender people.¹⁰⁻¹⁶ These elevated rates of psychopathology are likely the result of years of prejudice, discrimination, and stigma^{11,17}; conflict between one’s appearance and stated identity¹⁸; and general rejection by people in their social environments, including their families.^{19,20} There is now growing evidence that social support is linked to better mental health outcomes among transgender adolescents and adults.²¹⁻²⁶ These findings suggest the possibility that social transitions in children,

a form of affirmation and support by a prepubescent child’s parents, could be associated with good mental health outcomes in transgender children.

Although there are no large studies of transgender prepubescent children, a number of studies have examined children who were at the time diagnosed with what was called gender identity disorder (GID), now termed gender dysphoria (GD; for more on both terms and others used throughout this article, see Table 1). The group of children diagnosed with GID likely included children who were transgender as well as others (eg, children who wished and acted but did not believe they were a member of the other gender and were distressed as a result). Importantly, most of the studies of children with GID/GD were conducted at a time when parental support and affirmation of children’s gender nonconforming behaviors and identities were uncommon. In contrast, the current work focuses on what is likely a much narrower group of children, a small subset of the group that previously would have been diagnosed with GID: those who (1) identify as (not merely wish) they were the “opposite” gender as their sex at birth and (2) have socially transitioned so that they appear to others as the gender they feel, rather than that assumed by their sex at birth.

By and large, studies of children with GID reported high rates of psychopathology, especially internalizing disorders such as anxiety and depression²⁷⁻³². For example, 36% of a group of 7- to 12-year-olds with GID reached the clinical range for internalizing problems.³³ Furthermore, 2 large studies of 6- to 11-year-olds with GID (including >100 children in Utrecht, the Netherlands, and 300 children in Toronto, Canada) found average internalizing scores in the clinical and preclinical range,

respectively, suggesting that many children in both samples showed high levels of internalizing psychopathology. Some have argued that these high rates of internalizing psychopathology among children with GID/GD as a sign that GID/GD is itself a form or consequence of such psychopathology.²⁷

In contrast, 2 smaller studies suggest that children whose gender identities are affirmed and supported have relatively good mental health. One study reported on 26 children aged 3 to 12 years with GID who were recruited through a clinic that advised parents to support their children’s gender expression. These children showed reduced rates of psychopathology³⁴ compared with those reported in other studies conducted at clinics that do not support such gender expression.³⁵ However, this study has received some criticism for methodologic limitations³⁶ and had a small sample size. Furthermore, the degree to which these findings generalize to transgender children and especially to transgender children who have been allowed to fully socially transition, is unknown. In addition, a qualitative analysis of interviews of parents of 5 transgender children who had socially transitioned found that parents recalled a reduction in mental health problems after a social transition.³⁷ Although no formal quantitative measures were provided, these findings again suggest that socially supported transgender children might have better mental health than children with GD or transgender children who are not supported in their identities.

The current study addresses a critical gap in knowledge by examining parental reports of anxiety and depression among a relatively large cohort of transgender children, all of whom are supported by their families and have socially transitioned (ie, they present to others as the gender consistent with their identity, not

TABLE 1 Definitions of Terms

Term	Use in This Article	Other Uses, Terms, and Comments
Transgender	In this article, we use “transgender” to refer to children who have a binary identity (male or female) and for whom this identity is not aligned with their sex at birth. This means natal boys who identify as girls and natal girls who identify as boys. In our sample, these children have all socially transitioned as well.	“Transgender” is often used to mean a broader range of people—anyone whose gender identity does not align with his or her sex at birth. This categorization can include, for example, people who identify as male and female, neither male or female, or somewhere between male and female. The sample included in the current work does not include such children, hence our use of a narrower version of this term.
Social transition	This phrase is used to refer to a decision by a family to allow a child to begin to present, in all aspects of the child’s life, with a gender presentation that aligns with the child’s own sense of gender identity and that is the “opposite” of the gender assumed at the child’s birth. Social transitions involve changes in the child’s appearance (eg, hair, clothing), the pronoun used to refer to the child, and typically also a change in the child’s name.	Social transitions are currently controversial in clinical psychology and psychiatry, but are increasingly being pursued by parents. More and more pediatricians, therapists, and teachers are supporting these transitions as well. Importantly, these transitions do not involve any medical, physiologic, or hormonal intervention.
Natal sex	We use this term to refer to the sex assigned by a physician at the child’s birth. This phrase is meant as a synonym for “anatomical sex,” “biological sex,” or “sex assigned at birth.”	The term “natal sex” is controversial, with many using the phrase “sex assigned at birth” instead. However, the latter term is still unfamiliar to many people with limited exposure to transgender individuals. Because this paper is aimed at reaching a broad audience of pediatric health professionals, we use the more commonly understood term “natal sex.”
“Opposite” gender	We occasionally use the phrase “opposite” gender in this article when describing our sample of transgender children. Children whose gender is the “opposite” of their natal sex refers to natal boys who identify as girls and natal girls who identify as boys. Because the latter phrasing is longer and more awkward, we opted for the former.	This phrasing of “opposite” gender implies that gender is binary, when in fact it is not. There are many people who do not identify as male or female. We use this phrase because most readers will be more familiar with this terminology, and our goal is to reach a broad audience of pediatric health professionals.
Gender identity	We use this term to refer to a child’s sense of his or her own gender. Although in most children, gender identity “aligns” with a child’s natal sex, in transgender children, it does not.	Gender identity is often separated from gender presentation or gender expression (ie, the gender one appears to others as, or how a child expresses his or her gender identity). In this study, however, participants’ gender identities align with their gender presentation/expressions because children have socially transitioned.
Gender Identity Disorder (GID)/Gender Dysphoria (GD)	Until 2014, GID was the official diagnosis given to children who had behavioral preferences and identities (or desires to be) the “other” gender. With the publication of the <i>Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition</i> , this diagnostic category was renamed gender dysphoria (GD) after substantial debate about whether this is or is not a “disorder.”	The term GD describes a broader segment of the population than children qualifying as “transgender” for the current study. For example, a natal male who wishes to be a female, who behaves in accordance with female cultural stereotypes, and who has considerable concern about his identity but who does not believe he is female, would be diagnosed with GD but would not count as transgender in the current study.

their natal sex and use associated gender pronouns consistent with that identity). We focused on internalizing psychopathology because previous work indicates that transgender children are particularly likely to have internalizing, as opposed to externalizing, symptoms.^{33,35} We compared these supported, transgender children’s rates of anxiety and depression to their nontransgender siblings and to typically developing nontransgender children matched to transgender children on age and gender identity.

METHODS

This work, including recruitment and methods, was approved by the Institutional Review Board at the University of Washington.

Participants

To be included in this study, transgender children had to (1) identify as the gender “opposite” their natal sex in everyday life (ie, they identified as male or female, but not the gender that aligned with their sex at birth), (2) present

in all contexts (eg, at school, in public) as that gender identity, (3) use the pronoun matching their gender rather than their natal sex, (4) be 3 to 12 years old, and (5) be prepubescent (ie, anyone eligible for hormone blockers was excluded from the present study). We recruited a national, community sample via support groups, conferences, a Web site advertised via media stories, and word of mouth. Our sample included 73 transgender children ($M_{\text{age}} = 7.7$ years; $SD = 2.2$ years; 22 natal females, 51 natal males;

TABLE 2 Sociodemographic Characteristics for Transgender and Nontransgender Children ($n = 195$)

	Transgender ^a ($n = 73$)	Controls ^b ($n = 73$)	Siblings ^c ($n = 49$)
Gender, %			
Male	30	30	61
Female	70	70	39
Natal boys ^d	70	30	61
Natal girls	30	70	39
Race/ethnicity			
White, non-Hispanic	70	71	76
Hispanic	8	5	10
Asian	6	4	2
Multiracial/other	16	19	12
Mean age, y	7.7 y	7.8 y	8.3 y
Age distribution, %			
3–5 y	30	30	22
6–8 y	40	37	37
9–12 y	30	33	41
Annual family income, %			
<\$25 000	1	1	2
\$25 001–\$50 000	7	7	4
\$50 001–\$75 000	7	14	4
\$75 001–\$125 000	41	43	39
>\$125 000	44	38	51

^a Transgender children were all prepubescent and had socially transitioned.

^b Controls were matched to transgender children for gender identity and age within 4 months.

^c Siblings were the siblings who were closest in age to their transgender siblings.

^d One natal male was diagnosed with a minor disorder of sex development, hypospadias, but consultation with endocrinologist indicated this condition is not associated with female identity.

70% white non-Hispanic) and included all consecutive cases run by our research group meeting these criteria, starting with the first for whom we had these measures.

In addition, we recruited 2 control groups. Our first control group was a set of 49 siblings ($M_{\text{age}} = 8.3$ years; $SD = 2.5$ years; 19 natal females, 30 natal males; 76% white non-Hispanic) of the transgender children reported earlier who were also aged 3 to 12 years. Whenever possible, the sibling closest in age was recruited. The second group of controls consisted of 73 typically developing children with no history of cross-gender behavior ($M_{\text{age}} = 7.8$ years; $SD = 2.2$ months; 51 natal females, 22 natal males; 71% white non-Hispanic) who were matched to each transgender child based on age and gender identity (eg, transgender girls had female controls). These unrelated controls were recruited from a university database of families in the Seattle area interested in participating in research about

child development. Importantly, all parents were informed that this was part of a longitudinal study about gender nonconforming children's development, even though their children were not gender nonconforming. Recruitment and data collection is part of the TransYouth Project, a large, longitudinal study of American and Canadian transgender children's development, and matched controls from that larger study were used in the current work.

Measures

Internalizing Psychopathology

Symptoms of anxiety and depression were reported using the National Institutes of Health Patient Reported Outcomes Measurement Information System parental proxy short forms for anxiety and depression.³⁸ When possible, 2 parents completed these forms, and the averages are reported ($n = 90$); in all other cases, only 1 parent completed the forms ($n = 115$). (Importantly, results did not

change if only mothers' responses [most often the only parent present when there was one reporter] were analyzed.) These scales are nationally normed and provide t -scores such that a score of 50 represents the national mean, with a SD of 10.

Demographics

Parents completed several demographic questions, including their child's race, sex, and age, and their household income (in quintiles: 1 = <\$25 000/year, 2 = \$25 001–50 000, 3 = \$50 001–75 000, 4 = \$75 001–\$125 000, 5 = >\$125 000/year). This information is reported by participant group in Table 2. With the exception of gender (siblings were more likely to have a male gender identity than transgender or age-matched control participants; the latter 2 groups were matched on this variable), the 3 groups did not differ on demographic variables.

RESULTS

Anxiety and depression t scores are reported in Table 3 by participant sample and natal sex. Transgender children's rates of anxiety and depression were first compared with the scale's midpoint (50), an indicator of average levels of depression and anxiety symptoms.³⁸ In terms of depression, transgender children's symptoms ($M = 50.1$) did not differ from the population average, $P = .883$. In contrast, transgender children had elevated rates of anxiety compared with the population average ($M = 54.2$), $t(72) = 4.05$, $P < .001$. Mean anxiety symptoms of transgender children were not in the clinical, or even preclinical, range, but were elevated.

To assess differences between transgender and control children in our sample, we ran a 3 (group: transgender, siblings, controls) $\times$ 2 (natal sex) between-subjects analysis of variance for depression and anxiety. Natal sex was used in

this analysis, rather than affirmed gender, because work with children with GID/GD used this convention,³⁵ allowing interested readers to make comparisons to past work with that sample and because previous work has suggested differences in internalizing psychopathology between natal boys compared with girls with GID.^{35,39} For depression, there were no main effects of group, $P = .320$ or sex, $P = .498$, nor was there an interaction between condition and sex, $P = .979$. For anxiety, we found a marginally significant effect of group, $F(2189) = 2.91$, $P = .057$, and no effect of sex, $P = .990$, nor an interaction, $P = .664$.

DISCUSSION

Socially transitioned, prepubescent transgender children showed typical rates of depression and only slightly elevated rates of anxiety symptoms compared with population averages. These children did not differ on either measure from 2 groups of controls: their own siblings and a group of age and gender-matched controls. Critically, transgender children supported in their identities had internalizing symptoms that were well below even the preclinical range. These findings suggest that familial support in general, or specifically via the decision to allow their children to socially transition, may be associated with better mental health outcomes among transgender children. In particular, allowing children to present in everyday life as their gender identity rather than their natal sex is associated with developmentally normative levels of depression and anxiety.

Critically, socially transitioned transgender children showed substantially lower rates of internalizing symptoms than children with GID reported in previous studies³⁵ (see Table 4). Our findings align with at least 1 other report of low mental health problems among

TABLE 3 Anxiety and Depression t Scores by Sex and Sample

	Transgender ($n = 73$)	Controls ($n = 73$)	Siblings ($n = 49$)	P
Depression	50.1	48.4	49.3	.320
Anxiety	54.2 ^a	50.9	52.3	.057
Depression by gender ^b				.979 ^c
Natal boys	49.8 (trans-girls)	48.0	48.9	
Natal girls	50.8 (trans-boys)	48.5	49.9	
Anxiety by gender				.664 ^c
Natal boys	53.7	51.1	52.8	
Natal girls	55.3	50.8	51.5	

^a This is the only value that is significantly above the national average (50), although it is still substantially below the clinical (>63) or even preclinical (>60) range.

^b Transgender children who are natal boys and live with a female gender presentation are often called transgender girls or trans-girls; transgender children who are natal girls living with a male gender presentation are often called transgender boys or trans-boys.

^c Significance value of interaction between natal sex and group.

TABLE 4 Comparison of Present Sample With Previous Reports of Population-Normed Internalizing Scores for children with GID²⁴

	Current Sample ($n = 73$)	Toronto ($n = 343$)	Utrecht ($n = 123$)
Mean age	7.7 y	7.2 y	8.1 y
Sample	Transgender ^a	GID ^b	GID ^b
Measure of internalizing	PROMIS ^c	CBCL	CBCL
Mean internalizing t score	52.2	60.8	64.1

Both the PROMIS and CBCL are normed such that the population mean is $t = 50$ and SD is 10. CBCL, Child Behavior Checklist; PROMIS, Patient Reported Outcomes Measurement Information System.

^a The current participants were transgender, socially transitioned, and prepubescent.

^b Participants in both the Toronto and Utrecht samples either met criteria for GID or showed subthreshold symptoms of GID.

^c To compute an internalizing score for the PROMIS, depression and anxiety scores were averaged.

children with GID supported in their gender identities,³⁴ a sample that may have included some socially transitioned transgender children. Comparisons between previous reports of children with GID and the current sample should be made cautiously, however, because the criteria for inclusion (transgender identities vs GID) and specific measures of internalizing psychopathology (PROMIS vs CBCL) differ across studies.

One might reasonably ask whether this study provides support for all children with gender dysphoria to socially transition. A few points are key to consider. First, all children in our study (unlike many children with the GD classification), had binary identities, meaning they identified as male or female. Thus, we cannot make predictions about the expected mental health of children

who identify as male and female, as neither male nor female, or who identify as the gender associated with their natal sex but nonetheless exhibit behavior more often associated with the “other” gender after a social transition. Thus, just because a child behaves in a way consistent with a gender other than their natal sex does not mean that child is transgender nor that a social transition is advisable. Second, the children in this study were unique in many critical ways. They transitioned at a time when such transitions are quite controversial^{5–9} and yet did so anyway. Surely not all families with transgender children make this decision, meaning there are likely characteristics that are unique to these families. In addition, the transgender children in this study all socially transitioned much earlier than nearly all transgender adults alive today in the United States and

Canada. Why might they have done so? Possibilities that we cannot rule out are that these children displayed earlier signs of their transgender identities, that they were more insistent about those identities, that they represent the most extreme end of the spectrum of transgender identities, or that parents today are just more educated about the existence of transgender children. It is too early to tell the ways in which these children and these families are unique. Finally, the children in this study were not randomly assigned to social transitions, precluding the ability to make causal claims about the impact of social transitions on mental health. These data are suggestive, nonetheless, that social transitions are associated with positive mental health outcomes for transgender children.

We cannot rule out several alternative explanations for our findings. First, rather than a direct impact of parental support, these generally positive mental health findings could be a more indirect result of parent support: namely, feeling supported in general (independent of a social transition) may lead to higher self-esteem,⁴⁰ which in turn may lead to better mental health.⁴¹ Second, as alluded to earlier, there could be some unique third variable that explains the observed occurrence of typical mental health among socially transitioned transgender children. For example, perhaps some attribute unique to the subset of transgender children who are able to convince their parents to allow them to transition (eg, verbal skill, self-confidence) is responsible for these children having particularly good mental health, and it was this unique cognitive ability or aspect of personality that is either correlated with better mental health or leads to better mental health when a child feels he or she achieved his or her goal. Future studies examining

children before and after social transitions may be able to address this concern. Finally, parents of transgender children could have biased reporting, reflecting a desire for their children to appear healthier than they are. We have no reasons to believe this was an issue but in the future aim to include other reporters (eg, teachers) to address this concern that others are likely to raise.

In addition to studying other explanations for these data, the current work begs for more research not only on children with other transgender identities (eg, children who identify as both or neither male and female), but also for work with children who have clear binary transgender identities, like the children in the current study, but who are not supported or affirmed by their families in these identities. Finding such children and particularly convincing their parents to allow them to participate in research, will be a challenge but one that is ultimately necessary for a clear understanding of the specific impact of transitions for these children.

Despite their overall relatively good mental health, socially transitioned transgender children did experience slightly more anxiety than the population average, although still well below the preclinical range. What might explain this result? Despite receiving considerable support from their families, these children likely still experience relatively high rates of peer victimization or smaller daily micro-aggressions, particularly if their peers know that they are transgender⁴² which can in turn lead to marked elevations of anxiety symptoms and anxiety disorders.⁴³⁻⁴⁵ Additionally, any transgender children who are living “stealth” or “undisclosed” (ie, whose peers are unaware of their transgender status), may experience anxiety about others discovering their transgender identity; previous

work with adults has suggested that concealing a stigmatized identity can lead to psychological distress.⁴⁶ Furthermore, transgender children do not have the typical bodies of children with their gender identities, which could be a source of distress. Even when transgender children are allowed to use the bathroom, locker room, or be on the team with children who share their gender, the mere existence of these distinctions likely highlights the ways in which their bodies do not align with cultural expectations for children of their gender identity group. Relatedly, some children in our sample are approaching puberty, and most are aware that puberty will cause physical changes in an unwanted direction (unless puberty blockers are administered), which could generate considerable worry and anxiety.

Importantly, although these socially transitioned prepubescent children are doing quite well in terms of their mental health at this point, parents and clinicians of such children should still be on the lookout for potential changes in the status of their children’s mental health. In general, the prevalence of depression is relatively low in prepubescent children and rises dramatically during adolescence.⁴⁷ It is possible that transgender children will exhibit greater anxiety and depression than their peers during the adolescent transition because of the sources of distress mentioned earlier, which will likely become worse with time (a possibility we aim to test with prospective follow-up of this sample). Thus, while adolescence is a time of increased perceptions of stress for many adolescents,⁴⁸ many of these issues are exacerbated for transgender teens. Transgender adolescents, whether they do or do not delay puberty through medical intervention, often experience body dysphoria (as their bodies do not match the bodies of their

same-gender peers), making sex and relationships even more worrisome than among their nontransgender peers.⁴⁹

CONCLUSIONS

In sum, we provide novel evidence of low rates of internalizing psychopathology in young socially transitioned transgender children who are supported in their gender identity. These data suggest at least the possibility that being transgender

is not synonymous with, nor the direct result of, psychopathology in childhood.²⁷ Instead, these results provide clear evidence that transgender children have levels of anxiety and depression no different from their nontransgender siblings and peers. As more and more parents are deciding to socially transition their children, continuing to assess mental health in an increasingly diverse group of socially transitioned children will be of utmost importance.

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ABBREVIATIONS

GD: gender dysphoria
GID: gender identity disorder

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Parental and Coach Support or Pressure on Psychosocial Outcomes of Pediatric Athletes in Soccer

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Objective: The purpose of this article was to examine supportive and/or pressuring influences of parents and coaches on young athletes' maladaptive perfectionist tendencies, relationships to friends, and competency perceptions in soccer. Previous research has revealed that parents and coaches may give rise to both enjoyable and stressful sport experiences for the pediatric athlete and that parents and coaches are thus able to influence whether young people decide to quit sport or continue participating. Less is known about the relation of supportive versus pressuring parental and coach behaviors on the quality of athletes' achievement striving, relationships to friends in sport, and their competence perceptions. Such knowledge may help create a better psychological sport experience for pediatric athletes.

Data Sources/Synthesis: A questionnaire-based cross-sectional field study was carried out among 677 young Norwegian soccer players (aged 10 to 14 years; 504 boys, 173 girls; mean age: boys = 11.9 years, SD = 2.9; girls = 11.2 years, SD = 2.1) taking part in the Norway Cup international youth soccer tournament in 2001. Multivariate analysis of variance (MANOVA) with follow-up canonical correlation was used to examine multivariate relationships between supportive and pressuring behavior and athletes' psychosocial experiences.

Results: Joint pressuring behaviors from parents and coaches related positively to maladaptive achievement striving, as indicated by overconcern for mistakes, doubt about one's soccer actions, and lowered perceptions of soccer competence. Mirroring these findings, predominantly supportive coach-created psychological climates were related to a linear pattern of psychological outcomes comprising high-quality friendships, positive competency perceptions, and the absence of specific worries related to achievement striving.

Conclusions: Supportive, mastery-oriented coach influence seems beneficial for constructive psychosocial outcomes in pediatric athletes, and athletes experiencing a joint social pressure to excel from coaches and parents may benefit less psychosocially through sport.

Key Words: parental/coach support, pressure, perfectionism, friendship

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Physical activity and sport participation can play a role in young peoples' psychosocial health and functioning.¹ Participation in sports has been found to be associated with greater psychosocial maturity and more positive teacher ratings of academic competence.² Relative to those playing sports, not playing sports outside of school and being classified as physically inactive has been found to increase risk for depressive symptoms in children.³ Pediatric sport is, however, also laden with an array of potential sources of stress, including overemphasis on winning, poor coach/parent-athlete relationships, antisocial involvement, and pressure for young people to succeed.^{4,5}

Constructive behavior by parents and coaches is critical for enjoyable and developmentally appropriate sport experiences and sport outcomes for pediatric athletes. However, organized soccer provides ample opportunity for both constructive and detrimental coach and parental involvement. Young athletes identify their parents as sources of encouragement and positive affect,^{6,7} but, unfortunately, also as sources of pressure and negative affect in sport.^{8–11} Parents and coaches have been found to play an important role in positively or negatively shaping young athletes' psychosocial experiences in the sport domain. In particular, by creating specific motivational climates, communicating, and providing feedback, parents and coaches may be sources of stress and anxiety as well as enjoyment and motivation in sporting experiences.^{12–15}

There is, however, sparse evidence on how joint parental and coach influences relate to young athletes' psychosocial sport experience. Leff and Hoyle¹⁶ examined parental support and pressure in relation to young peoples' sport experiences, but they did not include the coach as a potential source of pressure and support. Further, the role of pressuring versus supportive parents and coaches on young athletes' maladaptive perfectionist tendencies, their quality of friendship in sport, and their self-referenced competency perceptions have gone relatively unexplored. Environmental influences on these outcomes need to be identified. First, maladaptive perfectionism in the form of being overly self-critical in terms of one's own performance, such that one is rarely satisfied with one's level of achievement, is indicative of psychosocial malfunctioning. Such malfunctioning includes low self-esteem, depression, and burn-out as well as development of symptoms of bulimia.^{17–21} Second, young athletes identify peers as preferred sources of competence estimation and self-esteem enhancement, and peers have been found to influence young athletes' affective and social-moral reasoning and

behavior.^{22,23} Third, competency perceptions in sport have been found to be the most salient source of enjoyment among young athletes, reflecting intrinsic processes of participation motivation.²⁴ Indeed, there is preliminary evidence that pressuring parental behavior goes along with self-reports of maladaptive perfectionism in adolescent athletes.²⁵ Moreover, a coach-induced mastery climate has been found to relate positively to perceptions of high-quality friendships among 14- to 19-year-old female soccer players.²⁶

The main purpose of the present study was to examine the linear multivariate association between indices of pressuring and supportive coaching and parental involvement and maladaptive perfectionism, quality of peer relations, and competency perceptions in a sample of young soccer players.

We expected that self-reports of pressuring coaches—those who are perceived by the athletes as generating a social-comparative performance climate embracing a strong pressure to win, giving most attention to the best players, and reinforcing intrateam rivalry—as well as pressuring parents who expect high performance standards and who are excessively critical of the athletes' performances, would relate negatively to the pediatric athletes' self-reports of constructive friendship formation and their competency perceptions. Coach and parental influences of this kind were also expected to relate positively to indices of maladaptive perfectionism as indicated by athletes' self-reports of doubt about actions and worrying about mistakes. We expected the opposite pattern for athletes who self-reported coaches and parents as supportive, nonpressuring, and mastery oriented.

DATA SOURCES/SYNTHESIS

Participants and Procedures

Participants in this field study were 677 young Norwegian male and female soccer players (aged 10 to 14 years; 504 boys, 173 girls; mean age: boys = 11.9 years, SD = 2.9; girls = 11.2 years, SD = 2.1). Players for the study were randomly drawn from a pool of teams taking part in the Norway Cup international youth soccer tournament in July/August 2001. The Norwegian teams taking part in this tournament are generally regarded as representative of Norwegian organized youth soccer. Adhering to pediatric ethical guidelines,²⁷ consent was obtained from parents or guardians before tournament participation. The participants responded to a questionnaire indicating support and pressure in soccer and adaptive and maladaptive psychosocial outcomes. All questionnaires were distributed in a quiet setting at or around the schools where the teams stayed during the tournament. Confidentiality regarding individual information was assured.

Measures

The measures used for this study consisted of several formerly validated paper and pencil instruments or scales with multiple-choice answer alternatives. Each test was made up of a number of items summed to form an index, or sum score, for further computations.

Perceived motivational climate was assessed by the 19-item Norwegian version²⁸ of the two-dimensional Perceived

Motivational Climate in Sport Questionnaire.²⁹ The mastery dimension focuses on effort, improvement, and cooperation. Example items are "trying hard is rewarded" and "every player has a role." The performance-oriented dimension taps a coach's levels of focus on social comparison, pushing players to win, giving the most attention to the best players, and the reinforcement of intrateam rivalry. Example items include "out-playing teammates is important" and "doing better than others and winning is important." Responses were scored on a five-point Likert scale, anchored from 1 (strongly agree) to 5 (strongly disagree). Satisfactory construct validity and internal consistency in previous research have been found (eg, Ommundsen et al²⁶). In the present study, Chronbach's alphas were 0.70 (mastery climate) and 0.79 (performance climate).

Pressuring parental expectations and parental criticism were assessed by asking players to complete the interpersonal dimensions of the Multidimensional Perfectionism Scale,³⁰ comprising the perceived parental expectations and criticism subscales. Example items for the five-item parental expectations and the four-item parental criticism subscales include "my parents set excessively high standards for me" and "I am often criticized for doing things less than perfectly." Each item is scored on a five-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). Previous studies have demonstrated the reliability and validity of the scale in several settings³⁰ as well as in competitive sport.^{19,26} In the present study, Chronbach's alphas were 0.80 (parental expectations), and 0.70 (parental criticism).

To measure maladaptive perfectionism in soccer, two intrapersonal subdimensions of the Multidimensional Perfectionism Scale³⁰ were used. The dimensions focus on the degree to which players engage in maladaptive perfectionist thinking. The nine-item Concern Over Mistakes subscale reflects a tendency to react negatively to mistakes and to believe that failure will result in a loss of respect from significant others. Items include "when playing soccer, I always get upset if I make mistakes." The four-item Doubts About Action subscale taps the extent to which individuals feel they lack the ability and strategies to accomplish achievement-related activities at certain standards. One example item is "even when I perform skills very carefully when playing soccer, I often feel that it is not quite right." Each item is scored on a five-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). Previous studies have demonstrated the reliability and validity of this scale in several settings^{17,30} as well as in competitive sport.^{19,26} For the current analytical purposes, the two subscales were combined into a total sum score, labelled "perfectionist worries." Chronbach's alpha was 0.87.

Quality of friendship in soccer was measured by two subdimensions of the Sport Friendship Quality Scale.^{26,31} The first is labelled Loyalty and Free discussion (seven items). One item from this scale is "in soccer, my friend and I can talk about everything." The second dimension (six items), companionship, reflects being together and talking together. One item is "in soccer, my friend and I are having fun together." The scoring goes from "not at all true" (1) to "completely true" (5). The reliability and factorial validity of this scale have been reported elsewhere (eg, Ommundsen et al²⁶). For the current analytical purposes, the two subscales were combined

into a total sum score, labelled “positive friendship.” Chronbach’s alpha was 0.88.

Competency perceptions were measured using the 18-item Intrinsic Motivation Inventory, which was developed in the sport context by McAuley et al³² to measure intrinsic motivation after sport tasks. For our current purposes, we used the perceived competence subscale of the inventory.

The scale has four items rated on five-point scales, ranging from “don’t agree at all” (1) to “agree completely” (5). One item is “I think I’m pretty good at playing soccer.” The validity and the internal consistency of this scale have been found to be acceptable in previous sports-based research with samples of Norwegian adolescent soccer players.³³ In the present study, Chronbach’s alpha was 0.72 after omitting one item [“I do not manage the soccer exercises very well” (reversed)].

Data Analysis and Synthesis

MANOVA with follow-up canonical correlation (R_C) analysis was used to examine the multivariate relationship between the parental and coach pressure and support variables and the three indices of psychosocial outcomes. This analysis tests the best-fitting linear relationship between these two variable sets. The coach-created mastery and performance climate and parental criticism and expectations subscales comprised the predictor set, and perfectionist worries, positive friendship, and competency perceptions comprised the criterion set.

RESULTS

Descriptive Statistics and Correlation Results

Means and standard deviations were computed for all variables. Included in Table 1 are also Cronbach’s alphas and intercorrelations among the variables.

As revealed by the min–max and mean values in Table 1, players scored moderately high on parental criticism and coach-created performance climate and quite low on parental expectations. They perceived the climate as strongly mastery oriented. Their score on perfectionist worries was moderate to low, whereas they perceived their friendship relations and their competency in soccer as quite positive. Correlations revealed that parental pressure, both in forms of expectations and criticism, was related positively to perfectionist worries and negatively to positive friendship and competency perceptions.

Coach pressure, in terms of a performance climate, held a similar pattern of relations to these psychosocial outcomes. In contrast, coach support (eg, a mastery climate) was unrelated to perfectionist worries, but positively related, albeit modestly, to positive friendship and competency perceptions. No intercorrelations were excessively high. Hence, there was no evidence that multicollinearity would threaten the remaining analyses.

Multivariate Relationship between Perceived Motivational Climate, Achievement Goals, Perfectionism, and Quality of Peer Relationship Indices

The MANOVA revealed that the overall multivariate relationship between the two variates was significant, Wilk’s lambda = 0.47, $F(12,1772) = 49.19$, $P < 0.001$. Follow-up canonical correlation analyses were performed to examine these sets of relationships more closely. Two unique significant canonical functions were found to best describe and explain the relationship between the canonical variates. The first canonical function revealed a canonical correlation of $R_{C1} = 0.72$, and the second function revealed a canonical correlation of $R_{C2} = 0.31$. Tabachnick and Fidell³⁴ note that most researchers set a R_C value of 0.30 as the minimum acceptable criterion for interpretation purposes. Both R_C values in the present analysis met this standard. The canonical correlation coefficient provides a measure of association between two composite set of variables. In the present case, results indicate that more than 10% of the variance is shared by the linear combinations of the canonical variates.³⁴

Table 2 contains the canonical loadings for both canonical functions. Canonical loadings represent the contribution of each original variable to the multivariate relationship (ie, to their respective canonical variates). Loadings greater than 0.30 are generally considered meaningful and thus interpreted.³⁴

In the first canonical function, performance climate (0.72), parental criticism (0.86), and parental expectations (0.82) had strong positive loadings on the predictor canonical variate, whereas positive friendship had a moderate negative loading (−0.41), perfectionist worries had a strong positive loading (0.99), and competency perceptions (−0.32) had a modest negative loading on the criterion canonical variate. The linear combination of these two canonical variates

TABLE 1. Descriptive Statistics (alphas, means, standard deviations) and Zero-order Correlations for Motivational Climate, Parental Expectations, Parental Criticism, Peer Friendship, Perfectionist Worries, and Self-referenced Competency (N = 677)

Variable	Alpha	M	SD	1	2	3	4	5	6	7
1. Parental criticism	0.70	2.42	0.90	—	0.57*	−0.06	0.43*	0.61*	−0.25*	−0.19*
2. Parental expectations	0.80	1.89	0.86	—	−0.07	0.40*	0.58*	−0.24*	−0.18*	—
3. Mastery climate	0.70	4.45	0.57	—	−0.06	−0.01	0.16*	0.13*	—	—
4. Performance climate	0.79	2.54	0.87	—	0.50*	−0.22*	−0.21*	—	—	—
5. Perfectionist worries	0.87	2.66	0.68	—	−0.28*	−0.24*	—	—	—	—
6. Positive friendship	0.82	3.72	0.73	—	0.25*	—	—	—	—	—
7. Competency perception	0.72	3.25	0.47	—	—	—	—	—	—	—

$P < 0.05$.

$P < 0.01$.

* $P < 0.001$ (Min–max all variables = 1–5).

TABLE 2. Canonical Loadings of Parental and Coach Pressure and Support Variables and Indices of Maladaptive Perfectionism, Friendship, and Competency Perceptions in Soccer

	Canonical Loadings	
	Function 1	Function 2
Pressure and support variables		
Coach created mastery climate	0.05	0.98
Coach created performance climate	0.72	-0.15
Parental criticism	0.86	0.04
Parental expectations	0.82	0.02
Psychosocial soccer outcome variables		
Positive friendship	-0.41	0.75
Perfectionist worries	0.99	-0.39
Competency perceptions	-0.32	0.64

indicates that when psychological pressure (eg, elevated expectations, criticism, and a pressuring, social-comparative, winning climate) from coaches and parents is high, this is associated with reduced positive friendships, strongly elevated perfectionist worries, and reduced competence perceptions. The redundancy index of the first canonical function reveals that 24.8% of the variance in the motivational climates was explained by the psychological outcomes in the first canonical function.

In the second canonical function, coach support (eg, a mastery climate) had a strong positive loading (0.98) on the predictor canonical variate. Positive friendship (0.75) and competency perceptions (0.64) both had relatively strong loadings on the criterion canonical variate, whereas perfectionist worries had a negative loading (-0.39). The results from this second canonical function may reflect that when coaches are perceived as creating a supportive, mastery-oriented environment, and parents are not perceived as behaving in a pressuring manner, positive friendships flourish, athletes' competency perceptions are quite strong, and players do not express worries in terms of their achievement striving. The redundancy index of the second canonical function reveals that 3.4% of the variance in the coach and parental support and pressure canonical variate was explained by the psychosocial outcome variables. Taken together, redundancy indexes of the two canonical functions reveal that perfectionist worries, positive friendship, and competency perceptions accounted for 28.2% of the variance in support and pressure generated by coaches and parents.

DISCUSSION AND CONCLUSIONS

Findings suggest that parents and coaches may play a significant joint role in influencing the quality of psychosocial sport experiences for pediatric athletes. In particular, when parents are perceived as critical of their performances and having high achievement standards and when coaches are perceived as emphasizing social comparison and winning and giving the most attention to the best athletes, pediatric athletes report believing less in their soccer capabilities, worrying about their performance, and perceiving a less friendly peer

atmosphere on their teams. This pattern of findings is troublesome for several reasons. First, maladaptive perfectionism tendencies may have detrimental psychological consequences in terms of health.²¹ Second, there is evidence that negative peer relations may facilitate the development of later antisocial psychopathology.³⁵ Third, reduced competency perceptions may generate reduced intrinsic motivation, even leading to amotivation and dropout from sport.^{36,37}

Indeed, in line with the present findings, previous studies have shown that parents with a high ability focus and who are punitively structured seem to facilitate concern over mistakes when involved in sport.²⁵ Further, results showing that the quality of friendships seems to suffer when coaches induce a climate filled with intrateam rivalry are consistent with previous findings among older adolescent soccer players.²⁶ We found that parental criticism and expectations related negatively with positive friendship formation as well as perfectionist worries. One possibility is that parental criticism and expectations turn athletes into overly self-critical perfectionists who, then, behave overly critical themselves towards peers who do not conform to their own perfectionist attitudes. This might easily lead to conflicts and harm friendships.³⁸

In contrast, when coaches are perceived as creating a supportive, mastery-oriented environment, and when parents are not perceived as being overly critical or communicating excessively high expectations, players are more likely to remain friendly towards peers and develop into adaptive, healthy, achievement strivers. Also, these findings add to previous ones that have revealed adaptive motivational patterns to be associated with a mastery-oriented, supportive motivational climate in sport.¹⁴

Indeed, the present study is cross-sectional, which precludes any conclusions regarding causal relationships. For example, we cannot rule out the possibility that perfectionist players might have beliefs about their parents' and coaches' expectations or that they might elicit competitive comments/behaviors from them. Hence, longitudinal designs or experimental studies might be necessary to determine whether environmental factors operate as prerequisites for young peoples' psychosocial sport experiences and outcomes. This being said, in light of the theoretical framework provided and empirical findings obtained, the study suggests that by being supportive or pressuring, coaches and parents may positively or negatively affect pediatric athletes' psychological experiences and welfare in soccer.

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I'd Rather Have a Living Son Than a Dead Daughter



Erica Kasper and her son, Drew Adams

Drew Adams: We've been in the car for eight hours now. And we are stuck in traffic.

Mary Harris: This is Drew Adams. He is 15 years old. He is riding shotgun in his mom's SUV.

[Drew & Erica Adams singing]

They are on an all-day road trip, recording the drive on Drew's phone.

Erica Adams: Okay, so legit question. If we have to stop and use the restroom, which one are you planning to use?

MH: Drew's mom Erica is asking her son which bathroom he's going to use. Because Drew is trans. He was born a girl. And this road trip is heading right into the heart of this whole transgender controversy, North Carolina. Drew sort of dodges his mom's question, and says he'll try not to stop at all.

DA: I'll figure it out when I get there. If I get there.

<https://www.wnycstudios.org/podcasts/onlyhuman/episodes/id-rather-have-living-son-dead-daughter>

Armistead Daubert App. 0660

EA: Okay, alright.

MH: You have probably heard about HB2 - North Carolina's "Bathroom Bill". It bans people like Drew from using public restrooms that don't match up with their biological sex. And it's made this state into a place a lot of people are trying to avoid. Ringo Starr and Bruce Springsteen have both canceled performances in North Carolina. PayPal and the NBA have pulled business deals out of the state. But Drew and his mom are driving eight hours from Jacksonville, Florida to get here because North Carolina is also home to one of the only clinics in the South that treats transgender kids.

EA: The drive up here every time we stopped for a bathroom break and Drew would go into a men's room, I held my breath because you just don't know. You don't know if he's going to walk out everything's going to be fine, you don't know if he's going to be in there awhile, you're going to stand there and go I wonder if anybody else is in there. I wonder if they're giving him trouble I wonder if he's having to defend himself I don't know what's going on in there.

MH: I'm Mary Harris and this is Only Human. This week, we followed Drew and his mom to the child and adolescent gender clinic at Duke University. We spent a day here, following patients and specialists in exam rooms and waiting rooms and break rooms because, while the debate about transgender rights keeps raging on, more and more kids are showing up here.

The clinic is only open a couple of days a month. It's part of Duke's children's hospital, a sunny, modern addition to the main hospital next door. There's a giant fish tank when you walk in, and everything - the armchairs, the art - is crayola-colored and bright. At 9 am, Drew and Erica check in at reception.

Receptionist: Drew, when's your date of birth?

DA: 9/29/2000

MH: A sign on the desk reads "We value diversity: tell us your pronouns!" They're all over the hospital, actually, asking kids to tell doctors whether they go by "him," "her," or "they."

R: Who's your primary care doctor?

DA: Dr. Tarbox.

DA: Drew looks pretty androgynous. Drew has blond hair cut short, with a sweep of bangs across his forehead. He has a ring through the center of his nose, and as the medical assistant gets his height and weight, Drew squints at her through his wide, wire-frame glasses.

Medical Assistant: I'm going to get your blood pressure.

MH: This is Drew's second time here. He has been living as a boy for about a year: asking friends and teachers to call him "he". Now he's looking to start his physical transition. He's hoping the doctor will prescribe testosterone, a once a month injection.

MA: Alright did you guys have any other questions or concerns about anything? No.

MH: While they're waiting for the doctor, my producer Jillian asks Drew about the shirt he's wearing.

Jillian Weinberger: Can you tell me what your t-shirt says?

DA: Yeah, it says this is what trans looks like and the word trans is in trans flag colors.

JW: Where did you get that T-shirt?

DA: Mom made it.

MH: A few months back, Drew's mom posted a "re birth announcement" on Facebook -- coming out as a mom of a trans kid. Today she's wearing this little button that says "I'll go with you." It means she'll go to the bathroom with anyone who feels unsafe going on their own.

Erica's learned to embrace Drew's new identity because when he was living as a girl, she says he was really anxious and depressed.

EA: Then after he came out as trans it was like flipping a light switch. Suddenly he has not had an issue with anxiety or depression pretty much since that day. He's been so confident, he's been so positive, he's so bright -- that's kind of his mood all the time now.

MH: She doesn't like talking about what Drew's life was like before he started transitioning. But when I asked her how she knew living as a boy was the right choice for Drew, she was blunt. She said: "I'd rather have a living son than a dead daughter."

Dr. Deanna Adkins: Hey! How are you?

DA: I'm great.

Dr. A: Excellent.

MH: Dr. Deanna Adkins started this clinic. She's an endocrinologist - a hormone doctor.

Dr. A: Anything new since I saw you last? Medically.

DA: No.

Dr. A: You've been healthy? Excellent.

MH: Drew is almost giddy to see her. When she walks in, his only question is when can I start testosterone.

Dr. A: Today. Sound good!? Yeah! All right.

MH: Drew will start out on a fraction of the dose an adult would get. But there are still a lot of unknowns about what these hormones will do, long-term. When Dr. Adkins leaves to write up a prescription, the clinic's social worker comes in. She's got this packet of paper that lists every potential side effect of this treatment, and she starts reading off these statements for Drew to agree with.

Kristen: I understand that the medical effects and the safety of testosterone are not completely known. There may be some long term risks that are not yet known.

MH: Drew is required to affirm that he's heard all of them, and it's a long list. The hormones might give him headaches, high blood pressure, an inflamed liver...

K: Emotional changes -- for example more aggression. I know that the effects of testosterone on fertility are unknown. I have been told that I may or may not be able to get pregnant even if I stop taking testosterone.

MH: Going through these side effects takes nearly 20 minutes.

K: I know that using testosterone to appear more masculine is an off-label use. I know this means that is not approved by the government.

MH: Drew signs one final form. And Dr. Adkins comes back with the prescription.

Dr. A: Alrighty. Guess what I have in my hand?

DA: Happy drugs.

Dr. A: Yay! Yay!

DA: I have one question. Yes. So you said you know you can give me a shot right now. No. What if I went to the hospital pharmacy, picked this up, and gave me the shot in the hotel. Can I do that?

Dr. A: Yes, you can do that.

DA: YAY! I can do that! I can get my shot today. Cause I told all my friends I was going to get it today.

MH: And Drew does give himself the shot that day -- in a conference room at the hospital. He sets up his iPhone to record it...

DA [recording]: This is a big moment for me, yes. So I want to blog it...purple needle...okay testosterone...put the needle in the thingy...I did it! I'm on testosterone. I did it!

MH: How do you feel?

DA: Great!

MH: OK so how many friends have you texted already?

DA: I posted about it on Instagram so that's about 550 right there. And then my best friend Ana.

MH: Drew has created a whole online identity as a trans kid. He has a youtube channel, and he sells pride tattoos on etsy.

[Cheering crowd on Ellen]

MH: Drew came out as transgender after watching an episode of "Ellen" featuring a trans man named Aydian Dowling. Aydian's online video chronicling his transition has more than half a million views.

Aydian Dowling: And I started Googling 'girl that becomes a boy' and 'how to grow up to be a man' and for the next 48 hours it was videos and links and articles and everything was just totally involved.

Ellen: I think I have to say at this point -- I think people's fear of like, oh my god, if it's just floating out there, then my child is going to just look on the internet and become a different gender. I don't think it works that way.

AD: No, it was more like this was the missing puzzle piece.

MH: But Aydian started his transition at 21. Drew is fifteen.

MH: Do you ever worry you're making this big decision. Like what if I change my mind.

DA: Absolutely not. This is the happiest I've been all my life. Like today getting that prescription -- that's probably the happiest I've been.

MH: Even just a few years ago, hormones might not have been an option for a kid like Drew. This clinic is brand new. Dr. Adkins opened it only a year ago.

MH: When did you see your first patient who was trans?

Dr. A: Oh wow. I have to think about that. I want to say 2012. 2012.

MH: So just four years ago.

Dr. A: Yeah.

MH: When she was in medical school, Dr. Adkins trained to treat kids with diabetes or growth hormone deficiencies. But in 2012, she got a call from a physician in New York City. He had a transgender patient who needed a local doctor.

Dr. A: I said wow I don't know what to do. I've never studied that, I hadn't been trained to do that and he said That's OK I wrote the articles, I'll send them to you [laughs] and so he sent me all his articles.

MH: Deciding to treat that first patient wasn't easy for Dr. Adkins. She spent about a month going back and forth about it. She knows that in North Carolina, patients like hers are targets. And that means she is too.

Dr. A: It was a big decision for me. I mean we're at risk too, just like our patients and there are some not so nice people that would push us around or say ugly things about us because we're doing this work.

MH: So safety is a big concern for her, but it's the patients she really worries about. Patients like Jaye.

Assistant: This is Jaye.

MH: Hi nice to meet you.

JW: Nice to meet you.

MH: I'm Mary.

JW: I'm Jillian.

MH: We walk into Jaye's appointment just after lunch. Jaye is an 18 year old African-American trans woman who lives just outside Raleigh. She's here to get a prescription for estrogen -- Dr. Adkins is ticking off the side effects.

Dr. A: Sometimes the risk increases for diabetes. Any in the family? (Yes). Your mom?

J: My mom, grandfather, brother.

MH: Jaye's dad was supposed to be here, but in the end, she is here alone.

Dr. A: Alright I'm going to give you a little bit of a once over. Just the usual. Let me wash my hands...

MH: Jaye is incredibly thin and perfectly styled. She has long fake eyelashes and lots of pink eyeshadow. The only real sign that she wasn't born a girl is the distinct shadow of hair on her neck. She's hoping that's about to change. She says she's going to pick up her prescription as soon as she leaves the doctor.

J: I'm going to go marching in there, I'm probably going to twerk to the counter (laughs). This is a really good feeling for me. I'm not able to scream like I would at home. But I would be screaming right now.

MH: What are you most looking forward to?

J: To be honest I'm ready for my boobies. [[laughs]] I'm been already been a long time for you know to be able to develop breasts.

MH: How long have you known that you're trans?

J: Well, at first, when I was younger, I would first get into nail polish and eyeliner and my mom would notice and asked me if I wanted to be a girl.

MH: When she was younger Jaye didn't think she did want to be a girl. She came out as gay, and her mom was pretty supportive of that. But when Jaye told her mom she was trans...

J: She was angry at me, she thought I was lying to her, I was living a lie. And it just just took me by surprise that she you know wouldn't accept me the way I thought she would.

MH: Because she'd been asking you: Do you want to be a girl, do you want to be a girl?

J: And I would say no, no I'm not.

MH: And then you were like hold it, maybe I am.

J: And that kind of confused her, threw her off. My dad had a really hard time with it -- it became an unspoken thing. But my mom she got most of the flack from it you know from my family they were asked why I was like that. And eventually they started to understand that I couldn't help the way I was and they started understanding that this is a real thing, I'm not acting, this isn't a phase. They don't use my pronouns.

MH: So your family still calls you he?

J: Yes

MH: Your mom and dad, too?

J: My mom -- she's saying she. My dad calls me he still.

MH: So part of the reason we're here is because North Carolina's been in the news so much because of this bathroom law. You got a look on your face when I said that.

J: Since I've lived here in North Carolina I know how it is, and people I know from out of state say it's not that bad and I'm like yes it is. I know a lot of discrimination, know places not to go I could be hurt. And I just knew for a long time it would end up coming to light and it would be nasty.

MH: She can recite the names of trans women of color who have been killed over the last couple of years. She's scared that if she does something kind of normal - like make the first move with a guy - she'll get hurt. Physically.

MH: How do you keep yourself safe in the outside world?

J: I stay home. It shouldn't be that way but, otherwise, you know I like to travel in groups; I don't like to go anywhere late at night. I don't like to-- I don't seek out men. A lot of places don't feel safe. Work doesn't feel safe sometimes. Home doesn't feel safe sometimes. I'm safe when I'm by myself.

Dr. A: Alright, here is the discharge information. It has your vitals from today, your medications that I sent to your pharmacy, and I put the side effects, once again, for the medications here and a reminder to put the estrogen under your tongue.

J: Awesome. Thank you.

MH: After seeing Jaye, Dr. Adkins goes into this little workroom to go over patient records and catch her breath.

Dr. A: I'm getting a little worried. I mean not that I wasn't worried already but I was just told by the third patient that they're moving out of state. Because they don't feel safe.

MH: Dr. Adkins tells patients about support groups, and makes sure they visit with a social worker. But she worries that it's not enough.

Dr. A: The thing that I fear is also something that I know will eventually happen. I hope not, but I feel from talking to other people who care for transgender kids that it's likely, highly likely, that one of my patients will kill themselves one day and that's that the day I don't I don't look forward to.

MH: Oh God. That's just heartbreaking.

Dr. A: But all of, all of the providers who've done this work for any length of time all have patients who have either taken their own life or someone's killed them.

MH: After the break: Dr. Adkins says the work she does is an art, more than a science. And for parents, that means there aren't a lot of easy answers.

Karen: Well, sometimes I feel hopeful, I'm thinking well maybe it'll change, maybe he'll wake up one day and say no this is not for me, this was a mistake. The likelihood of that happening is probably really low, so I try not to get excited about it, hoping that something would happen.

**** MIDROLL ****

MH: Hey everybody, thanks for listening. We've got a quick favor to ask of you. We're working on an episode about how learning a bit about your genes can totally shift your perspective, and we're looking for your stories. So, have you ever taken a DNA test to figure out your ancestry? And did the results surprise you? Maybe you were inspired to learn a bit about a remote place you never knew you were connected to. Write to us. Send us an email at onlyhuman@wnyc.org or @onlyhuman on twitter and Only Human podcast on Facebook. We want to hear from you, and you might get to be part of an upcoming show.

MH: I'm Mary Harris, this is Only Human. Today we're visiting the only gender clinic for kids in the state of North Carolina. It's really busy.

Dr. A: The next new patient appointment is in November now.

MH: And this is the beginning of June.

Dr. A: Yeah.

MH: Dr. Deanna Adkins opened this place about a year ago. And a few months after that, the state passed their "bathroom bill," also known as HB2. It's changed how Dr. Adkins sees her work and herself. She says it's made her "mama bear" come out. And she's become an expert witness in the case against that bathroom bill.

Following Dr. Adkins around, though - I noticed something else. A lot of her teenage patients had severe depression and anxiety. Their parents were coming to Dr. Adkins for answers. But she didn't have a quick fix.

Dr. A: The big question that I get is what's the test. Are they transgender or not. We're here to find that out. And I'm like ooooh. There's no test. [laughs] You know it's takes a lot of understanding, a lot of

conversation, a lot of things to really figure that out. I think they just really want me to tell them no and they can move on with their life.

MH: They want you to say like no I'm the doctor you can't have the medicine.

Dr. A: Yeah, yeah. And you know. Sometimes that's where we end up, that's not the usual case. You know we got to sort through it we got to figure out really where you are really where you want to go. Is that transgender, is it not transgender, is it -- where is it?

MH: The day we visited, Dr. Adkins saw ten patients. The last one came in at around 4:30, and I caught up with him in the waiting room first.

MH: What's your like biggest question from this appointment.

Martin: Um. Why am I so tired all the time, I guess.

MH: We're calling this patient Martin -- but we're using pseudonyms for him and his mom, Karen.

M: I thought that when I started the hormones I would get more energy, and I was looking forward to that, actually.

MH: Martin is slouched in the waiting room chair. He's sixteen, and he's really thin, in baggy clothes. He has short brown hair with blond highlights. And it's kind of hard to tell his gender just by looking at him.

He says he first remembers feeling like his body wasn't quite right when he was 7. He was at summer camp, and he didn't want to use the girls' changing room. A year and a half ago, he came out as transgender.

MH: Tell me about when you first told your mom about being trans.

M: It was one of the last days of the year. I couldn't sleep and one night I went to my mom's room and I was like I need to talk to you about something right now. I can't stop thinking about it.

MH: Martin's mom, Karen, didn't really believe what he was saying.

M: She was like it could be that you're just you know curious. It could be that you're just not like most girls.

MH: Before Martin's appointment, I pulled Martin's mom aside to talk to her one-on one. Because it was clear - she's still struggling.

Karen: The whole thing was just very shocking. I mean I gave birth to this child, this is my daughter, and I just it was just hard out of habit. Just knowing her.

MH: Gender isn't the only thing Martin is having a hard time with. When Martin hit puberty, he got depressed. He refused to go to school. After he started cutting himself, his mom had him hospitalized. She worries now that coming out as trans is one more expression of how unhappy Martin is. And that's made accepting his new identity even more difficult.

K: I felt almost like I was lying by calling her he felt like I was lying to myself to everybody and I just it just didn't seem natural to me at all.

MH: Was there a point when that stopped or does it still kind of feel like that?

K: It's gotten much better. I've been working really hard at trying to do that and I do I do slip every now and then still. I've talked to other parents who have transgender children and they still make mistakes every now and then in fact on the way here I made a mistake and he corrected me. But it's it's really odd. I feel like I'm talking about somebody else sometimes when I talk about this is my son.

MH: Most of the time we were talking, Karen was literally shaking, she was so nervous. She desperately wants her kid to be OK. And transitioning has made a huge difference for her him. She says the changes were --

K: Almost like immediate -- yeah. I saw immediate changes.

MH: When he was living as a girl, Martin was withdrawn. But now, after a couple of months on testosterone --

K: He's really opened up to me he confides in me he will sit down and have dinner with me have a conversation with me. You know it's more like we've become friends again and we've reconnected. I think it's because he realizes that I accept him for who he is and I'm going to support him.

MH: But Martin's become really sluggish. He's been sleeping all day when he can, sometimes for stretches of 11 hours at a time. When they get into the exam room, Dr. Adkins wants to figure out why.

Dr. A: Alrighty, I just want to give you a once-over, if you'll hop up there...

MH: She asks a few questions and does a quick physical exam. When Martin rolls up his sleeves, I can see his arms are covered in delicate white scar tissue from cutting.

Dr. A: Blood sugar was good. Kidney, liver function was all normal. Testosterone was 294, which is a good number. Have you seen any change in facial hair, acne, oiliness?

M: Acne and oiliness. Definitely a lot more. Also on my back a lot.

MH: Dr. Adkins eventually convinces Martin to take a little less testosterone to see if that helps him feel less tired.

Dr. A: Yeah I'm a little worried about the fatigue that --you too?

M: Yeah.

Dr. A: OK.

MH: Martin is not thrilled with this decision. He's been so much happier since he began transitioning. But Dr. Adkins is insistent. And she asks him to get one more round of blood work before he goes.

DA: She's going to come grab you for the labs in a minute and then you can check out. For right now I put in for a 4-month follow-up, so you can make that out front.

MH: When I started reporting this story, the one question I kept coming back to was "how do these kids know what they want when they are so young?" So before Martin left, I asked him to explain to me how he knew.

M: I could never see myself being the woman in a relationship and it was the most uncomfortable idea to me.

MH: To be the woman. (Yeah) Why?

M: It's something that I really can't put into words exactly like it's sort of has to do with like traditional roles in a relationship that a woman has like you know the man would ask the woman out kind of thing but also something that you can't really explain you just have to feel it.

MH: Martin told me he doesn't think he'll ever change his mind about his transition. But when I listen back to him trying to explain exactly what trans feels like to him, I can hear him struggling to do it. His mom hears it, too.

K: Even his therapist said, you know, this may not be forever, we don't know for sure, nothing is one hundred percent guaranteed. He could change his mind two months from now. Six months. Ten years. We don't know. But right now this is where he's at.

MH: How do you feel about that?

K: Well I know it's sometimes I feel hopeful I'm thinking well maybe it'll change, maybe he'll wake up one day and say no this is this is not for me, this is not this was a mistake. But the likelihood of that happening is probably really low, so I try not to get you know excited about it, hoping that something would happen.

MH: And she does worry that Martin can't know how he'll feel, down the line. Remember all those side effects?

K: His ovaries may become destroyed. But he said that he's fine with that because he never really planned on having children, but he's only sixteen so, you know, I hope that he doesn't change his mind down the road and regret -- have any regrets.

MH: By the time Martin leaves, this clinic has been seeing patients for almost 12 hours straight. Back in the clinic workroom, Dr. Adkins goes over paperwork with the clinic's social worker.

Dr. A: We made it. End of the day. Yay.

Kristen: We made it before 6:30.

Dr. A: Yeah. It's been 7 before.

MH: How do you feel at the end of a day like this.

Dr. A: Exhausted and rewarding definitely feel like I've done good but it takes a lot of me.

In about a month, Martin will head back to school, in Raleigh. And, for the first time, he'll walk through those doors as a boy. I asked him what bathroom he'll use. He said, it will depend how brave he's feeling.

Only Human is a production of WNYC Studios. This episode was produced by Jillian Weinberger. Our team includes Amanda Aronczyk, Elaine Chen, Paige Cowett, Julia Longoria, Kenny Malone, Fred Mogul, and Lisa Rapaport. Our technical director is Cayce Means. Our executive producer is Leital Molad. Thanks this week to Ben Adair, along with Danielle Fox and Stephanie Daniel.

Jim Schachter is the Vice President of news at WNYC. I'm Mary Harris, talk to you next week.

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Predicting Early-Childhood Gender Transitions

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Abstract

Increasing numbers of gender-nonconforming children are socially transitioning—changing pronouns to live as their identified genders. We studied a cohort of gender-nonconforming children ($n = 85$) and contacted them again approximately 2 years later. When recontacted, 36 of the children had socially transitioned. We found that stronger cross-sex identification and preferences expressed by gender-nonconforming children at initial testing predicted whether they later socially transitioned. We then compared the gender-nonconforming children with groups of transitioned transgender children ($n = 84$) and gender-conforming controls ($n = 85$). Children from our longitudinal cohort who would later transition were highly similar to transgender children (children who had already socially transitioned) and to control children of the gender to which they would eventually transition. Gender-nonconforming children who would not go on to transition were different from these groups. These results suggest that (a) social transitions may be predictable from gender identification and preferences and (b) gender identification and preferences may not meaningfully differ before and after social transitions.

Keywords

transgender, gender nonconformity, social transitions, gender development

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In any given classroom, one will likely find many children who disregard some gender norms, such as boys who like pink and girls who engage in rough-and-tumble play (e.g., Sandberg, Meyer-Bahlburg, Ehrhardt, & Yager, 1993). Less common are children who consistently show a preference for opposite-sex¹ peers, prefer toys and clothing that are culturally associated with the opposite sex, or express a wish to be members of the opposite gender group—children whom we term *gender nonconforming*. Parents, scientists, and clinicians have often wondered about these children's later outcomes. Longitudinal data suggest that most gender-nonconforming children do not end up identifying as transgender² (i.e., identifying as a gender opposite their assigned sex³) later in life, though in every study at least some do (Green, 1987; Steensma, McGuire, Kreukels, Beekman, & Cohen-Kettenis, 2013; Wallien & Cohen-Kettenis, 2008; Zucker & Bradley, 1995).

Interest in early-childhood gender nonconformity and later transgender identity has recently become especially pronounced (Dreger, 2009; Green, 2017), as some families are supporting their prepubescent children through social transitions (Edwards-Leeper, Leibowitz, & Sangganjanavanich, 2016; Sherer, 2016; Turban, 2017). Social transitions, as they apply to prepubescent gender-nonconforming children, involve changing a child's pronouns, hairstyle, clothing, and sometimes name to align with the child's identity rather than his or her assigned sex (Malpas, 2011; Steensma et al., 2013). Relatively unheard-of 10 years ago, early-childhood social transitions are a contentious issue

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within the clinical, scientific, and broader public communities (Edwards-Leeper et al., 2016; Green, 2017; Steensma & Cohen-Kettenis, 2011). Despite the increasing occurrence of such transitions, we know little about who does and does not transition, the predictors of social transitions, and whether transitions impact children's views of their own gender. These are the central questions of the current article.

Past longitudinal work has found that gender-nonconforming children who identify as transgender in adolescence and adulthood tended to show more extreme childhood gender nonconformity than gender-nonconforming children who did not later identify as transgender (Singh, 2012; Steensma et al., 2013; Wallien & Cohen-Kettenis, 2008). Most or all participants in these studies had not completed a full social transition as prepubescent children (i.e., had not changed pronouns), as social transitions are a fairly recent practice. Therefore, it is an open question whether individuals who socially transition in early childhood also show systematic differences in gender nonconformity from those who do not.

On the one hand, if the findings from postpubertal transitions apply to transitions undertaken earlier, children showing more extreme gender-nonconforming identities and preferences should be more likely to socially transition in childhood. Supporters of social transitioning as a practice often argue that social transitions should be considered for children exhibiting particularly strong and consistent cross-gender identification for extended periods of time (e.g., assigned males who identify most strongly as girls; Ehrensaft, Giammattei, Storck, Tishelman, & Keo-Meier, 2018; Malpas, 2011). These supporters suggest that a child's degree of gender identification (as perceived by parents, therapists, etc.) may contribute to the family's or clinician's support for the child's decision to transition. On the other hand, there is no standardized protocol or measure to help families or clinicians decide which children to support through a transition or any battery of tasks to describe how extreme a given child's cross-gender behavior is relative to other gender-nonconforming children. Thus, social transitions may be occurring randomly or without regard to variation in children's identities or preferences.

To test these possibilities, we recruited a group of gender-nonconforming children who had not socially transitioned and assessed their gender identification and preferences. An average of 2 years later, we asked their parents whether each child had socially transitioned. This approach allowed us to prospectively investigate whether children who went on to socially transition (*future transitioners*) differed from those who did not socially transition (*nontransitioners*) in terms of earlier extremity in cross-sex gender identification

and preferences. Importantly, parents were not told how their child's results compared with those of other children in the study, nor were they given an individual report of their children's results.

As a second research question, we also investigated whether social transitions are associated with changes in the degree to which children express their gender identity and preferences. That is, would an assigned male who is living as a girl (i.e., a transgender girl) be more feminine than an assigned male who has not yet transitioned but later does? On the one hand, after a transition, a child is more likely to be treated as a member of his or her identified gender in everyday interactions because the child now appears (e.g., through clothing or pronouns) to be a member of that gender group. This treatment may reinforce the child's sense of identity, thereby leading to more extreme preferences and identity expression. In this case, a child tested before transitioning might not show preferences and identity expression to the same extreme as a child who has already transitioned. On the other hand, perhaps the child's gender identification and preferences were already very strong before the transition. In such cases, children tested before transitioning may not differ from children tested after transitioning. To assess this question, we recruited a comparison group of transgender children (i.e., those who had already socially transitioned), had them complete the same assessments of gender identity and preferences, and compared the two groups.

Finally, we asked whether children tested before transitioning (future transitioners) and children tested after transitioning (transgender children) differed in terms of their gender identity and preferences from control children assigned the opposite sex at birth. Past work has suggested that after transitions, transgender children show comparable gender identity and preferences to peers with the opposite assigned sex (Fast & Olson, 2018; Olson, Key, & Eaton, 2015), so the inclusion of a comparison group of control children provided an opportunity for replication (for comparison with transgender children) and possible extension (to future transitioners).

Method

Participants

Recruitment. Gender-nonconforming and transgender children were recruited through a wide range of community groups. Controls were recruited through a university database of families interested in participating in research. All children completed measures individually with an experimenter, beyond earshot of their parents.

Table 1. Demographic Characteristics for All Participants

Variable	Gender nonconforming		Transgender		Control	
	Future transitioners (<i>n</i> = 36)	Nontransitioners (<i>n</i> = 49)	Matched to future transitioners (<i>n</i> = 35)	Matched to nontransitioners (<i>n</i> = 49)	Matched to future transitioners (<i>n</i> = 36)	Matched to nontransitioners (<i>n</i> = 49)
Assigned sex (% male)	83	61	86	61	17	39
Age (mean; in months)	83.4 (27.6)	95.1 (30.2)	84.4 (27.1)	94.2 (31.0)	84.6 (27.4)	95.5 (30.0)
Race (% White)	75	65	49	63	67	73
Time between testing and transition check-in (mean; in months)	28.8 (8.8)	24.2 (10.0)				
Parent political orientation (mean; on a scale from 1 to 7)	6.1 (1.0)	6.4 (0.8)	6.7 (0.5)	6.3 (0.9)	5.8 (1.3)	5.6 (1.3)
Parent income (mean; on a scale from 1 to 5)	3.7 (1.1)	3.7 (1.2)	4.2 (0.8)	4.2 (0.9)	4.4 (1.0)	4.2 (1.1)

Note: Standard deviations are given in parentheses. We followed up with only gender-nonconforming families; thus, time since initial test is not reported for transgender and control participants. Three parents did not report their political orientation, and one parent did not report household income.

See Table 1 for demographics of each participant group, and see the Supplemental Material available online for more details on recruitment and testing sessions.⁴

Gender-nonconforming children (future transitioners and nontransitioners). Every gender-nonconforming child who participated in research between the start of the project in July 2013 and December 2016 was included in this research except one child who did not complete any of the measures reported in this article. Thus, our sample size was determined by the number of participants we could recruit in this 3.5-year period rather than by a target sample size. Because gender-nonconforming children are rare and hard to reach, and because they were not the primary participants recruited during this time by the research team (they signed up in the course of recruitment for a study of transgender children), estimating a sample size in advance was impossible. Children were defined as having socially transitioned if they changed pronouns to align with the gender opposite their assigned sex (e.g., an assigned male going by “she”; Fast & Olson, 2018; what is called a “complete transition” by Steensma et al., 2013, p. 585). By the time children change their pronouns, or at the same time, they typically change their first name (if their original first name was gendered), hairstyle, and clothing. To assess later transition status, we contacted parents for confirmation or we received an update via an in-person follow-up visit or parental online survey. If there had been multiple contacts after the initial data collection, the most recent contact before the article submission was used to determine whether the child had socially transitioned (all gender-nonconforming children who met the criteria for a social transition at one point continued to do so for all subsequent points). The average time from original testing to follow-up was 25 months (*SD* = 10 months).

Of the original sample, 36 had transitioned (i.e., changed pronouns to those opposite their assigned sex) and 49 had not.

Transgender children. A transgender comparison group (i.e., a group of children who had socially transitioned before completing the battery) was recruited from an ongoing longitudinal study of transgender youth. For each gender-nonconforming participant, a transgender child who had the same assigned sex and was within 4 months of age at time of testing was included in the transgender comparison group. Matching was completed using a master file that included the child’s assigned sex and age on day of first testing but lacked any responses from the child to ensure that responses could not inform participant selection. Matches were available for all children except one (no one in the database met the matching criteria for one child).

Control children. Gender-nonconforming children were also matched to control participants of the same age (within 4 months) but with the opposite assigned sex. This matching approach has been utilized in related past work with transgender children (e.g., Fast & Olson, 2018; Olson et al., 2015).

Measures and data preparation

Gender identity and preferences. The present analyses focused on a composite of five gender-development measures, which were selected because they are the general battery of measures given to all children in this line of work in our research group. The contributing measures were peer preference, toy preference, clothing preference, gender similarity, and gender identity.

Peer preference. Peer preferences were assessed on six trials in which children were presented with pictures of a boy and a girl and were asked whom they would prefer to be friends with (from Olson et al., 2015). The proportion of trials on which they selected girls was recorded.

Toy preference and clothing preference. Toy and clothing preferences were each assessed via four trials (from Fast & Olson, 2018). On each trial, children were shown five images of toys or clothing at a time. Pictures were pilot tested with a separate set of children to represent very feminine, slightly feminine, gender-neutral, slightly masculine, or very masculine items. Responses were coded on a 5-point scale, with higher scores indicating more feminine responses. Within each measure, responses from the four trials were averaged and then rescaled to range from 0 to 1 (P. Cohen, Cohen, Aiken, & West, 1999). Different toys and clothes were used for 5- to 7-year-olds than for 8- to 11-year-olds because children generally play with different toys and wear different clothes at these ages.

Gender similarity. Children indicated how similar they felt to boys and girls on five items using a visual 5-point scale (Martin, Andrews, England, Zosuls, & Ruble, 2017). Following Fast and Olson (2018), we computed a difference score by subtracting the average of the five boy items from the average of the five girl items. The scores were rescaled to range from 0 (*most similar to boys and most dissimilar to girls*) to 1 (*most similar to girls and most dissimilar to boys*).

Gender identity. Children were asked whether they (a) are currently and (b) will in the future be boys, girls, both, or neither; it changes over time; or they are not sure (Fast & Olson, 2018). Each “girl” response was assigned 1 point, each “boy” response was assigned –1 point, and all other answers were given a score of 0. The two items were added together and, again, rescaled to a scale of 0 to 1.

Composite score. Because all five measures were scaled between 0 and 1, we created a gender-identity-and-preference composite score by taking the average. This variable demonstrated acceptable reliability ($\alpha = .74$). For masculine children (i.e., assigned male controls and assigned female gender-nonconforming and transgender children), items were then reverse-scored so that higher numbers indicated more extreme cross-sex responding for gender-nonconforming and transgender children and more extreme same-sex responding for controls, as has been done in related work (e.g., Fast & Olson, 2018).

Demographics. We collected several demographic variables (see Table 1). We recorded participants’ age (months),

assigned sex (0 = female, 1 = male), race (0 = non-White, 1 = White), and time between the initial testing session and follow-up (in months). We further recorded information about their family, including participating parents’ political orientation (1 = *least liberal*, 7 = *most liberal*) and household income (1 = *lowest income*, 7 = *highest income*). Participating children tended to be White, and their parents tended to be high income and politically liberal.

Missing data

Missing data on items ranged from 0% to 15.7%, which we addressed via multiple imputation by chained equations (MICE; White, Royston, & Wood, 2011). Using the *mice* package (van Buuren & Groothuis-Oudshoorn, 2011) in the R programming environment (R Core Team, 2016), we used predictive mean matching (i.e., imputed values are draws from observed values; Vink, Frank, Pannekoek, & van Buuren, 2014) to generate 20 “complete” data sets—a rule of thumb for the degree of missingness in our data set (White et al., 2011). We then created the gender-identity-and-preference composite (see above). Statistical analyses were conducted on each imputed data set, and estimates were obtained by pooling results across these analyses. R code for all analyses is available on the Open Science Framework (OSF; <https://osf.io/m6zac/>).

Analytic strategy

Following the new statistics (Cumming, 2014), we employed Bayesian estimation for our statistical analyses (Kruschke & Liddell, 2018). Bayesian methods offer numerous advantages over frequentist methods; indeed, as Bayesian statistics do not rely on large sample sizes, they may be a better method for modeling data with small samples such as those used here (Depaoli & van de Schoot, 2017). In the Bayesian estimation framework, uncertainty about the value of each model parameter is encoded in a probability distribution of possible values—a *prior distribution*—before the data are observed. After the data have been obtained, the prior distribution is combined with the *likelihood* (the probability of the observed data given certain parameter values), yielding a *posterior distribution* that reflects the updated uncertainty about the value of each parameter. (For detailed coverage of Bayesian methods, see Gelman et al., 2014; Kruschke, 2015; and McElreath, 2016.) In practice, the posterior distribution is typically approximated (rather than obtained analytically) using simulation methods, such as Markov chain Monte Carlo (MCMC). We used medians and 95% highest-density

intervals (HDIs) to summarize the central tendency and uncertainty of the posterior distribution, respectively. Unlike frequentist confidence intervals (Hoekstra, Morey, Rouder, & Wagenmakers, 2014), HDIs have a natural interpretation; if 95% of the most credible values for a parameter are between .50 and .75 (i.e., the 95% HDI = [.50, .75]), we are 95% sure that the population value lies between .50 and .75 (Kruschke & Liddell, 2018). Critically, HDIs can also quantify evidence for null values; a parameter is zero for practical purposes if only values deemed to be functionally equivalent to zero (i.e., in the *region of practical equivalence*; ROPE) are contained within an HDI (Kruschke, 2015).

We assessed whether gender nonconformity predicted social-transition status by fitting a logistic regression model in which transition status (0 = no, 1 = yes) was regressed on gender-identity-and-preference scores. We estimated the model using the *brms* package (Bürkner, 2017) as a front end to the probabilistic programming language Stan (Carpenter et al., 2017). Details of our analyses (e.g., the priors we used, a sensitivity analysis comparing our results using more and less informative priors, our results using a model-comparison approach) are presented in the Supplemental Material. Next, we re-estimated our model after controlling for covariates (recommended by Simmons, Nelson, & Simonsohn, 2011). To facilitate comparisons of coefficients for binary and continuous variables, we scaled regression inputs by 2 standard deviations (Gelman, 2008). Finally, coefficients were transformed into odds ratios (*ORs*); values greater than 1 provide evidence of a positive association between the predictor and socially transitioning (and values less than 1 provide evidence of a negative association).

We used a different approach to determine whether future transitioners differed in their gender identity and preferences from transgender and control participants. As these scores were bounded (i.e., between 0 and 1), we applied a recommended transformation that prevents 0s or 1s (Smithson & Verkuilen, 2006). We then fitted a beta regression (Ferrari & Cribari-Neto, 2004) with a logit link function to estimate the gender-identity-and-preference scores of future transitioners and matched transgender and control participants. Bayesian multilevel modeling alleviates concerns of multiple comparisons (Gelman, Hill, & Yajima, 2012), such as the between-group comparisons examined here. Accordingly, we estimated a multilevel model that included a unique intercept for each group of participants (i.e., varying-intercept model). We then calculated posterior differences in the parameter estimates across groups (Kruschke, 2015). Finally, we re-estimated our initial model after including covariates to obtain covariate-adjusted mean differences. MCMC samples of the posteriors are available on the OSF (<https://osf.io/m6zac/>).⁵

Results

Figure 1 shows how individual participants responded to the gender-identity-and-preference measures (missing values were replaced with the average score across imputed data sets). Figure 1a shows responses for non-transitioners with their matched transgender and control groups, whereas Figure 1b shows responses for future nontransitioners with their matched transgender and control group. The Supplemental Material contains group means for the scores presented in Figure 1, descriptive statistics, and zero-order correlations among measures.

Analysis 1: do gender identity and preferences predict social transitions?

Pooled results from logistic regression models containing no covariates suggested that participants expressing greater gender nonconformity in the initial testing session were more likely to socially transition before follow-up, *OR* = 4.22, 95% HDI = [1.55, 12.20]. That is, assigned males who tended to have more extreme feminine preferences and gender identities were more likely to socially transition to live as girls after testing than assigned males who exhibited less extreme feminine identities and preferences. Our model predicted that a child with a gender-nonconformity score of .50 would have roughly a .30 probability (95% HDI = [.17–.42]) of socially transitioning. By contrast, a child with a gender-nonconformity score of .75 would have roughly a .48 probability, 95% HDI = [.37, .60], of transitioning.

We next introduced covariates to our model to examine whether they accounted for the association between gender nonconformity and socially transitioning. One possible explanation for the association between social-transition status and gender nonconformity is that future transitioners may have more politically liberal parents who could be more likely to support or encourage social transitions. However, we found that the coefficient for parent political orientation was not credibly different from 1.0, *OR* = 0.93, 95% HDI = [0.33, 2.67]. That is, because 1.0 was among the most plausible values for parent political orientation, we have little confidence that there is a meaningful association between parent political orientation and transition status in this sample. Another possible explanation is that future transitioners might have been further along a path toward transitioning than nontransitioners when initial testing occurred, in which case future transitioners might be older or might have had a longer period between the initial testing session and follow-up. Although the coefficient for age was not credibly different from 1.0, *OR* = 0.43, 95% HDI = [0.15, 1.24], months between the initial testing session and follow-up was associated with higher

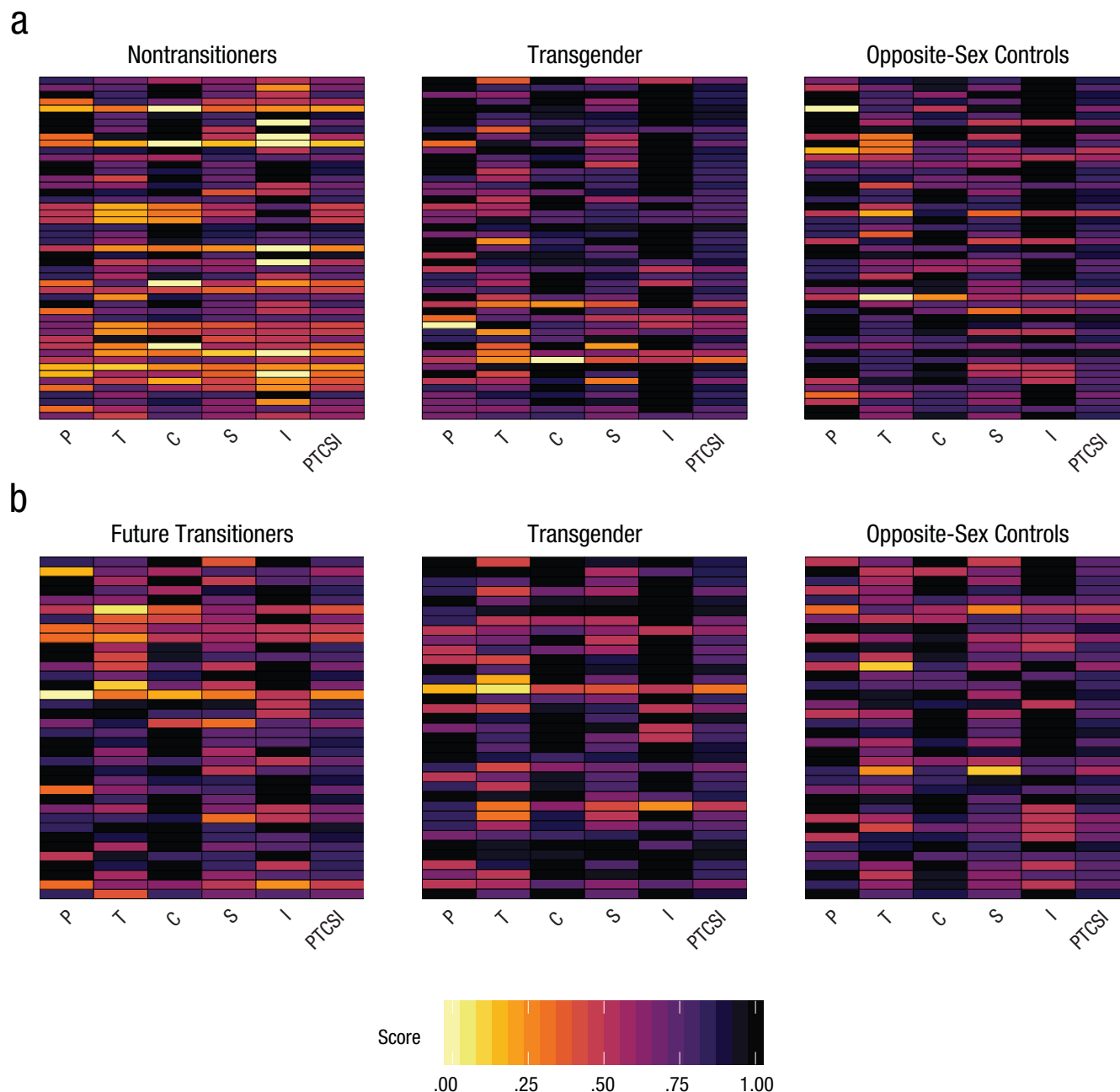


Fig. 1. Scores on the gender-identity-and-preference measures and the gender-composite score by participant. Results are shown separately for (a) nontransitioners and their matched transgender and control groups and (b) future transitioners and their matched transgender and control groups. The five measures—peer preferences (P), toy preferences (T), clothing preferences (C), gender similarity (S), and gender identity (I)—and the composite (average of all five measures) are each represented as a column within each cluster of data. Each row within a cluster represents one child's responses on all measures (when data were missing, we used the mean score across 20 imputed data sets). The darker the color (i.e., the higher the score), the more the gender-nonconforming or transgender child's answer was stereotypically associated with the opposite assigned sex. For control participants, the darker the color, the more children's answers were stereotypically associated with their assigned sex.

levels of social transitioning, $OR = 3.51$, 95% HDI = [1.14, 11.01].⁶ Critically, more extreme gender nonconformity continued to predict whether a child socially transitioned even after these and other covariates were added to the

model, $OR = 5.20$, 95% HDI = [1.60, 17.11], suggesting that differences on the covariates we measured did not explain the association between gender nonconformity and social transitioning.

Analysis 2: do future transitioners, transgender children, and controls differ in their gender identity and preferences?

Pooled results from our multilevel beta regression models yielded median gender-identity-and-preferences estimates of .74 for future transitioners (95% HDI = [.69, .78]), .77 for transgender children (95% HDI = [.73, .81]), and .76 for controls (95% HDI = [.72, .81]). As shown in Figure 2a, the median differences between groups (represented as the effect size for proportions, or Cohen's *b*) were $\leq |.07|$. To examine whether group differences were functionally equivalent, we identified a ROPE value of $\pm .20$ (a small effect; J. Cohen, 1988). We estimated both the 95% HDI of the effect size for the difference between groups and the proportion of the posterior inside the ROPE values.⁷ The 95% HDI for the difference between (a) control and transgender participants and (b) control and future transitioners fell entirely inside (or bordered the upper bound) of the ROPE values (see Fig. 2a). Thus, we are 95% sure that the differences between these groups are smaller than small. Similarly, at least 97% of the posterior density for these differences fell inside the ROPE values. For the difference between transgender participants and future transitioners, the 95% HDI was not completely contained within the ROPE values (see Fig. 2a). Nonetheless, over 95% of the posterior density for the difference between future transitioners and transgender participants fell inside the ROPE values, which provides some evidence that most of the plausible values for the difference are smaller than a small effect.

The estimated covariates-adjusted median was .75 for future transitioners (95% HDI = [.70, .79]), .80 for transgender participants (95% HDI = [.75, .84]), and .75 for controls (95% HDI = [.70, .80]). The median differences between groups were less than or equal to $|.12|$ (see Fig. 2b). The 95% HDI (and over 97% of the posterior) for the difference between control and future transitioners fell inside the ROPE values, whereas the 95% HDIs for the difference between transgender participants and both control participants and future transitioners did not fall completely inside the ROPE (see Fig. 2b). So how confident are we that the differences between groups were functionally equivalent to zero? For the difference between control and transgender participants, we found that 83% of the posterior distribution was in the ROPE. For the difference between transgender participants and future transitioners, 85% of the posterior distribution fell within the ROPE cutoffs. Thus, we are at least 83% sure that the covariate-adjusted differences between future transitioners and

both control and transgender participants are smaller than a small effect. (The Supplemental Material displays the proportion of the posterior inside the ROPE when using smaller and larger effect sizes to define ROPE cutoffs.)

One could wonder whether our analytic approach made the null hypothesis easier to support. The Supplemental Material presents evidence that nontransitioners had lower scores than their matched control and transgender peers. Thus, our analytic approach itself did not make all differences null; rather, future transitioners look quite similar to their comparison groups, whereas nontransitioners look substantially different.

Multiverse analyses

A multiverse analysis repeats a statistical analysis across all plausible combinations of data-processing decisions (e.g., how data are selected, cleaned, or coded) to quantify the extent to which these decisions influence a result (Steege, Tuerlinckx, Gelman, & Vanpaemel, 2016). We conducted multiverse analyses to explore how our results differed across three data-processing decisions that were not explored in the analyses above. First, the analyses above used a gender-identity-and-preference composite created by averaging five gender development measures: peer preferences, clothing preferences, toy preferences, gender similarity, and gender identity. However, there are 31 variables that we could have constructed from assessing the impact of each measure by itself or from different combinations of these five measures. Second, while we chose to address missing data via multiple imputation, we could have instead ignored missingness and used only the data provided by participants (e.g., if a child completed five of the six peer-preference items, instead of imputing a value for the sixth item, we could have just averaged the five items that child completed). Third, while we elected to retain all respondents in our analyses, an alternative strategy would have been to exclude observations deemed to be influential on the posterior (see Gabry, Simpson, Vehtari, Betancourt, & Gelman, 2017). Combining these data-analytic decisions should have resulted in 124 data sets to analyze: 31 (all possible combinations of the five gender-developmental measures) $\times$ 2 (missing-data approach: ignore missingness vs. multiple imputation) $\times$ 2 (influential observations: ignore vs. exclude influential cases). However, we did not identify any cases that were highly influential (see the Supplemental Material for details), leaving us 62 data sets (i.e., 31×2) for each analysis. For each data set, we fitted statistical models from Analysis 1 and Analysis 2 that excluded covariates (see above).

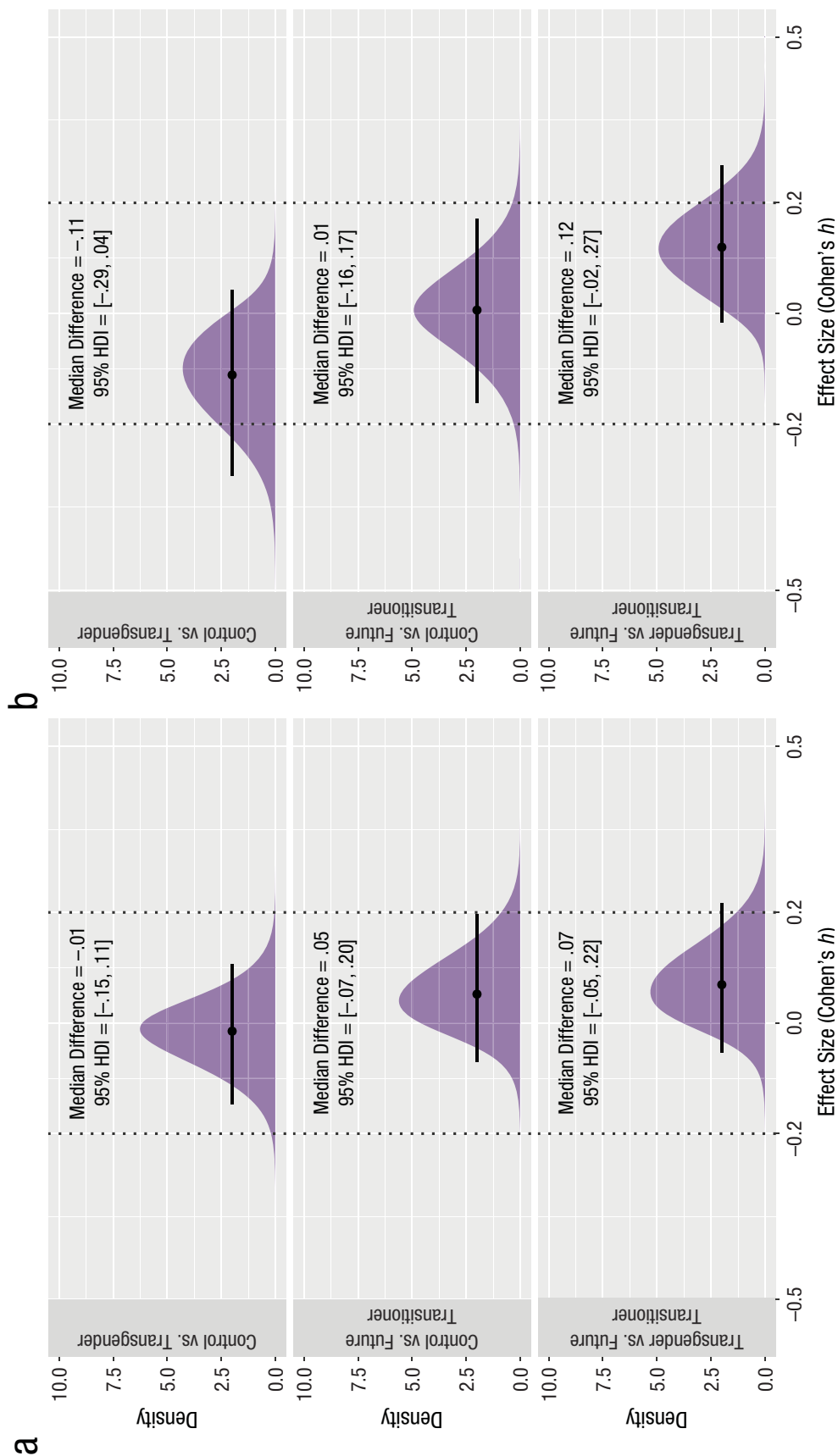


Fig. 2. Posterior distributions for the differences (represented as the effect size for proportions; Cohen's h) in gender-identity-and-preference scores between controls, transgender children, and future transioners (a) without covariates and (b) after controlling for covariates. Dots show medians, and horizontal bars show 95% highest-density intervals (HDIs). The vertical dotted lines correspond to a small negative effect size (Cohen's $h = -.20$) and a small positive effect size (Cohen's $h = .20$). The area between these lines is the region of practical equivalence (ROPE), and evidence that the groups are not different comes from either 95% HDIs that fall completely inside the ROPE or a large portion of the posterior distribution that falls inside the ROPE.

Multiverse Analysis 1: do gender identity and preferences predict social transitions? Figure 3 presents the estimates (as odds ratios) and 95% HDIs from our multiverse analysis testing the association between social-transition status and gender nonconformity. Figure 3 provides four takeaways. First, most of the possible data sets we could have analyzed would have supported the conclusion that greater gender nonconformity predicts later social-transition status. Indeed, 50 of the 62 analyses (81%) yielded 95% HDIs that entirely exceeded 1.0. Second, even when we were less confident that there was a positive association between social-transition status and gender nonconformity (i.e., when the 95% HDI included 1.0), it was always true that the majority of all 95% HDIs was greater than 1.0 (i.e., the most plausible values of the slope were positive). Third, more 95% HDIs exceeded 1.0 as additional gender-development measures were included in the composite variable. In fact, only two of five gender-development measures (clothing preferences and gender identity) predicted social-transition status in isolation, whereas in all cases but one—31 of 32—composite variables consisting of three or more gender-development measures always predicted social-transition status. Lastly, our results were extremely consistent across both missing-data approaches.

Multiverse Analysis 2: do future transitioners, transgender children, and controls differ in their gender identity and preferences? Figure 4 presents the median differences between groups along with 95% HDIs of the differences (represented as the effect sizes) from our multiverse analysis comparing future transitioners with matched control and transgender participants. Across the 186 comparisons (62 data sets $\times$ 3 between-group comparisons per data set), 130 (i.e., 70%) of the comparisons fell completely inside the ROPE cutoffs. However, the percentage of comparisons in the ROPE varied as a function of whether the comparison was between future transitioners and control participants (48/62 = 77%), control and transgender participants (52/62 = 84%), or future transitioners and transgender participants (30/62 = 48%). While there was variability in terms of which comparisons strictly fell inside the ROPE cutoffs, the more striking conclusion from Figure 4 is that small or smaller-than-small differences between groups were almost always the most credible, especially for composite variables containing four or more gender-development measures. Indeed, many of the between-group comparisons narrowly exceeded the ROPE boundaries, which was apparent in our examination of the percentage of the posterior distribution of the ROPE for each of the 186

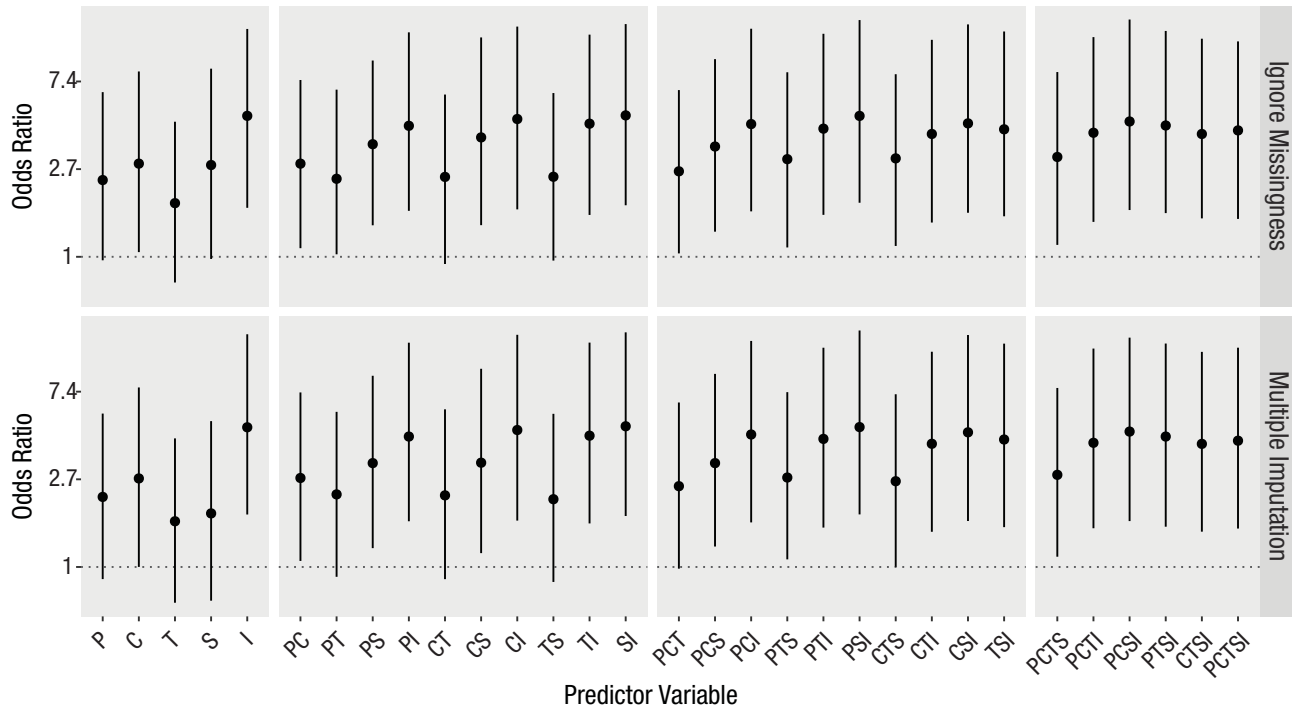


Fig. 3. Results of Multiverse Analysis 1: social-transition status across all gender-development measures and combinations of measures, separately for each missing-data approach. Each estimate (dot) is the odds ratio from a simple logistic regression model predicting transition status from different combinations of gender-development measures in data sets in which missingness was either ignored (upper row) or addressed via multiple imputation (bottom row). Bars are 95% highest-density intervals. P = peer preferences, C = clothing preferences, S = gender similarity, I = gender identity.

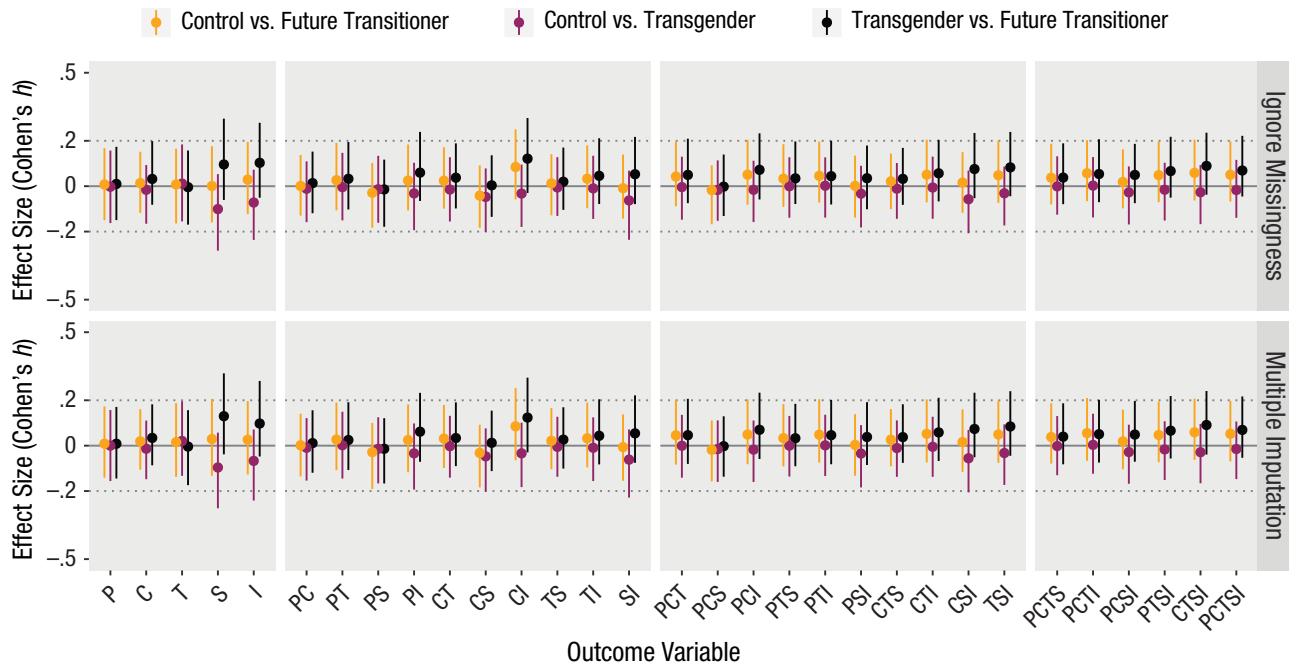


Fig. 4. Results of Multiverse Analysis 2, in which all gender-development measures were used as outcomes in multilevel beta regression models with unique intercepts for each group. Results are shown separately for each missing-data approach. Between-group differences were created, and each estimate (dot) is the median between-group difference; error bars are 95% highest-density intervals (HDIs). Estimates and HDIs are represented as effect-size measures (Cohen's h). Dashed lines correspond to small negative (Cohen's $h = -0.2$) and small positive (Cohen's $h = 0.2$) effects, respectively. The region of practical equivalence is the area between these dashed lines. P = peer preferences, T = toy preferences, C = clothing preferences, S = gender similarity, I = gender identity.

comparisons shown in Figure 4. We found that (with few exceptions) most of the posterior distribution (often near 100%) was inside the ROPE for all between-group comparisons. Indeed, 162 of the 186 comparisons (87%) had more than 95% of the posterior distribution inside the ROPE (see Fig. S7 in the Supplemental Material for these results). Finally, we found that the missing-data approach had little impact on our results (see Fig. 4).

In stark contrast to the results presented in Figure 4, a multiverse analysis comparing nontransitioners and covariate-matched control and transgender participants showed consistent evidence for differences between groups, demonstrating again that the major conclusions were not tied to a particular analytic decision or two (see the Supplemental Material).

Discussion

The degree of gender identification and preferences expressed by gender-nonconforming children predicted which children later socially transitioned. For example, assigned males that had stronger feminine gender identities and preferences were more likely to be living as girls 2 years later than assigned males who exhibited less feminine identities and preferences. This pattern

was observed even though there are no agreed-on standards or measures to determine whether to support a given child through a social transition. Past work has linked extremity of gender nonconformity in the absence of early social transitions to transgender identification later in life (e.g., Singh, 2012; Steensma et al., 2013; Wallien & Cohen-Kettenis, 2008), so these findings could suggest that the children transitioning at early ages may also be more likely to identify as transgender later in life. Critically, these results were robust to a large number of analytic decisions (e.g., inclusion of covariates or using different prior distributions for our Bayesian analyses) and data-processing decisions (e.g., how we combined the five gender-development measures or handled missing data).

Children who went on to socially transition showed gender identification and preferences comparable in magnitude with those of children who had already transitioned (i.e., transgender participants) and children whose assigned sex and gender identity had aligned for their entire life (i.e., control participants). Stated differently, an assigned male who will later transition to live as a girl is roughly as feminine before transition as a transgender girl is after a transition, and both are comparable in degree of feminine identity and

preferences to a nontransgender girl. Again, this effect was remarkably robust across different analytic and data-processing decisions. Although replication of this effect is needed, preferably from a longitudinal study comparing a single group of children before and after transition, this finding could reduce worries that the transition itself is leading children to identify as, or behave in ways more stereotypically associated with, the opposite assigned sex.

One previous study examined the relation between early social transitions and later transgender identity (Steensma et al., 2013). All four children in that study who had socially transitioned in childhood identified as transgender in adolescence, while only 35% of the 123 children who did not completely socially transition (i.e., children who did not change pronouns) in childhood identified as transgender later. Green (2017) identified two explanations for this finding. First, children who socially transition could differ from those who do not even before transitioning. Second, transitioning could change children's sense of identity, making them identify more with the opposite-sex group. Consistent with the first explanation, our results showed that the children who transitioned showed more extreme cross-sex identification and preferences before transitioning. In contrast, we found evidence that children tested after transitioning (i.e., transgender participants) did not differ meaningfully from those tested before transitioning (i.e., future transitioners) in terms of identification and preferences.

Limitations

A primary limitation of this work is the small sample size. We tried to address this concern by utilizing a Bayesian approach, which may be better suited to model data with small samples (Depaoli & van de Schoot, 2017). Further, we tested a sample skewed by race, class, parental education, and political orientation. This may or may not reflect the set of children who are socially transitioning now or in the future. Thus, replication with a larger and more diverse sample would increase confidence in our conclusions and suggest that these results are not sample specific. Another limitation is that follow-up occurred only 2 years after testing. Some of the 49 children who had not transitioned when the present study ended could transition in the future, and some of the 36 children who did transition could transition again to the gender aligning with their assigned sex. Therefore, reanalysis of data at later points will be necessary. Finally, as this research was exploratory (in that we did not preregister our analytic plan before collecting the data), there could be concern

that we used "researcher degrees of freedom" to obtain a desired pattern of results (Simmons et al., 2011, p. 1359). However, we examined the sensitivity of our results to a variety of data-processing and analytic decisions (e.g., by conducting multiverse analyses), which demonstrated that the results from this small sample were robust to many researcher degrees of freedom.

We found that 41% of our sample of gender-nonconforming children had transitioned roughly 2 years after initial testing sessions. We believe this percentage is likely an overestimate of how many gender-nonconforming children in the general population will socially transition. We recruited through LISTSERVs and events serving transgender children and gender-nonconforming children, and the word *transyouth* was widely utilized in recruitment materials. The parents responding to our recruitment may have already been questioning whether their child could be transgender, while parents of children showing less extreme gender nonconformity might be less likely to have made contact. As evidence, Figure 1 shows that nearly all participants showed cross-sex identification and preferences (i.e., these were not simply "less masculine" boys). We therefore caution against using this work as a broad reference point for rates of social transition.

Finally, as in all studies reporting means of groups, care should be taken in extending group-level results to individuals. Some children who showed high levels of preference for, and identification with, the sex opposite their assigned sex did not transition; some children who did transition did not display the same high levels.

Conclusion

Despite limitations and a need for future replications, this study provides preliminary evidence that extremity of identification with the gender opposite one's assigned sex predicts childhood social transitions. Moreover, differences in gender extremity likely exist prior to—and not because of—social transitions.

Action Editor

Brent W. Roberts served as action editor for this article.

Author Contributions

This project was originally conceived by K. R. Olson, and analyses were conducted by J. R. Rae. K. R. Olson and J. R. Rae wrote the manuscript together. All other authors assisted with measure development, data collection, and feedback on the study design; they also edited the final manuscript. All authors approved the final manuscript for submission.

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Declaration of Conflicting Interests

The author(s) declared that there were no conflicts of interest with respect to the authorship or the publication of this article.

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Supplemental Material

Additional supporting information can be found at <http://journals.sagepub.com/doi/10.1177/0956797619830649>

Open Practices

We cannot share the raw data from this study because of issues of identifiability in the rare sample used. R code for all analyses and Markov chain Monte Carlo samples of the posterior distributions are available on the Open Science Framework at <https://osf.io/m6zac/>. Materials have not been made publicly available, and the design and analysis plans were not preregistered.

Notes

1. Our use of the term *opposite* implies that “boy” and “girl” or “male” and “female” contrast one another. We use this term for ease of comprehension and linguistic simplicity. We agree with the many scholars who point out that sex and gender are non-binary and are likely better conceptualized continuously (e.g., Bem, 1974; Ehrensaft, 2010).
2. Many of these studies used *gender dysphoria* as an outcome. Gender dysphoria is a medical term for experiencing distress related to one’s assigned sex and a desire to be a member of the other gender group.
3. We use the term *assigned sex* to refer to the categorization made at birth on the basis of external genitalia or chromosomes, in line with the recommendations of the World Professional Association for Transgender Health (Bouman et al., 2017), whereas we use *gender* or *gender identity* to refer to a person’s self-categorization. We use the term *gender nonconformity* rather than *sex nonconformity* because colloquially and in past research this term is used to refer to behaviors and identities not typically associated with one’s assigned sex.
4. Data from 26 transgender children included in the present work were also included in past published work (19 from Fast & Olson, 2018; 7 from Olson et al., 2015). None of the current controls or gender-nonconforming children were reported in past work.

5. We cannot share the raw data because of issues of identifiability in this rare sample. Figure 1 shows the data at the individual level in a way that has been approved by our institutional review board. As recommended by Kruschke (2015), MCMC samples of the posteriors are available, which allows readers to (a) explore posterior comparisons not reported in this manuscript and (b) use our results as a prior for future analyses that use a similar design and model.
6. Assigned males were more likely to transition than assigned females, $OR = 4.26$, 95% HDI = [1.34, 14.13]. All other covariates had 95% HDIs that contained zero. See the Supplemental Material for full results.
7. Unlike HDIs, ROPE values were constrained to be symmetrical around zero. Thus, the proportion of the posterior in the ROPE may be different than the HDI, especially for nonsymmetrical posteriors.

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Effect of gender affirming hormones on athletic performance in transwomen and transmen: implications for sporting organisations and legislators

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ABSTRACT:

Objective To examine the effect of gender affirming hormones on athletic performance among transwomen and transmen.

Methods We reviewed fitness test results and medical records of 29 transmen and 46 transwomen who started gender affirming hormones while in the United States Air Force. We compared pre- and post-hormone fitness test results of the transwomen and transmen with the average performance of all women and men under the age of 30 in the Air Force between 2004 and 2014. We also measured the rate of hormone associated changes in body composition and athletic performance.

Results Participants were 26.2 years old (SD 5.5). Prior to gender affirming hormones, transwomen performed 31% more push-ups and 15% more sit-ups in 1 min and ran 1.5 miles 21% faster than their female counterparts. After 2 years of taking feminising hormones, the push-up and sit-up differences disappeared but transwomen were still 12% faster. Prior to gender affirming hormones, transmen performed 43% fewer push-ups and ran 1.5 miles 15% slower than their male counterparts. After 1 year of taking masculinising hormones, there was no longer a difference in push-ups or run times, and the number of sit-ups performed in 1 min by transmen exceeded the average performance of their male counterparts.

Summary The 15–31% athletic advantage that transwomen displayed over their female counterparts prior to starting gender affirming hormones declined with feminising therapy. However, transwomen still had a 9% faster mean run speed after the 1 year period of testosterone suppression that is recommended by World Athletics for inclusion in women's events.

BACKGROUND

Most competitive sports segregate male and female athletes due to biologic differences between the sexes. Because exposure to testosterone in males leads to physiologic advantages in strength and endurance, female sports need to be a protected category to ensure fairness in competition.¹ Questions arise then as to which category a transgender athlete competes in and how society balances benefits to the athlete of sports participation in their experienced gender with perceptions of fairness to other athletes.^{2–5} Supraphysiologic doses of androgens have a positive effect on athletic performance.^{6–7} However, gender affirming hormones have an unknown effect on athletic performance among transgender individuals during gender transition, making it difficult to develop guidelines for

transgender inclusion in sports. Several guidelines for inclusion of transgender athletes in elite international or professional sports exist but they are based on limited research.^{8–9} The World Athletics (IAAF) and the International Olympic Committee (IOC) created guidelines requiring female athletes to demonstrate suppression of testosterone levels to less than 5–10 nmol/L for at least 12 months prior to competing in women's events. However, athletes have challenged the section of these guidelines applying to women with disorders of sexual development and other causes of hyperandrogenism, citing a lack of supporting evidence, which calls these guidelines into question.^{10–11}

Gender affirming administration of testosterone in transmen decreases adiposity, and increases muscle mass, thigh muscle volume, haemoglobin, grip strength and thigh strength.^{9–12–14} Gender affirming blockage of testosterone and administration of oestrogen in transwomen (oestrogen) has the opposite effect, but transwomen retain an advantage in muscle mass, volume, and strength over female controls after 1 year on oestrogen.^{9–14–17} Most changes in body composition occur within the first year on testosterone or oestrogen, with slower changes after that time.^{9–16–18–20}

How do these body composition changes affect athletic performance? A retrospective review of self-reported run times among eight transwomen runners found an overall decline in times collected months to years before and after starting oestrogen but not in the runners' performance relative to runners of the same age and gender. No other studies have examined the effect of testosterone or oestrogen on athletic performance.²¹

We conducted this study to examine the effect of gender affirming hormones on body composition and athletic performance among transgender individuals to help improve future guidelines for transgender inclusion in sporting competition.

METHODS

Study population

This was a retrospective review of medical records and fitness tests results from 222 self-identified military personnel who filed a request to begin gender transition or continue testosterone or oestrogen while serving in the United States Air Force (Air Force).

Patient involvement

The idea for this study arose from our discussions with servicemembers seen in the Air Force



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Transgender Clinic about the effect of testosterone or oestrogen on body composition and athletic performance on the Air Force physical fitness assessment. We did not know how to advise them based on the medical literature. We conducted this study to address this concern.

Demographic variables

We recorded the servicemember's age, service branch, military rank, gender assigned at birth, date testosterone or oestrogen started, type of testosterone or oestrogen used and days between starting testosterone or oestrogen and the first serum hormone level in the adult range recorded in the military electronic medical record. For transwomen, we also recorded the days between starting oestrogen and the first laboratory test indicating suppression of endogenous testosterone. We had incomplete records of testosterone or oestrogen obtained outside the military healthcare system.

Outcome measures

The Air Force requires servicemembers to participate in a physical fitness assessment every 12 months, including measurement of height, weight, waist circumference, number of push-ups and sit-ups performed in 1 min each, and time required to run 1.5 miles. The Air Force uses these tests to assess suitability for promotion, inclusion in specialised programmes and retention in the military service. The Air Force requires servicemembers to participate in all events unless a medical provider grants them a waiver for participation in a specific event secondary to a medical condition. Servicemembers with a waiver for a portion of the assessment must retake the assessment every 6 months. Enlisted servicemembers engage in regular group exercise. However, the type and intensity of training vary by occupation. The Air Force requires servicemembers who fail to meet physical fitness standards to attend additional physical training sessions outside of normal work hours until they can meet the fitness requirements or leave military service.

We assessed pretreatment fitness using the most recent score from each event on the physical fitness assessment prior to starting testosterone or oestrogen. We assessed post-treatment fitness using all fitness test scores occurring in the first 30 months after starting testosterone or oestrogen. We also recorded the time elapsed between starting testosterone or oestrogen and the occurrence of each event. The primary outcome for this study was change in fitness assessment score between the pre-hormone assessment and post-hormone assessment.

We used the results of the Air Force fitness tests performed by men (>2.3 million) and women (>567 000) under the age of 30 between 2004 and 2014 as a proxy for average performance among men (CM) and women (CW) in the Air Force.²² We used the results of all fitness tests performed by men (>3.5 million) and women (>777 000) in the Air Force between 2004 and 2014 as a proxy for height and weight among men (CM) and women (CW) in the Air Force.²²

Statistical analysis

We used generalised linear mixed models with a first order autoregressive repeated covariance type in SPSS V.24 to assess the association of hormonal therapy with changes in physical fitness assessment scores. We selected this analysis method to account for correlation between repeated measures, variable number of follow-up assessments, variable follow-up times and missing data points for each participant. From this analysis we obtained an estimated mean of push-ups performed in 1 min,

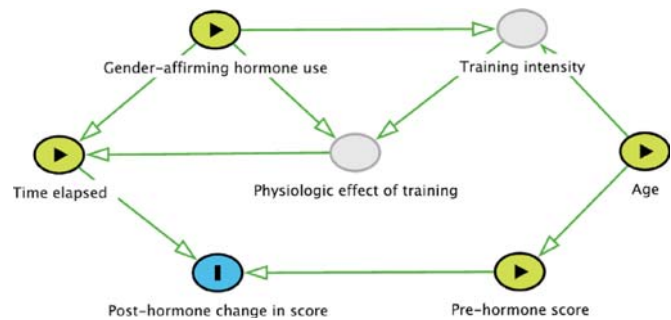


Figure 1 Directed acyclic graph of our multivariable model. Pre-hormone score: the results of the most recent physical fitness assessment prior to starting gender affirming therapy. Age: age in years when starting gender affirming hormone therapy. Training intensity: type and amount of exercise performed by the servicemember. Physiologic effect of training: effect of training performed on the servicemember's strength and endurance. Time elapsed: time interval (months) between starting gender affirming hormone therapy and the assessment of physical performance. Post-hormone change in score: change in push-ups, sit-ups and run times between the pre-hormone assessment and the current assessment (primary study outcome).

sit-ups performed in 1 min and 1.5 mile run times for transmen and transwomen before testosterone or oestrogen, between 0 and 1 years on testosterone or oestrogen, 1–2 years on testosterone or oestrogen and over 2 years on testosterone or oestrogen. We then compared these results with the average performance of CM and CW.

We conducted a multivariable assessment of the association between months on gender affirming hormones and changes from pre-testosterone or oestrogen fitness after adjusting for pre-testosterone or oestrogen performance and age at initiation of testosterone or oestrogen. Figure 1 is a directed acyclic graph representing the conceptual model underlying our multivariable model. Our null hypothesis for this model is that testosterone and oestrogen are not associated with a subsequent change in athletic performance for any length of testosterone or oestrogen use or pre-testosterone or oestrogen athletic performance. We performed analyses separately for transmen and transwomen.

RESULTS

Research participant characteristics

Two hundred and twenty-two servicemembers self-identified as transgender in 2016–2018 and filed a request to begin or continue gender affirming care while serving in the Air Force. We excluded 147 of these participants for the following reasons: 28 had not started testosterone or oestrogen, 3 were on testosterone or oestrogen but did not have a start date available, 99 did not have pre-testosterone or oestrogen physical assessment scores available and 16 did not have any post-testosterone or oestrogen physical assessment scores available. We included the remaining 29 transmen and 46 transwomen in our study. (table 1) The mean age of our sample was 26.2 years (SD 5.5) with a median age of 25 years (range 19–46). The majority (78.3%) of our participants were <age 30 when they began testosterone or oestrogen. Among CM, mean height was 178.2 cm (6.8) and weight was 83.5 kg (12.0). Among CW, mean height was 164.4 cm (6.4) and weight was 65.7 kg (9.8).

The baseline physical fitness assessment occurred an average of 144.4 ± 101.4 days before starting testosterone or oestrogen. We followed participants for an average of 394.0 ± 288.2 days after they started testosterone or oestrogen. Participants had an

Pretreatment demographics and body composition	Transwomen (n=46)	Transmen (n=29)
	Mean (SD)	Mean (SD)
Age at initiation of gender affirming hormones (years)	26.6 (4.8)	25.6 (6.6)
Height (cm)	176.3 (7.1)	165.6 (5.3)
Weight (kg)	76.7 (12.6)	69.5 (10.0)
Body mass index (kg/m ²)	24.4 (3.7)	25.3 (3.3)
Waist circumference (cm)	80.8 (8.4)	76.7 (8.9)
Rank (%)		
Enlisted	100	93.10
Officer		6.90
Duty status (%)		
Active duty	95.70	86.20
Reserves	2.20	6.90
Air National Guard	2.20	6.90

average of 2.2 ± 0.9 assessments after starting testosterone or oestrogen (median 2, range 1–4). Among transmen, two participants were medically excused from the push-up assessment during the follow-up period, and 11 were excused from the run. Among transwomen, two were excused from the push-up assessment, one from the sit-up assessment, and four from the run. Details of the testosterone or oestrogen prescribed and time to first therapeutic hormone levels are listed in [table 2](#).

Effect of gender affirming hormones on body composition and athletic performance

[Tables 3–5](#) and [figure 2](#) provide a summary of changes in patient outcomes while on testosterone or oestrogen. In multivariable analyses, including baseline performance, age at initiation of testosterone or oestrogen, and months on testosterone or oestrogen, we rejected the null hypothesis. In our analyses, a higher baseline score was associated with a greater decline (or smaller increase) in score at follow-up for all outcomes except for 1.5 mile run time among transwomen, where baseline run time had no effect on the changes observed at follow-up (data not shown). Age at initiation of testosterone or oestrogen had no significant effect on outcomes (data not shown). For transwomen, time on oestrogen was associated with an increase in weight ([table 3](#)) and a decline in athletic performance ([table 4](#) and [figure 2](#)). For transmen, time on testosterone had no effect on

	Transwomen	Transmen
Weight (kg)	Mean (95% CI)	Mean (95% CI)
Time on gender affirming hormones		
Pretreatment	76.7 (73.3 to 80.2)	69.5 (66.0 to 72.9)
0–1 years	75.6 (72.1 to 79.1)	72.1 (68.6 to 75.5)
1–2 years	77.1 (73.4 to 80.9)	71.1 (67.4 to 74.8)
2–2.5 years	76.7 (70.8 to 82.6)	70.0 (65.8 to 74.2)
	β (95% CI)	β (95% CI)
Change in weight per month on hormones*	0.15 (0.04 to 0.25)	–0.07 (–0.21 to 0.06)
Waist circumference (cm)		
	Mean (95% CI)	Mean (95% CI)
Time on gender affirming hormones		
Preretreatment	80.8 (78.7 to 82.8)	76.7 (74.2 to 79.2)
0–1 years	79.0 (77.0 to 81.0)	79.2 (76.5 to 81.8)
1–2 years	78.9 (76.2 to 81.5)	78.5 (75.2 to 81.8)
2–2.5 years	82.0 (76.5 to 87.5)	78.4 (74.4 to 82.3)
	β (95% CI)	β (95% CI)
Change in waist per month on hormones*	0.05 (–0.08 to 0.18)	–0.03 (–0.15 to 0.10)

All analyses adjusted for variation in the number of measurements per research participant.

*Adjusted for pretreatment measurements and age when started gender affirming hormones.

body composition ([table 3](#)) but was associated with an improvement in athletic performance ([table 5](#) and [figure 2](#)). Prior to treatment, transwomen were heavier than CW (mean difference 11.0 kg, 95% CI 7.6 to 14.4) and lighter than CM (–6.8 kg, –10.2 to –3.4). Transmen were lighter than CM (–14.0 kg, –17.5 to –10.5) and heavier than CW (3.8 kg, 0.3 to 7.3). Both transwomen and transmen maintained these differences over the first 2.5 years on testosterone or oestrogen (data not shown).

Athletic performance among transgender servicemembers

Prior to oestrogen, transwomen performed fewer push-ups in 1 min than CM and this gap increased with oestrogen. Transwomen performed more push-ups than CW prior to oestrogen but this difference disappeared after 2 years on oestrogen ([table 4](#) and [figure 2](#)). Prior to oestrogen there was no difference in sit-ups performed in 1 min among transwomen compared with CM but there was a difference with CW. After 2 years on oestrogen,

	Transwomen (n=46)	Transmen (n=29)
Gender affirming hormones prescribed	Oral oestradiol: 67.4% Transdermal oestradiol: 15.2% Oestradiol valerate IM: 13.0% Oestradiol cypionate IM: 2.2% Unknown: 2.2%	Testosterone cypionate: 89.7% Testosterone enanthate: 3.4% Transdermal testosterone: 3.4% Testosterone 2% gel: 3.4%
Time to first therapeutic level (39 transwomen, 26 transmen) (days) (median (range))	234.0 (27–1270)	98.5 (23–1116)
Testosterone blockade prescribed (transwomen only)	Spironolactone: 80.4% Spironolactone and finasteride: 13.0% GnRH agonist IM: 2.2% GnRH agonist and spironolactone: 2.2% Unknown: 2.2%	
Time to first documented suppression (n=35) (days) (median (range))	200 (27–979)	
GnRH, gonadotropin releasing hormone.		

Table 4 Effect of gender affirming hormones on athletic performance among transwomen

	Mean (95% CI)	Mean difference transwomen vs CW (95% CI)	Mean difference transwomen vs CM (95% CI)
Push-ups in 1 min			
Time on hormones			
Pretreatment	47.3 (44.6 to 50.0)	14.8 (12.1 to 17.4)	-6.2 (-8.9 to -3.6)
0-1 years	44.6 (41.8 to 47.4)	12.1 (9.3 to 14.8)	-8.9 (-11.7 to -6.1)
1-2 years	43.2 (39.3 to 47.1)	10.7 (6.8 to 14.5)	-10.3 (-14.2 to -6.5)
2-2.5 years	34.6 (26.1 to 43.1)	2.1 (-6.4 to 10.5)	-18.9 (-27.3 to -10.5)
	β (95% CI)		
Change in push-ups per month on hormones*	-0.38 (-0.63 to -0.13)		
Sit-ups in 1 min			
Time on hormones			
Pretreatment	53.5 (51.3 to 55.7)	7.9 (5.7 to 10.0)	1.1 (-1.7 to 3.2)
0-1 years	54.1 (51.9 to 56.3)	8.5 (6.3 to 10.7)	1.7 (-0.5 to 3.9)
1-2 years	51.8 (48.6 to 55.0)	6.2 (3.0 to 9.3)	-0.6 (-3.8 to 2.5)
2-2.5 years	44.8 (37.1 to 52.4)	-0.9 (-8.4 to 6.7)	-7.7 (-15.2 to -0.1)
	β (95% CI)		
Change in sit-ups per month on hormones*	-0.37 (-0.58 to -0.15)		
1.5 mile run time (s)			
Time on hormones			
Pretreatment	708 (681 to 734)	-147 (-173 to -121)	-12 (-38 to 14)
0-1 years	758 (731 to 786)	-97 (-124 to -70)	39 (12 to 65)
1-2 years	791 (753 to 829)	-64 (-101 to -26)	72 (34 to 109)
2-2.5 years	765 (685 to 846)	-90 (-169 to -10)	45 (-34 to 125)
	β (95% CI)		
Change in run time per month on hormones*	2.9 (0.5 to 5.3)		

All analyses adjusted for variation in the number of measurements per research participant.

CW, average performance on Air Force physical fitness tests by females <30 years old conducted between 2004 and 2014.²²

CM, average performance on Air Force physical fitness tests by males <30 years old conducted between 2004 and 2014.²²

*Adjusted for pretreatment measurements and age when started gender affirming hormones.

transwomen performed fewer sit-ups than CM, but the difference with CW had disappeared (table 4 and figure 2). Run times among transwomen were similar to times among CM and faster than times among CW prior to oestrogen. Run times worsened among transwomen after starting oestrogen and became slower than times in CM but remained faster than CW at all time points (table 4 and figure 2).

Transmen performed more push-ups in 1 min than CW prior to testosterone and this gap increased with testosterone. Transmen performed fewer push-ups than CM prior to testosterone but this gap closed after 1 year on testosterone (table 5, figure 2). Transmen consistently performed more sit-ups than CW before and after testosterone. Transmen and CM completed a similar number of sit-ups in 1 min prior to starting testosterone, and transmen performance exceeded that of CM after 1 year on testosterone. There was no difference in 1.5 mile run times between transmen and CW prior to testosterone, but transmen were faster after 1 year on testosterone. Transmen were slower than CM prior to testosterone but had closed the time gap after 1 year (table 5 and figure 2).

DISCUSSION

In this study, we assessed the effects of gender affirming hormones on transgender individuals over time by means of a standardised test in a non-laboratory setting. Athletic performance improved among transmen and declined among transwomen. Among transwomen, competitive advantages from the effects of prior testosterone exposure continued beyond the 12 month standard currently proposed for inclusion in women's elite competition.¹⁰

This finding suggests that governing bodies for sporting competition should require more than 1 year of testosterone suppression prior to competition when creating guidelines for inclusion of transwomen in women's elite athletics.

Study findings and prior research

Like previous studies, our study showed an association between testosterone and increased strength among transgender men.^{13 17} We confirmed the decrease in strength associated with oestrogen in transgender women that was found in some studies,¹⁴⁻¹⁶ but not others.¹⁷ Unlike several of these previous studies, our measures of muscular strength assessed repeated submaximal efforts (push-ups and sit-ups) over a 1 min period as opposed to a single maximal effort. Our results capture differences in both endurance and strength rather than just strength and probably have more relevance to sports that require sustained effort over time rather than single explosive efforts like power lifting. Our assessments of muscular strength are also confounded by differences in weight between our transgender participants and reference populations. For example, as a group, transwomen weigh more than CW. Thus transwomen will have a higher power output than CW when performing an equivalent number of push-ups. Therefore, our study may underestimate the advantage in strength that transwomen have over CW. Further studies are needed to determine if the changes we saw in our study also apply to measures of explosive strength. Participants' exercise intentions or training habits were unknown, making it difficult to determine the aetiology of the pretreatment differences in push-up performance between transgender servicemembers and all servicemembers

Table 5 Effect of gender affirming hormones on athletic performance among transmen

Push-ups in 1 min	Mean (95% CI)	Mean difference transmen vs CW (95% CI)	Mean difference transmen vs CM (95% CI)
Time on hormones			
Pretreatment	37.4 (33.2 to 41.5)	4.8 (0.7 to 9.0)	-16.1 (-20.3 to -12.0)
0-1 years	44.8 (40.5 to 49.0)	12.2 (8.1 to 16.4)	-8.7 (-12.9 to -4.6)
1-2 years	51.8 (46.2 to 57.5)	19.3 (13.8 to 24.8)	-1.7 (-7.2 to 3.9)
2-2.5 years	56.1 (49.9 to 62.4)	25.6 (19.4 to 31.8)	4.6 (-6.4 to 10.5)
	β (95% CI)		
Change in push-ups per month on hormones*	0.46 (0.22 to 0.70)		
Sit-ups in 1 min			
Time on hormones			
Pretreatment	50.4 (47.4 to 53.4)	4.8 (1.8 to 7.7)	-2.0 (-4.9 to 0.9)
0-1 years	52.8 (49.8 to 55.8)	7.2 (4.2 to 10.2)	0.4 (-2.6 to 3.4)
1-2 years	58.2 (54.0 to 62.3)	12.5 (8.5 to 16.6)	5.7 (1.7 to 9.8)
2-2.5 years	58.3 (53.8 to 62.8)	12.7 (8.2 to 17.1)	5.9 (1.4 to 10.3)
	β (95% CI)		
Change in sit-ups per month on hormones*	0.32 (0.16 to 0.49)		
1.5 mile run time (s)			
Time on hormones			
Pretreatment	850 (802 to 899)	-4 (-52 to 43)	131 (83 to 178)
0-1 years	826 (776 to 876)	-29 (-78 to 20)	106 (57 to 155)
1-2 years	751 (687 to 815)	-104 (-167 to -41)	31 (-32 to 94)
2-2.5 years	711 (640 to 783)	-144 (-214 to -74)	-9 (-79 to 61)
	β (95% CI)		
Change in run time per month on hormones*	-3.2 (-5.3 to -1.2)		

All analyses adjusted for variation in the number of measurements per research participant.

CW, average performance on Air Force physical fitness tests by females aged <30 years conducted between 2004 and 2014.²²

CM, average performance on Air Force physical fitness tests by males aged <30 years conducted between 2004 and 2014.²²

*Adjusted for pretreatment measurements and age when started gender affirming hormones.

under the age of 30 in the Air Force. It is possible that transmen performed exercises to increase upper body muscle mass in order to give them a more masculine appearance and decrease their gender dysphoria while also improving push-up performance relative to CW. Gender dysphoria could stimulate the opposite behaviour in transwomen, decreasing push-up performance and explaining why transwomen performed fewer push-ups than CM prior to starting oestrogen. Differences in exercise habits could also influence the relationship between athletic performance and testosterone or oestrogen examined in this study. However, without the information on strength training it is impossible to make any definitive determinations.

Transmen also performed more sit-ups in 1 min than CW prior to starting testosterone. This difference in sit-up performance may also reflect a behavioural response to gender dysphoria among transmen. There was no difference between transmen and CM in sit-up performance. Unlike the increased size of upper body musculature associated with push-ups, a flat and toned appearing abdomen is seen as a positive attribute for achieving an ideal masculine or feminine appearance, making it less likely that transwomen would avoid this exercise type at a greater rate than CM.

In addition, we demonstrated a worsening of run times associated with oestrogen among transwomen that was seen in a previous study using a smaller sample and self-reported data.²¹ Testosterone exposure is associated with an increase in muscle volume and blood haemoglobin content, producing most of the ergogenic effects.¹ The improvement in run times seen among transmen with exposure to testosterone and the decline among

transwomen undergoing testosterone blockade demonstrates this ergogenic effect of testosterone. However, exposure to testosterone during puberty results in sex differences in height, pelvic architecture and leg bones in the lower limbs that confer an athletic advantage to males after puberty.¹ These anatomical differences do not respond to changes in testosterone exposure among post-pubertal adults. These pretreatment anatomical differences may explain why transwomen retained an advantage in 1.5 mile run times over CW after beginning oestrogen as an adult, while push-up and sit-up performance, which are less influenced by differences in skeletal architecture, declined to the level of CW after 2 years on oestrogen. It is possible that these results could be different among transwomen who begin gender affirming hormone therapy shortly after the onset of puberty and never experienced the ergogenic benefits of testosterone exposure. Further research is required to determine if the effects of testosterone or oestrogen on athletic performance vary by level of pubertal development at the time of initiating testosterone or oestrogen and if guidelines for transgender inclusion in sports need to account for the athlete's pubertal stage when testosterone or oestrogen began.

Study limitations and future directions

The strengths of this study include a larger sample size than previous studies, a longer follow-up period and a focus on performance on a standardised fitness test rather than isolated muscle strength. This study has limitations as well. The lack of a longitudinal control group not on testosterone or oestrogen makes

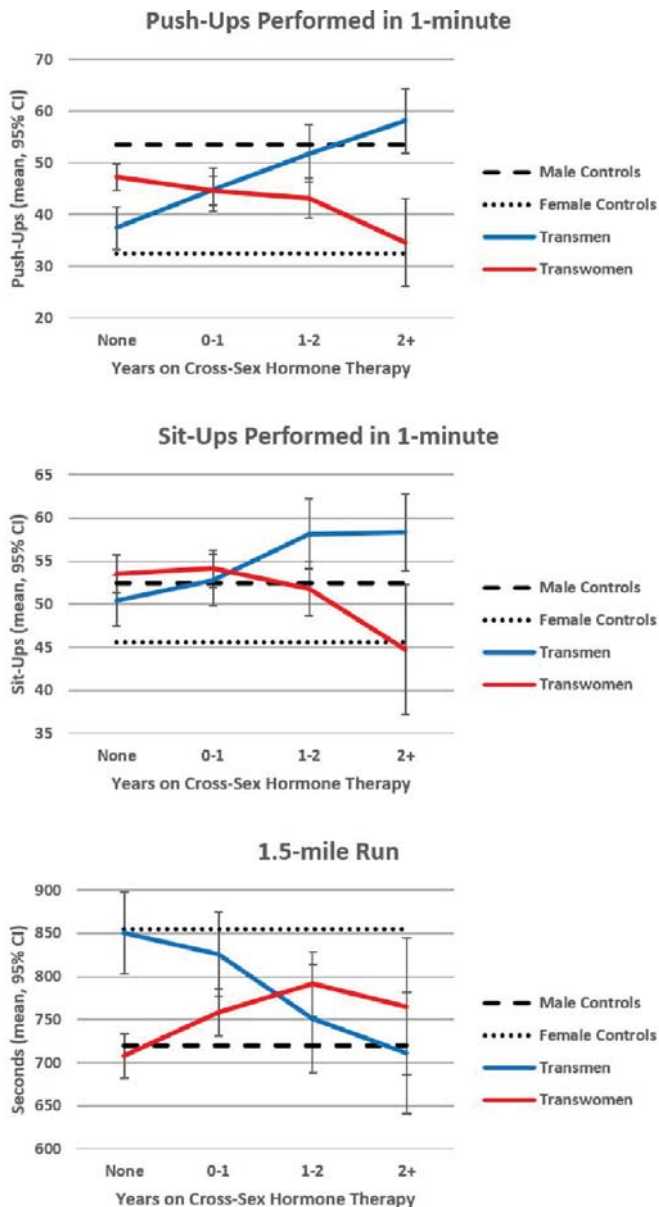


Figure 2 Gender affirming therapy and athletic performance. Male controls line represents the average performance on over 2.3 million Air Force physical fitness tests performed by males under the age of 30 between 2004 and 2014.²² Female controls line represents the average performance on over 567 000 Air Force physical fitness tests performed by females under the age of 30 between 2004 and 2014.²²

changes in performance due to the passage of time a potential confounding factor. The high variability in time between baseline assessment and starting testosterone or oestrogen could also confound our assessment of the effect of time on testosterone or oestrogen. However, the uniformity of the data showing improvement in performance scores in transmen and the decline in transwomen makes it unlikely that the changes in performance are random or can be attributed to changes over time alone. The conceptual model for our multivariable analysis could be wrong and incorrectly estimate the relationship of testosterone or oestrogen with changes in athletic performance. Finally, testosterone and oestrogen protocols were not standardised for our participants. Variations in hormonal exposure between patients could confound our measurement of the effects of testosterone

What are the new findings?

- ▶ Transwomen retain an advantage in upper body strength (push-ups) over female controls for 1–2 years after starting gender affirming hormones.
- ▶ Transwomen retain an advantage in endurance (1.5 mile run) over female controls for over 2 years after starting gender affirming hormones.
- ▶ Transwomen are currently mandated to have 1 year of testosterone suppression before being permitted to compete at the elite level. This may be too short if the aim is a level playing field.

or oestrogen on athletic performance and body composition. Most participants had documentation of therapeutic hormone levels and suppression of testosterone, suggesting dosing at physiologic levels, although the time between starting testosterone or oestrogen and documentation of physiologic levels varied widely between participants. We do not know to what extent this variability represents differences in medication dosing or inadequate access to medical records from outside the military healthcare system. Future studies should address these limitations. Development of evidence based guidelines for transgender inclusion in elite athletic competition by governing bodies for athletics, such as the IOC and World Athletics, requires further research to define the timing of changes associated with testosterone or oestrogen.

CONCLUSION

In this study, we confirmed that use of gender affirming hormones are associated with changes in athletic performance and demonstrated that the pretreatment differences between transgender and cis gender women persist beyond the 12 month time requirement currently being proposed for athletic competition by the World Athletics and the IOC.¹⁰ This study suggests that more than 12 months of testosterone suppression may be needed to ensure that transgender women do not have an unfair competitive advantage when participating in elite level athletic competition.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the methods section for further details.

Patient consent for publication Not required.

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Commentary

Is Research on Transgender Children What It Seems? Comments on Recent Research on Transgender Children with High Levels of Parental Support

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Abstract

Recent research on transgender children who have had support from their parents for their transitioning has concluded that their mental health is virtually no different than that of nontransgender children. Such research has been extensively cited, over 370 times in the past three years. Most of the hundreds of reviews received the stated results of the studies with little caution. However, the research featured numerous statistical errors and omissions, the implications of which would likely lead neutral observers to conclude that the mental health of transgender children, even when supported by their parents, was poorer than that of the groups of control children. In particular, levels of anxiety as reported by both parents and their transgender children appear to be significantly higher, and the transgender children's reports of self-worth appear to be significantly lower. Although reports regarding depression are not as significantly different, the effect sizes were generally in a similar direction as the other outcomes, being less favorable for the transgender children. Such issues highlight the need for careful examination of statistical research, even when published in highly regarded medical journals. As with other research, findings from the early stages of controversial research may often be premature. Further research is needed to explore factors underlying these results.

Summary: Some scholars have believed that if transgender children were supported by their parents before the children reached puberty, the generally higher rates of mental illness experienced by many transgender persons might be prevented or alleviated. Dr. Kristina Olson of the Department of Psychology at the University of Seattle was the first scholar to have studied groups of transgender children who were being supported by their parents and to have compared them to a control group of children and to siblings of the same transgender children. Her conclusion was that there were minimal, if any, differences in anxiety, depression, and self-worth among the groups of children; her research has since been cited extensively as having found just that. We reanalyzed her raw data and found that, to the contrary, the transgender children, even when supported by their parents, had significantly lower average scores on anxiety and self-worth. Often, a significantly higher percentage of transgender children, compared to controls, featured preclinical or clinical levels of anxiety. Parental support of transgender children may temporarily reduce levels of poor mental health for some transgender children, but it does not appear to eliminate those problems for all transgender children. Our findings should serve as a warning against accepting research at a surface level, which can lead to acceptance of invalid information and pursuit of ineffective interventions.

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Introduction

A recent article in *The Atlantic* magazine (Yong 2019) discussed the controversial issue of treatment of transgender children (Fitzgibbons 2015), citing the research of Dr. Kristina Olson of the Department of Psychology of the University of Seattle, Washington. While the article focused on factors related to a child's future transitioning, it also mentioned Olson's earlier studies that suggested "that children who are supported and affirmed in their transitions are just as mentally healthy as cisgender peers." Two of the articles published by Dr. Olson and her colleagues (Olson et al. 2016b; Durwood, McLaughlin, and Olson 2017) have been cited over 370 times in just two to three years. Most of those citations and literature reviews have accepted their results as having proven that the mental health of transgender children is on a par with that of cisgender children *if* the parents of the transgender children affirm the gender identity of their transgender children. In the same article in *The Atlantic* magazine, Yong cited Professor Aaron Devor (University of British Columbia) who hoped that Olson's seminal work would have an "Evelyn Hooker effect," (Hooker 1957, 1958), meaning that Olson's research would change the entire field of social science with respect to the treatment of transgender children as Hooker's research (Schumm 2012; Cameron and Cameron 2012) had done for homosexuality. However, the quality of literature reviews relies on their correct interpretation of the research they cite. Arriving at a correct interpretation is only as likely as the original authors' accurate interpretation of their own results. This issue boils down to whether or not Olson's research was accurately conducted and interpreted by herself and her colleagues. A number of statistical errors that were detected alerted us to question those matters (Schumm et al. 2019).

Objectives

Therefore, our plan here is (1) to explain what Olson and her colleagues reported in their research and (2) to show, with our reanalysis of their data, that their own conclusions about and interpretations of their data were not merely incorrect but led readers to assume conclusions about their findings that were the opposite of what their data actually imply. Furthermore, we will (3) evaluate whether Olson

and her colleagues used the best scientific procedures for their analyses, using a checklist from Du Prel, Rohrig, and Blettner (2009). Then, we will (4) observe how some scientific papers and literature reviews have gone on to report even more incorrect findings from the research of Olson and her colleagues.

Background: Olson's Research with Transgender Children**First Study**

Olson et al. (2016b) compared seventy-three transgender children (ages 3 to 12 years, who had been supported by their parents for their transitioning gender identity) with a control group of seventy-three age- and gender-matched cisgender children and forty-nine nontransgender siblings of the transgender children. Most of the children were white, with average ages between 7.7 and 8.3 years. Most of their families, 81–90 percent, earned more than US\$75,000 annually. Specifically, Olson et al. (2016b) measured anxiety and depression for each of the children, as reported by their parents, and reported results for all children and results for each natal gender as subgroups of the children. They did not find significant results for the main effects of gender or group or for any interactions between gender and group. They found that the parents of the transgender children in their study reported lower internalizing (based on an average of anxiety and depression scores) scores for their children than had been found for transgender children in two other samples, from Canada and from the Netherlands (Olson et al. 2016b, 5).

The apparent conclusion was that if parents would only affirm their children's transgender status, then mental health problems would be prevented so strongly that the children would become essentially similar in mental health to their own siblings or to cisgender children from other comparable families. It is not clear what type of statistical analyses were used.

The expected positive correlation between the scores of the transgender children and their siblings would normally indicate that they used a repeated measures analysis of variance, while the independence of the scores between the transgender children and their control group of children suggests the use

of an independent samples analysis of variance. While we suspect they used the latter approach, using that approach would increase error rates in their statistics. Because they did not report standard deviations for their results, it was not possible to calculate effect sizes (the magnitude of their effects) as opposed to the statistical significance levels of their results. With small samples, such as those used by Olson et al., large effects may not be statistically significant.

Olson et al. (2016b) concluded that they had found no differences in depression and only marginally elevated levels of anxiety for the transgender children compared to those children from the other two groups. That interpretation was modified in their final conclusion section to “these results provide clear evidence that transgender children have levels of anxiety and depression no different from their nontransgender siblings and peers” (p. 7). McKean, Vande Voort, and Croarkin (2016) noted that nearly a third of the children in the Olson study were so young, the measures used had not been validated for such a young age-group; they also noted that the sample used was of very high socioeconomic status, whose results might not generalize to the average family.

Second Study

Durwood, McLaughlin, and Olson (2017, 117) included 63 transgender children, 63 age-matched controls, and 38 siblings aged 9 to 14 years, all of whom completed measures of depression and anxiety; parents also reported on their children’s apparent depression and anxiety. Some of the parents had participated in the earlier study (Olson et al. 2016a, b). In addition, 116 transgender children, 122 control children, and 72 siblings, ages 6 to 14 years of age, completed a measure of self-worth. The children were older than those in the Olson et al. (2016b) sample, with average ages from 10.6 to 10.9 for those who were measured on depression and anxiety. For those assessed on self-worth, average ages ranged between 9.1 and 9.3 years. The percentage of white children ranged between 50 percent and 66 percent, while the percentage of families earning more than US\$75,000 a year ranged between 71 percent and 82 percent. Mean scores and standard deviations, as well as the percent of children in a clinically high range for both depression and anxiety, were reported for all children and for those children from families earning US\$75,000 or less annually. Without explanation, scores for children from higher income families were not reported. Overall scores on

self-worth were not reported; however, Durwood, McLaughlin, and Olson (2017) broke the self-worth scores into three subgroups based on age of the children (youngest, oldest, in between) across the transgender, control, and sibling groups of children. With respect to comparisons of the mean scores across the three groups of children, the only statistically significant finding reported by Durwood et al. was from parents with respect to anxiety ($p = .002$).

Missing Information

Olson et al. (2016b) did not report clinical levels of anxiety or depression and did not report standard deviations. Without standard deviations, it is not possible for other scholars to calculate significance levels or effect sizes. Durwood, McLaughlin, and Olson (2017) did not report results for high-income families nor did they report overall mean scores and standard deviations for self-worth over their entire sample. Accordingly, we asked the authors to provide us with that information. Readers can read some of our back-and-forth discussion of these issues in the comment section associated with the Olson et al. (2016b) article, with dates between May 4 and August 8, 2018.

Research Questions

While we have questioned some of the details of their statistics elsewhere (Schumm et al. 2019), here the objective was to examine the validity of their major conclusions by assessing the accuracy of their statistical design and testing.

Thus, our primary research question was whether or not Olson et al. (2016b) and Durwood, McLaughlin, and Olson (2017) found, as many reviews have suggested, that there were no significant differences and only minimal, if any, substantial differences (interpreted as an effect size of .20 or greater being of substantive importance) in depression, anxiety, or self-worth in the two studies. At least one review of these two studies concluded that transgender children scored as well as other on both anxiety and depression (Allen, Watson, and VanMattson 2019, 3). The two studies have been cited over 370 times (Google Scholar), an indication of their impact on medical science concerning transgender children. We also wanted to consider whether they used the best methods available (Du Prel, Rohrig, and Blettner 2009) for conducting their research and/or reporting their results and the scholarly impact of their research.

Method

In the spring of 2018, the Alliance for Defending Freedom asked the author to review the research published by Olson et al. (2016b). The author agreed to take that article to the class he was teaching in basic statistics at the Wamego campus of Highland Community College and engage in a critique of its use of statistics as an applied exercise that might result in a publication for the students who were interested in participating in that project. Students were given course credit for their participation. Numerous statistical concerns were noted, as published elsewhere (Schumm et al. 2019). However, in many cases, Olson et al. (2016b) had not reported standard deviations or other data that were necessary to independently assess the statistical significance or the effect sizes of their findings. The author e-mailed Professor Olson and asked for the missing information, which was graciously provided.

Participants

Olson provided enough data in her reports or by inquiry to permit reconstruction of sample data for both groups. The sibling group was not included in the analyses because the sibling group came from the same families as the transgender children and the most appropriate statistical tests would have been paired samples *t*-tests, which cannot be calculated without knowing the correlation of results across the two related samples. Because the transgender and cisgender groups of children were independent of each other, it was possible to compare those two groups statistically with independent samples *t*-tests.

Analyses

Olson et al. (2016b) and Durwood, McLaughlin, and Olson (2017) used two types of comparison between their transgender children and the cisgender children. First, they compared mean scores between the two groups on depression and anxiety and self-worth; second, in some cases, they reported the percentages of children in each group that scored at or above certain clinical or preclinical levels of anxiety or depression.

Given a mean and standard deviation for two groups, along with sample sizes for each group, one can conduct independent samples *t*-tests from freely available websites (see Schumm et al. 2019). Given a percentage of children in each sample at or above clinical levels, it is possible to reconstruct the data and use binary logistic regression to obtain an odds

ratio that provides information on the relative odds of a child from one group versus the other group of scoring at or above the same clinical levels (for depression or anxiety). We used an α level of .05 to assess statistical significance and did not use Bonferroni procedures (dividing α by the number of tests) because their use inflates the chance of type II error. We took into consideration one- and two-tailed tests because most previous research has found that transgender children tend to score higher with respect to depression and anxiety than control groups of children. In addition to assessing statistical significance, the effect sizes of differences were calculated, with effect sizes of .20 or greater deemed of substantive significance and those of .24 or greater (per Cuijpers 2017) deemed of clinical significance. Effect sizes of .50 or greater will be deemed of sufficient magnitude to be observable to a careful observer, without using statistical methods (Cohen 1992). In order to provide a more conservative approach, where data were available, we performed Bayesian analyses (BF_{10}) and reported results when $BF > 3.0$. We also investigated the statistical power of Olson et al.'s analyses, using a power calculator at www.anzmtg.org/stats/PowerCalculator/PowerTest.

Hypotheses

The following hypotheses will be tested for statistical ($p < .05$) and for substantive significance (i.e., effect sizes $\geq .20$), using both one-tailed and two-tailed tests. Transgender children and/or their parents will report higher anxiety and higher depression scores for the transgender children than will children and/or their parents for cisgender children in the control group. When possible, results will be assessed for families above and below selected cut points on total family income. Differences by natal gender will be examined where data were available.

Transgender children, as reported by their parents or by the children themselves, will experience a higher odds ratio (≥ 1.5 deemed of substance) of reaching or exceeding clinical levels of depression or anxiety than parents or their children will report for cisgender children in the control group. Transgender children will report lower self-worth scores than will cisgender children, for the whole sample and for each of three different age groups in the overall sample.

Results

Raw data reported in Olson et al. (2016b) or Durwood, McLaughlin, and Olson (2017) as well as that

provided to us by the authors are presented in Table 1. Our analyses of the data in Table 1 are reported in Table 2. Tables 3 and 4 present data from Table 1 in a format that makes it easier to observe differences as a function of the natal and chosen gender identities of the children in terms of their scores on depression (Table 3) and anxiety (Table 4). Table 5 is a summary of our findings in Table 2. When odds ratios could not be calculated, we fit the results into one of three likely outcomes, of odds ratios of less than 1.5, 1.5–2.99, and 3.0 or higher, based on the effect size found with the *t*-tests. For depression, five results fell into the 1.5–2.99 range, with one above 3.0 and two below 1.5. For anxiety, one fell below 1.5 while seven were above 3.0. Table 3 shows that natal girls reported higher levels of depression than did natal boys, but the effect was about twice as strong for transgender children as for cisgender children. Table 4 shows that in terms of anxiety, transgender children reported higher levels, regardless of natal gender, but the difference was greater for transboys than for transgirls. Table 6 represents a power analysis of the samples used by Olson and her colleagues.

Even though depression was associated with fewer significant results (5.3 percent), most of the results with respect to depression favored cisgender children (78.9 percent, 15/19) in terms of having positive effect sizes while 52.6 percent (10/19) involved effect sizes of .20 or greater. If the underlying population results for the depression tests had been even (50/50), the chances of getting fifteen or more on one side out of the nineteen tests would be $p < .01$, $z = 2.29$. Anxiety outcomes were mostly in favor of cisgender children (94.7 percent, 18/19), with 84 percent involving effect sizes of .20 or greater with 53 percent (10/19) being significant statistically. The chances of getting eighteen of nineteen results for anxiety in favor of cisgender children, if the true chance per test was only 50 percent, were $p < .0001$, $z = 3.67$. In terms of self-worth, all (4/4) of the results favored cisgender children with 75 percent (3/4) involving effect sizes of .20 or greater and 50 percent being significant statistically. Combining the results for depression and anxiety together, the chances of getting thirty-three or more of thirty-eight tests to favor cisgender children would be $p < .00001$, $z = 4.37$. The chance of finding thirty-seven of all of the forty-two tests on the side of cisgender children would be $p < .000001$, $z = 4.78$. Altogether, 88 percent (37/42) of the tests favored cisgender children with over two-thirds (29/42) featuring effect sizes of .20 or greater, with 31 percent (13/42) being significant statistically by two-tailed

tests and nearly 48 percent (20/42) significant by one-tailed tests. In terms of effect sizes of .24 or greater, we found nearly 62 percent (26/42) of that size or larger. The issue of statistical power is important for studies with the range of sample sizes involved in Olson et al. (2016b) and Durwood, McLaughlin, and Olson (2017). For the *t*-tests, we correlated sample size, measured in terms of the degrees of freedom for each *t*-test, against the significance level obtained and found $r = -.44$ ($p < .03$) with Spearman's $\rho = -.46$ ($p < .02$), such that the larger the sample used, the lower the observed level of significance, with a large effect size for this calculation ($d > .80$). This indicates that sample size played a key role in whether or not the observed results, regardless of their actual substantive importance, were statistically significant.

Statistical Power

Table 6 contains information on the statistical power associated with many of the statistical tests conducted with Olson et al.'s data. For most of their analyses, statistical power was sufficient for a high chance of detecting effect sizes of .50 at $\alpha = .05$. However, at the same time, most of their analyses did not have sufficient ($>.50$) statistical power to detect effect sizes of .20 or smaller. That situation may account for the difference between having effect sizes of .20 or greater for 69 percent of the forty-two tests but two-sided significant results for only 31 percent of the results and one-sided significant results for only 48 percent of the forty-two tests.

Objections

The primary objection to our methodology might be that we did not use a Bonferroni correction—that we did not divide α (.05) by forty-two, yielding an α of .0012 as the new criterion for any of the forty-two test results to have been deemed significant (using that criterion would have yielded only one significant result, for parental reports of child's anxiety in Durwood, McLaughlin, and Olson 2017). If the results were entirely due to chance, we would expect 5 percent to be significant, not 31 percent—or 10 percent to be significant (α set to .10) rather than 48 percent. Clearly, there are more significant results than would have been expected by chance alone. Thus, the evidence appears to indicate that a Bonferroni approach would *over correct* for the risk or problem of getting significant results that were actually obtained by chance alone. A thought experiment can reveal the limitations of the Bonferroni

Table 1. Raw Data from Olson et al. (2016b) and Durwood, McLaughlin, and Olson (2017).

Article	Group Reporting	Outcome	Mean/SD for Transgender Children	Mean/SD for Control Group Children	Percentage of Preclinical/Clinical for Transgender Children	Percentage of Preclinical/Clinical for Control Children
Olson	Parents, for boys and girls	Depression	50.13/7.42 N = 73	48.36/7.31 N = 73	11.0/5.5	5.5/2.7
	Parents, for boys and girls	Anxiety	54.17/8.82 N = 73	50.87/6.97 N = 73	26.0/15.1	9.6/1.4
	Parents, transboys versus control boys	Depression	50.80/7.20 N = 21	48.04/8.31 N = 21		
	Parents, transboys versus control boys	Anxiety	55.17/7.23 N = 21	51.06/7.64 N = 21		
	Parents, transgirls versus control girls	Depression	49.84/7.56 N = 52	48.50/6.92 N = 52		
	Parents, transgirls versus control girls	Anxiety	53.70/9.44 N = 52	50.78/6.74 N = 52		
	Parents, transboys versus control girls	Depression	50.80/7.20 N = 21	48.50/6.92 N = 52		
	Parents, transboys versus control girls	Anxiety	55.27/7.23 N = 21	50.78/6.74 N = 52		
	Parents, transgirls versus control boys	Depression	49.84/7.56 N = 52	48.04/8.31 N = 21		
	Parents, transgirls versus control boys	Anxiety	53.70/9.44 N = 52	51.06/7.64 N = 21		
Percent Clinical Levels for Transgender Children						
Durwood	All parents	Depression	50.2/8.8 N = 63	49.4/7.8 N = 63	6.3	3.2
	Low-income parents	Depression	53.4/8.6 N = 18	50.8/11.1 N = 13	5.6	7.7
	High-income parents	Depression	48.84/8.66 N = 45	49.01/6.83 N = 50	4.4	2.0
	All parents	Anxiety	54.9/9.0 N = 63	49.6/8.6 N = 63	22.2	4.8
	Low-income parents	Anxiety	56.2/8.4 N = 18	50.0/6.8 N = 13	22.2	0.0
	High-income parents	Anxiety	54.39/9.30 N = 45	49.94/9.06 N = 50	17.8	6.0
	All children	Depression	48.7/9.4 N = 63	46.4/8.0 N = 63	6.3	1.6
	Low-income children	Depression	46.7/9.3 N = 18	47.3/10.8 N = 13	0.0	7.7
	High-income children	Depression	49.56/9.45 N = 45	46.20/7.25 N = 50	8.9	0.0
	All children	Anxiety	52.0/9.6 N = 63	49.0/7.7 N = 63	12.7	3.2
	Low-income children	Anxiety	49.5/7.5 N = 18	48.5/10.5 N = 13	5.6	15.4
	High-income children	Anxiety	53.06/10.21 N = 45	49.19/6.96 N = 50	15.6	0.0
	All children	Self-worth	3.46/0.542 N = 116	3.61/0.415 N = 121		
	Younger children	Self-worth	3.50/0.54 N = 53	3.62/0.39 N = 59		
	Middle children	Self-worth	3.47/0.55 N = 49	3.68/0.35 N = 48		
	Older children	Self-worth	3.30/0.51 N = 14	3.37/0.64 N = 14		
Percent Clinical Levels for Control Children						

Note: Data are reported on what Olson et al. reported to us by e-mail (two decimal points) or in their original reports (one decimal point). Results of clinical or subclinical levels did not always add from the high- and low-income groups to the total group, for unexplained reasons (we used what we were sent). Columns 6 and 7 report the results for transgender and cisgender children, respectively, in terms of both the percentage of children scored at preclinical and clinical levels of the mental health outcome variables. The larger percentage represents the preclinical level.

Table 2. Results for Analysis of Data from Olson et al. (2016b) and Durwood, McLaughlin, and Olson (2017).

Article	Group Reporting	Outcome	Test Used	Results <i>t/df</i> or Odds Ratio	Effect Size	<i>p</i> (two-tailed)
Olson et al.	Parents, all children	Depression	t-test	1.45 (144)	0.23	<.15
		Anxiety	t-test	2.51 (144)	0.42	<.02
		Depression, preclinical	Odds ratio	2.12	0.20	<.24
		Depression, clinical	Odds ratio	2.06	0.14	<.42
		Anxiety, preclinical	Odds ratio	3.32	0.44	=.012
		Anxiety, clinical	Odds ratio	12.8	0.51	=.016
	Parents, transboys versus control boys	Depression	t-test	1.15 (40)	0.36	<.26
		Anxiety	t-test	1.83 (40)	0.57	<.08
		Depression	t-test	0.94 (102)	0.18	<.35
		Anxiety	t-test	1.82 (102)	0.36	<.08
		Depression	t-test	1.27 (71)	0.33	<.21
		Anxiety	t-test	2.52 (71)	0.65	<.02
		Depression	t-test	0.90 (71)	0.23	<.38
		Anxiety	t-test	1.14 (71)	0.29	<.26
		Depression	t-test	0.54 (124)	0.10	<.60
		Depression	t-test	0.74 (29)	0.27	<.47
		Depression	t-test	0.11 (93)	−0.02	<.92
		Anxiety	t-test	3.38 (124)	0.60	=.001
		Anxiety	t-test	2.19 (29)	0.80	<.04
		Anxiety	t-test	2.36 (93)	0.53	=.02
		Depression	Odds ratio	2.07	0.15	<.42
Durwood et al.	Low-income parents	Depression	Odds ratio	0.71	−0.09	<.82
	High-income parents	Depression	Odds ratio	2.28	0.14	<.51
	All parents, clinical levels	Anxiety	Odds ratio	5.71	0.53	<.005
	Low-income parents	Anxiety	Odds ratio	Cannot be calculated	0.14	<.08
	High-income parents	Anxiety	Odds ratio	3.39	0.38	<.09
	All children	Depression	t-test	1.48 (124)	0.26	<.15
	Low-income children	Depression	t-test	0.17 (29)	−0.06	<.87
	High-income children	Depression	t-test	1.96 (93)	0.40	<.054
	All children, clinical levels	Depression	Odds ratio	4.20	0.25	<.21
	Low-income children	Depression	Odds ratio	Cannot be calculated	−0.44	<.42

(continued)

Table 2. (continued)

Article	Group Reporting	Outcome	Test Used	Results <i>t/df</i> or Odds Ratio	Effect Size	<i>p</i> (two-tailed)
	High-income children	Depression	Odds ratio	Cannot be calculated	0.45	<.05
	All children	Anxiety	<i>t</i> -test	1.93 (124)	0.34	<.06
	Low-income children	Anxiety	<i>t</i> -test	0.31 (29)	0.11	<.76
	High-income children	Anxiety	<i>t</i> -test	2.18 (93)	0.45	<.04
	All children, clinical levels	Anxiety	Odds ratio	4.44	0.36	<.07
	Low-income children	Anxiety	Odds ratio	0.32	−0.33	=.38
	High-income children	Anxiety	Odds ratio	Cannot be calculated	0.62 BF = 9.17	<.005
	All children	Self-worth	<i>t</i> -test	2.40 (235)	0.31	<.02
	Younger children	Self-worth	<i>t</i> -test	1.36 (110)	0.26	<.18
	Middle children	Self-worth	<i>t</i> -test	2.24 (95)	0.45	<.03
	Older children	Self-worth	<i>t</i> -test	0.32 (26)	0.12	<.76

Note: Positive effect sizes indicate that parents of cisgender children or their children reported better mental health scores than did the transgender children or their parents. Even though our one-sided directional hypotheses would permit one-sided statistical tests, we used more conservative two-sided tests through Table 2. One-sided test results can be obtained by dividing the reported *p* values by 2. If one of the groups has no cases (0 percent) at or above clinical levels, then an odds ratio cannot be calculated; in those cases, effect sizes and significance levels were derived from Pearson zero-order correlations and/or a two-sided Fisher's Exact Test. BF_{10} = Bayes factor where scores from 3 to 10 represent moderate support for the alternative hypothesis and scores above 10 represent strong support.

Table 3. Raw Data (Mean/*SD*/*N*) from Olson et al. (2016b) on Depression as a Combination Pattern of Natal Gender and Transgender Status.

	Cisgender Children	Transgender Children
Natal boys	48.04 (8.31), <i>N</i> = 21	49.84 (7.56), <i>N</i> = 52
Natal girls	48.50 (6.92), <i>N</i> = 52	50.80 (7.20), <i>N</i> = 21

Table 4. Raw Data (Mean/*SD*/*N*) from Olson et al. (2016b) on Anxiety as a Combination Pattern of Natal Gender and Transgender Status.

	Cisgender Children	Transgender Children
Natal boys	51.06 (7.64), <i>N</i> = 21	53.70 (9.44), <i>N</i> = 52
Natal girls	50.78 (6.74), <i>N</i> = 52	55.27 (7.23), <i>N</i> = 21

correction. Let us suppose that we had five subscales for each of which the results were significant at $p = .01$. If the five subscales were combined to form a total scale, we might find it significant at $p = .01$. Even though all six of our tests would have been significant statistically, if we divide α (.05) by six for the six tests, then none of our tests would remain significant at the new Bonferroni level of α (.008). Thus, we think that Bonferroni corrections are too conservative, especially when the research objective is to not reject the null hypothesis.

A secondary objection might be that Olson's kindness in providing most of the information that was requested about her data (that had been

omitted in her published articles) was punished by contradicting her results in a published article. The intention is not to punish any attempt at transparency because transparency helps drive the proper functioning of science, which is to slowly, over time get us to a better understanding of reality. Results are results. The implications of results can vary. As is discussed shortly, the results in Tables 1 and 2 could be used to argue that transgender children need more support and/or that, for at least some transgender children, even with parental affirmation, their transitioning experience is somehow associated with lower conditions of mental health.

Table 5. Summary of Results from Table 2.

Article	Report from	Outcome	Number of Tests	Percentage of Positive	Percentage of $d \geq .20$	Percentage of $p < .05$	Percentage of $p < .10$
Olson et al.	Parents	Depression	7	100	71.4	None	None
	Parents	Anxiety	7	100	100	57.1	85.7
Durwood et al.	Parents	Depression	6	66.7	33.3	8.3	16.7
	Children	Depression	6	66.7	66.7	16.7	33.3
	Parents	Anxiety	6	100	83.3	66.7	100
	Children	Anxiety	6	83.3	66.7	33.3	66.7
	Children	Self-worth	4	100	75.0	50.0	50.0
Combined	Parents and children	Depression	19	78.9	52.6	5.3	10.5
Combined	Parents and children	Anxiety	19	94.7	84.2	52.6	84.2
Combined, all outcomes	Parents and children	All outcomes	42	88.1	69.0	31.0	47.6

Note: Percentage of negative are not counted in percentage for d and p .

Table 6. Statistical Power Calculations for Olson et al.'s Samples.

Transgender Sample Size	Control Group Sample Size	Power for $d = .50$, One-sided	Power for $d = .50$, Two-sided	Power for $d = .20$, One-sided	Power for $d = .20$, Two-sided
14	14	.58	.45	.18	.11
21	21	.73	.62	.23	.15
49	48	.97	.93	.40	.28
52	52	.97	.95	.42	.30
63	63	.99	.98	.48	.35
73	73	.996	.989	.52	.40
116	121	.999	.999	.70	.58

Note: Power calculations from www.anzmtg.org/stats/PowerCalculator/PowerTest with $\alpha = .05$.

A third objection might be my sources of funding, which have included some conservative organizations as well as government agencies such as the National Science Foundation. However, we have provided the data used in all of our calculations, so if our funding sources caused bias, it should be testable.

A fourth objection might be that the tests that were used were not independent as some were tests of subgroups of the main group. That is a reasonable concern, although Olson et al. (2016b) and Durwood, McLaughlin, and Olson (2017) did not find it necessary to adjust their methods accordingly. Because determining the exact effect of nonindependence is very complex (Schumm and Canfield 2011), we have deferred that sort of reanalysis of the data.

A fifth objection might relate to not using the sibling group in our analyses. We were concerned that the comparison between the transgender children and the control group of cisgender children was clearly an independent samples type of problem while the comparison between the transgender children and their siblings was *not* an independent samples type of problem. We wanted to focus on what we were sure of. However, when we treated the sibling group as an independent sample and ran a one-way analysis of variance on self-worth, the results, $F(2, 306) = 3.84$, were still significant ($p = .023$). It is unclear why Durwood, McLaughlin, and Olson (2017) did not report those results as statistically significant.

A sixth objection might be that we did not rely upon Bayesian statistics (Aczel et al. 2018). We tried

to use SPSS to obtain a Bayesian statistic for the oldest group of children regarding self-worth, but both the means and standard deviations failed tests for legitimacy (Heathers et al. 2018), preventing us from reconstructing the data, so we could perform a Bayesian analysis. It could be argued that if part of the data failed the Granularity-Related Inconsistency of Means (GRIM) and other tests, the legitimacy of the data and conclusions are in question (Brown and Heathers, 2017). We were able to run Bayesian analyses for the percentage comparisons; we found that the results for associations gave stronger results against the null hypothesis, so we used *t*-test Bayesian results in order to be even more conservative. Our four strongest Bayesian results were associated with effect sizes from 0.44 to 0.62, which would make sense, the strongest results yielding the best Bayesian results.

A seventh objection might be that we used control group values to compare with the values for transgender children, when it would be more appropriate to use national norms as comparisons. Some reviews of Olson et al.'s reports mentioned that the transgender children were doing well compared to national norms. However, for each of the five (*t*-test) anxiety comparisons from Olson et al. (2016b), when we compared the transgender results to a national norm of 50.0 (*SD* = 10.0, *N* = 100), instead of effect sizes of .42 ($p < .02$), .57 ($p < .08$), .36 ($p < .08$), .65 ($p < .02$), and .29 ($p < .26$) from Table 2, we obtained effect sizes of .44 ($p < .05$), .55 ($p < .05$), .38 ($p < .05$), .55 ($p < .05$), and .37 ($p < .05$), effects comparable in magnitude but usually of stronger statistical significance because we used a larger sample size for the simulated national comparison group. In other words, in terms of anxiety, Olson et al.'s (2016) results show the transgender children having higher levels of anxiety whether they are compared to the control group or to a national norm. In Durwood, McLaughlin, and Olson (2017), the results for anxiety are similar, regardless of the comparison used, because the control group scores are very close to the national norm of 50.0. For depression scores in both reports, the results are mixed, with some scores below national norms and others above them.

An eighth objection might be that we didn't compare the transgender children's scores to the comparison samples from Canada and the Netherlands that Olson et al. (2016b) used, based on clinic-referred children with possible gender identity disorder. We didn't focus on that because one might well expect clinic-referred children to score lower on mental health measures than children who were not referred. However, in the interests of completeness, we

compared anxiety scores for Olson's transgender children ($n = 73$) against the internalizing scores of Canada ($n = 343$) and from the Netherlands ($n = 123$). Using the original scores from Cohen-Kettenis et al. (2003), we obtained *t*-test results of 4.78 ($df = 414$, $d = 0.62$, $p < .0001$) and 6.78 ($df = 194$, $d = 1.00$, $p < .0001$). While those differences are substantial and statistically significant, they are not surprising given the selection effect differential between the samples. Interestingly, Olson et al. (2016b, 5) did not report any statistical tests across the three samples.

Discussion

"Comrade, your statement is factually incorrect."
"Yes, it is. But it is politically correct." (Codevilla 2016, 37)

Quality of Methodological Analysis

Du Prel, Rohrig, and Blettner (2009) provided several criteria for evaluating the quality of scientific articles published in medical journals. They indicated that higher quality studies would have statistical power $> .50$, that the statistical methods used would be clearly described, that the statistical results would be presented comprehensively and clearly, the effect sizes or confidence intervals would be presented, and that the conclusions would be supported by the study's findings. As we observed in Table 6, their data had insufficient statistical power for detecting small effect sizes, though adequate for detecting medium effect sizes. The statistical methods were not clearly described, particularly with respect to the fact that data from the transgender children and their siblings should have been positively correlated, lending itself to paired samples testing while the data for the transgender children and the control group of children lent itself to independent samples testing.

Some of these concerns about scientific quality and statistical clarity have been addressed elsewhere (Schumm et al. 2019). Effect sizes were not presented nor were confidence intervals. Moreover, as shown in Table 5, the study's conclusions of virtually no differences were not supported by the actual data. Among other issues, the participants were not randomly assigned to the tested groups, and it was not clear what proportion of the participants overlapped between the two studies and how dropouts may have differed between the two studies. Though the studies were "pioneering" (Kuvallanka, Gardner, and Munroe 2019), they had many substantial and

important limitations according to the criteria discussed by Du Prel, Rohrig, and Blettner (2009).

Scholarly Impact

Together, both articles have been cited over 370 times in the past two or three years. Chen et al. (2018, 76) found the two studies to be the *only* ones that had yet “explored psychosocial functioning in socially transitioned prepubertal children,” highlighting the critical importance of the two studies. As noted, Kuvalanka, Gardner, and Munroe (2019, 103) cited the research as “pioneering.” It is clear that the reported results of these two studies have had a huge impact on the field of social science and medicine.

Most of the scholars who have cited their articles have interpreted the findings in the same way as did Olson et al. (2016b) and Durwood, McLaughlin, and Olson (2017). Some articles repeated what the two articles claimed—that there are no differences in depression or self-worth between transgender children and control children with only slight or minimal differences in anxiety. Turban (2017, 101) stated clearly that “Transgender youth in this study showed only mildly increased levels of anxiety (below the subclinical range)” and that “child-report levels of self-worth were similar to those of matched non-transgender controls.” Chen et al. (2018, 76) noted that “Results show that transgender children did not differ from either control group on depression scores and had only marginally higher anxiety scores” and the two groups did not differ “on ratings of depression or self-worth and had marginally higher anxiety scores.” Other studies came to similar conclusions regarding either or both of the two articles (Alberse et al. 2019, 389; Alegria 2018, 132; Bonifacio et al. 2019, e72; Campo-Engelstein 2019, 85; Cartaya and Lopez 2018, 47; Chen, Hidalgo, and Garofalo 2017, 342; Deardorff et al. 2019, 143; Janicka and Forcier 2016, 33; Oswald and Lederer 2017, 7; Reilly et al. 2019; Saleem and Rizvi 2017, 3; Shumer 2018, 1; Toomey, Syvertsen, and Shramko 2018, 7; Valdiserri et al. 2019, 579; Wanta and Unger 2017, 126).

Other reports have concluded that mental health outcomes were similar between transgender children and age-matched controls and did not mention even minimal differences in anxiety symptoms (Becerra-Culqui et al. 2018, 8; Busa, Janssen, and Lakshman 2018, 28; Chodzen et al. 2019, 468; Cicero and Wesp 2017, 7; Ehrensaft et al. 2018, 255; Green 2017, 81; Nahata et al. 2017, 189;

Newhook et al. 2018, 333; Telfer et al. 2018, 134; Turban and Ehrensaft 2018, 1232).

Going further, some reviews concluded that being affirmed socially in their identified gender provided “substantial improvements in their mental health” (Riley 2018, 204) compared to transgender children not affirmed (even though there was no such comparison group in the studies) or that mental health disparities would be resolved “immediately” (Cicero and Wesp 2017, 6) if children were affirmed in their gender identity or that, if children were so affirmed, disparities in “emotional distress are reduced or eliminated” (Gower et al. 2018, 788). One review concluded that given parental support, transgender children would “thrive” (Ehrensaft 2017, 64), while another review concluded that anxiety and depression were *both* found to have decreased in Olson’s (2016b) study (Allen, Watson, and VanMattson 2019, 3). Another review (Kuvalanka, Gardner, and Munroe 2019, 103) mentioned that there were no differences in depression in Olson et al.’s (2016b) study, but said nothing about anxiety or self-worth, leaving the impression that there were probably no other variables of interest besides depression.

It is interesting that the seriousness of differences between transgender and cisgender children may be partly a function of how those differences are reported. While a difference in mean scores of 54 versus 51 may not seem like much (anxiety; Olson et al. 2016b), a difference of 26 percent versus less than 10 percent having preclinical levels of anxiety may seem more substantial. A parent may not care whether their child scores a point or two lower on some particular psychological test, but if asked whether they’d rather have a 26 percent risk of having a child with preclinical or clinical levels of significant depression or anxiety versus less than a 10 percent risk, it is presumed that most would choose the latter. It’s good that 74 percent of the transgender children didn’t show preclinical levels of anxiety, but that leaves an important question of how to help the other 26 percent of the transgender children. Do they need more protection in school from bullying? Do they need more peer support? Are their schools lacking in evidence-based policies to support transgender children? Are there ways in which their parents or other relatives could be more supportive than they have been? Are there other ways they could be helped? Unfortunately, the data at present don’t give us much guidance for those questions.

The scientific consensus would seem to be that transgender children are no different than cisgender children if they have parental support. However, our

reanalysis of Olson et al. (2016b) and Durwood, McLaughlin, and Olson (2017) would seem to indicate otherwise. While differences for depression were fewer, 79 percent favored cisgender children and over half (52.6 percent) involved effect sizes of .20 or greater in favor of cisgender children. Results for anxiety and self-worth were more notable in that nearly 95 percent (22/23) of those two outcomes favored cisgender children with over 82 percent (19/23) involving effect sizes of .20 or greater, with over 52 percent (12/23) being statistically significant (two-tailed) and over 78 percent (18/23) being significant (one-tailed). Olson et al. (2016b, 1) stated that the transgender children “had only marginally higher anxiety symptoms.” The effect size to which they referred was 0.42, nearly the 0.50 at which Cohen (1992) indicated an effect could be seen by a naked eye observer. In Durwood, McLaughlin, and Olson (2017) at least one effect size for anxiety reached the 0.80 level, which Cohen (1992) deemed “large,” well beyond what could be observed by the naked eye, without statistics. The results should have been interpreted as evidence that even with high levels of parental support, transgender children have lower levels of mental health, especially with respect to higher levels of anxiety and lower levels of self-worth, though marginally with respect to depression, supporting for the most part our three research hypotheses. It would seem that Ioannidis (2005) was correct, that much early research is taken too seriously, with major flaws being overlooked.

Clinical Implications

The most apparent implication would be to search for other sources of minority stress (Valentine and Shipherd 2018), such as discrimination or bullying from peers as an explanation for the higher levels of anxiety or depression observed among the transgender youth. Yet, if the bullying or discrimination from peers seems able to overcome the positive effects of parental support, school systems may be failing to adequately protect transgender children. However, if one accepts the scientific consensus viewpoint, those school systems may be getting an underserved “pass” in terms of their lack of effectiveness in protecting transgender children. In their response to a letter to the editor by McKean, Vande Voort, and Croarkin (2016), Olson et al. (2016a) reported that the mental health of their sample of transgender children had changed from a mean of 50.2 for the youngest to 56.9 for the oldest children (higher scores representing lower mental health).

Without standard deviations, it is not possible to know the exact effect sizes or significance levels involved in that change, but if we assumed both standard deviations to be 8.0, then the effect size of the decline would be 0.84, with $t(32) = 2.33$ ($p < .03$). Furthermore, examination of Durwood, McLaughlin, and Olson (2017) indicates that the self-worth of both transgender, effect size of 0.37, n.s., and cisgender, effect size of 0.56, $t(71) = 1.88$, $p < .07$, children appears to be declining with older age, which may suggest that school systems (or parents?) are not being as effective at supporting all children, transgender or cisgender, as they advance through higher grades (lacking the raw data, independent-samples t -tests were used in lieu of paired samples t -tests across times). However, if minority stress were the only explanation, it would not account for the parallel decline in self-worth reported by cisgender children, who presumably are not victims of minority stress in the same way that transgender children might be. Olson et al. (2016a, b) and Durwood, McLaughlin, and Olson (2017) did not offer any scientific tests of these more detailed hypotheses, so we remain in the dark as to why these observed differences seemed to occur.

Another clinical implication may be related to the higher anxiety and depression scores reported for the transboys in Olson et al.’s (2016b) sample (Durwood et al. did not break down their results by gender). It would seem that natal and transgender girls retained a depression differential associated with being female (Table 3) while acquiring a much higher anxiety score than those children in the other three groups (Table 4). Those unusual results may deserve further investigation. Our thought is that many cisgender boys have a hard time learning what it means to be a man, when they have the biological advantage of being natal males; how much more challenging would it be for a natal girl to figure out how to be a man, without the advantage of being a natal male? The threat of starting to menstruate or to develop breasts might add to the anxiety of trying to be a man. Conversely, natal males might have to worry less about developing more muscle as that would fit in with being a tomboy, so it might arouse less anxiety. While natal male transgender girls might develop a larger penis, unlike breasts, the penis may be easier to hide under clothing. Further research might clarify some of these issues.

Research Implications

Even though it is also untested, another hypothesis could be that transgender children’s concerns are not

being resolved through parental support or through social transitioning. This hypothesizes that even if it is assumed that the transgender children express a desire to transition and receive support for doing so, perhaps that transitioning experience is not as satisfying to them as they might have expected, leaving some of the transgender children with anxiety about having made the right decision (or not), or having associated questions of their own self-worth, if not other co-occurring mental health concerns (Bechard et al. 2017). It is also possible that some transgender children may not feel as much like their opposite sex as simply having sexual attractions to the same sex and feel that one way to resolve feeling “gay or lesbian” is to change their gender rather than accepting their sexual orientation (perhaps children who want to transition suddenly, without prior indications of being transgender, may be more likely to belong to this latter group). That doesn’t mean that all transgender children might feel that way, just enough of them to lower the average mean scores for transgender children as a whole. Future research should attempt to compare and test such competing hypotheses, though both or neither might be correct for some of the children.

Leaving the mental health of transgender children aside, the results raise serious questions about the validity of at least some medical or social science research (Ioannidis 2005). Results that are interpreted in one direction when the data actually speak in another direction have not been not an isolated phenomenon. It has been seen since the 1950s with Evelyn Hooker’s research (Hooker 1957, 1958; Schumm, 2012), later with same-sex parenting research (Schumm 2018; Schumm and Crawford 2019), and now with research on transgender children. In the case of Olson et al. (2016b) and Durwood, McLaughlin, and Olson (2017), not only were there numerous statistical errors (Schumm et al. 2019), but a great deal of data and results, including some significant results, were *not* reported until the authors were queried. Not reporting significant results may occur but when the apparent conclusion is that there weren’t any significant results, leaving out significant findings can be seen as self-serving to the idea of maintaining support for the null hypothesis regardless of the facts. Is good science being thrown under the bus for the sake of politically correct agendas? It’s difficult to escape a sense that such is not an uncommon occurrence in areas of considerable political controversy. One has to wonder what other areas of controversial science may have been infected with this type of problem.

It seems apparent that the methodological recommendations of Du Prel, Rohrig, and Blettner (2009) were not followed in these two studies. Outright errors were made. The issues we have brought up were significant enough to have caught the attention of peer reviewers and been corrected prior to publication; for that matter, the journal editors might have caught at least some of them on their own, prior to peer review. Furthermore, many of the scholars who have cited Olson et al. (2016b) and Durwood, McLaughlin, and Olson (2017) have also reported conclusions even less accurate than that reported by the original authors, raising concerns about the accuracy of the interpretation of literature in literature reviews.

Conclusion

Whereas Olson et al. (2016b) and Durwood, McLaughlin, and Olson (2017) concluded that transgender children with strong parental support had, at worst, only *slightly* higher levels of anxiety with no differences in self-worth or depression; a reanalysis of their findings suggests otherwise, with slightly higher levels of depression but significantly and substantively meaningful differences in anxiety and self-worth, and with results favoring cisgender children, *even when* the transgender children *had* high levels of parental support for their gender transitioning.

Such results leave open the possibility that discrimination from outside the families of the transgender children is having a corrosive effect on their mental health, especially as they get older, a possibility that should not be glossed over because of initially positive results and a possibility that if ignored could do further harm to transgender children by delaying preventive or remedial programs to prevent or ameliorate discrimination and bullying.

It is possible that one reason the two articles have been so highly cited is that they essentially let all other parts of society “off the hook” for the care of transgender children, assuming those children have parental support. It may also be possible that factors intrinsic to transgenderism or related to comorbid mental health concerns might be playing a role in mental health or self-worth. Further research is needed to sort out those different possibilities. Not only do we have to guard against science becoming little more than polemic (Green 2017), but we need to be sure that scientists remain dedicated to reporting their data and statistical testing fully and accurately.

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Puberty suppression and executive functioning: An fMRI-study in adolescents with gender dysphoria



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Summary Adolescents with gender dysphoria (GD) may be treated with gonadotropin releasing hormone analogs (GnRHa) to suppress puberty and, thus, the development of (unwanted) secondary sex characteristics. Since adolescence marks an important period for the development of executive functioning (EF), we determined whether the performance on the Tower of London task (ToL), a commonly used EF task, was altered in adolescents with GD when treated with GnRHa. Furthermore, since GD has been proposed to result from an atypical sexual differentiation of the brain, we determined whether untreated adolescents with GD showed sex-atypical brain activations during ToL performance. We found no significant effect of GnRHa on ToL performance scores (reaction times and accuracy) when comparing GnRHa treated

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male-to-females (suppressed MFs, $n=8$) with untreated MFs ($n=10$) or when comparing GnRHa treated female-to-males (suppressed FMs, $n=12$) with untreated FMs ($n=10$). However, the suppressed MFs had significantly lower accuracy scores than the control groups and the untreated FMs. Region-of-interest (ROI) analyses showed significantly greater activation in control boys ($n=21$) than control girls ($n=24$) during high task load ToL items in the bilateral precuneus and a trend ($p < 0.1$) for greater activation in the right DLPFC. In contrast, untreated adolescents with GD did not show significant sex differences in task load-related activation and had intermediate activation levels compared to the two control groups. GnRHa treated adolescents with GD showed sex differences in neural activation similar to their natal sex control groups. Furthermore, activation in the other ROIs (left DLPFC and bilateral RLPFC) was also significantly greater in GnRHa treated MFs compared to GnRHa treated FMs. These findings suggest that (1) GnRHa treatment had no effect on ToL performance in adolescents with GD, and (2) pubertal hormones may induce sex-atypical brain activations during EF in adolescents with GD.

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1. Introduction

Gender dysphoria (GD) is a condition in which people suffer from an incongruence between their natal sex and their gender identity, *i.e.* their experienced gender (American Psychiatric Association, 2013). For young individuals with GD, puberty is a period that causes great distress because it is characterized by unwanted physical changes, the development of the secondary sex characteristics. Therefore puberty inhibiting hormones may be prescribed such as the gonadotropin releasing hormone analogs (GnRHa) leuprolide or triptorelin (Gooren and Delemarre-van de Waal, 1996).

Some researchers expressed concerns about the possible disadvantages of GnRHa administration during adolescence (Spriggs, 2004; Viner, 2005; Houk and Lee, 2006; Korte et al., 2008). They fear that it may lead to misdiagnosis or that adolescents cannot make complex life decisions. Moreover, some have questioned whether hormonal suppression affects psychological functioning and if it may entail medical risks. Indeed, during adolescence the brain is still developing. Furthermore, puberty has been suggested to represent a second organizational period during brain development in rodents (Juraska et al., 2013) and in humans (Romeo, 2003; Sisk and Zehr, 2005). The prefrontal cortex (PFC) in particular appears to develop much later than other brain areas (Huttenlocher, 1979). Histological studies suggest that there is a second wave of synaptic proliferation in the PFC at the onset of puberty (Huttenlocher, 1979; Bourgeois et al., 1994; Woo et al., 1997), followed by a plateau phase and synaptic pruning. Executive functioning (EF), which is believed to depend heavily on prefrontal activation, also develops relatively slowly. For instance, performance on the Tower of London task (ToL), a frequently used EF task, improves with age until early adulthood (De Luca et al., 2003; Huizinga et al., 2006; Asato et al., 2006; Albert and Steinberg, 2011).

Since puberty marks an important period in the development of EF, the question arises if pubertal suppression affects this development. Therefore, in the present study, adolescents with GD who received GnRHa to suppress their puberty were compared with a group of control adolescents regarding ToL performance and brain activation patterns (using functional magnetic resonance imaging, fMRI). To check whether potential differences between the groups were due to the suppression (and not due to GD), we also

compared them with a group of age matched adolescents with GD who were not – yet – using GnRHa but were already in puberty.

Most of the previous ToL neuroimaging studies did not report – or perhaps did not look for – any sex effects (Owen et al., 1996; Baker et al., 1996; Dagher et al., 1999; Lazonen et al., 2000; Rowe et al., 2001; Van den Heuvel et al., 2003; Newman et al., 2003; Schall et al., 2003; Wagner et al., 2006; Boghi et al., 2006). However, one study reported sex differences in precuneus and dorsolateral prefrontal cortex (DLPFC) activation (Boghi et al., 2006). Therefore we examined sex differences as well.

Furthermore, it has been hypothesized that sexual differentiation of the brain might be different in individuals with GD (Cohen-Kettenis and Gooren, 1999; Van Goozen et al., 2002; Swaab, 2004). Functional neuroimaging studies comparing adults with GD (before the start of treatment) to controls demonstrated that MFs differed from their natal sex in parietal activation during a mental rotation task (Schöning et al., 2010) and showed female-like activity during processing of erotic stimuli (Gizewski et al., 2009) and after exposure to androstadienone, an odorous steroid compound (Berglund et al., 2008). In a verbal fluency study with adolescents performed by our group (Soleman et al., 2013), activation levels of untreated FMs and MFs fell in between those of the control groups. Structural neuroimaging studies have also shown intermediate values in adult FMs and MFs compared to control groups (Rametti et al., 2011a,b; Kranz et al., 2014) and several structural studies have shown differences between adults with GD and controls sharing their natal sex (Luders et al., 2009, 2012; Simon et al., 2013; Zubiaurre-Elorza et al., 2013; Hoekzema et al., 2015) although another study reported brain volumes largely in line with their natal sex (Savic and Arver, 2011).

As mentioned above, our group has examined the effect of GD on VF performance and brain activation in untreated adolescents (Soleman et al., 2013). Although the VF task may be considered an executive functioning task, the effect of GnRHa treatment on VF performance and brain activation was not investigated. In this study we examined if ToL-related brain activation of adolescents with GD, before start of GnRHa and while on GnRHa, was more in line with that of individuals of their experienced gender or of their natal sex. We believe that the present study is the first to examine the effects of puberty suppression on executive functioning.

2. Methods

2.1. Subjects

Adolescents who were diagnosed with Gender Identity Disorder according to the DSM-IV-TR (American Psychiatric Association, 2000) at VU University Medical Center in Amsterdam were recruited (Kreukels and Cohen-Kettenis, 2011). During preparation of this manuscript the DSM-5 was published (American Psychiatric Association, 2013), therefore DSM-5 terminology is used throughout this manuscript.

Forty-one adolescents with GD were included in this study; 22 female-to-males, 12 of which were using GnRHa (suppressed FM) and 10 who were not (untreated FM) and 18 male-to-females, of which 8 were using GnRHa (suppressed MF) and 10 were not (untreated MF). The suppressed adolescents with GD had been receiving 3.75 mg Triptorelin (Decapeptyl-CR®) every 4 weeks, subcutaneously or intramuscularly (mean duration $\pm$ standard deviation: 1.6 ± 1.0 years). To receive GnRHa, participants had to be at least 12 years old. Furthermore, girls needed to have breast development as described in Tanner stage B2 (Marshall and Tanner, 1969) and the genital development of the boys had to be at Tanner stage G2-G3 (testicular volume of 6–8 ml) (Marshall and Tanner, 1970) with measurable estradiol and testosterone levels, respectively. Relatives and friends of the participants were asked to participate, serving as age-matched controls. Only 3 siblings participated as controls: both a brother and sister of one GnRHa treated FM and one sister of an untreated FM. Thus, the majority of the controls were friends. The control group consisted of 24 girls (F) and 21 boys (M). Subject characteristics are presented in Table 1. According to the Declaration of Helsinki, all participants and their legal guardians gave their informed consent, and the study was approved by the Ethics Committee of the VU University Medical Center Amsterdam.

For all groups exclusion criteria were: (1) insufficient command of the Dutch language, (2) unadjusted endocrine disorders, (3) neurological or psychiatric disorders that could lead to deviant test results, (4) use of psychotropic medication, and (5) contra indications for an MRI scan. Adolescents receiving puberty delaying medication or any form of hormones besides oral contraceptives were excluded as controls. In consultation with the treating clinicians, only adolescents with GD functioning within the normal range were asked to participate in the study. One instrument (amongst other things) to measure psychological functioning was the Dutch translation of the Child Behavior Check List (Achenbach and Edelbrock, 1983; Verhulst et al., 1996), a well-known parent report questionnaire measuring psychological and behavioral problems. Control subjects received the CBCL as part of this study (average CBCL scores of the groups are depicted in Table 1). The gender identity of all controls was in line with their natal sex and was checked by asking them if they felt they belonged to the other gender or wished to be the other gender. All controls had a heterosexual orientation. The adolescents with GD were all sexually attracted to partners of their natal sex.

From the initial selection ten subjects had to be removed from further data analysis due to excessive movement during scanning, two because of scan artifacts (MR signal dropout)

due to braces, fifteen due to insufficient mask coverage, two because of performance at chance level, and one due to scanner failure.

2.2. Experimental setup and procedure

In this study an event-related parametric version of the ToL was used (for a detailed description see Van den Heuvel et al., 2003). On each trial, a start configuration (top) and a target configuration (bottom) were displayed simultaneously (see Fig. 1). In the planning condition subjects were asked to work out the minimum number of steps (ranging from 1 to 5) required to reach the target configuration. As a baseline condition, participants had to count the total amount of blue and yellow beads. The task lasted about 12 min and timing of the stimuli was self-paced, with a maximum response duration of 60 s per trial.

Participants practiced the task outside the scanner and performed some practice trials inside the scanner immediately before starting the task. Three other cognitive tasks were performed as well, a verbal fluency task (Soleman et al., 2013), a mental rotation task and a face recognition task (data to be published elsewhere). The four tasks were presented randomly during the scanning session and the entire session lasted 1 h. Prior to the MRI session a physical examination was performed by a clinician and intelligence was estimated with four subscales (arithmetic, vocabulary, picture arrangement, and block design) of the Wechsler Intelligence Scale for Children, third edition (WISC-III®) (Wechsler, 1991) or the Wechsler Adult Intelligence Scale, third edition (WAIS-III®) (Wechsler, 1997), depending on the participant's age. Handedness was measured by means of a Dutch questionnaire (Van Strien, 1992).

2.3. MRI acquisition

Imaging data were acquired on a 3.0T Philips Intera (Best, The Netherlands) MRI scanner at the Academic Medical Center, Amsterdam, The Netherlands. Axial T2*-weighted whole-brain volumes sensitive to blood oxygen level dependent (BOLD) contrast (Ogawa et al., 1990) were acquired

Count the number of steps

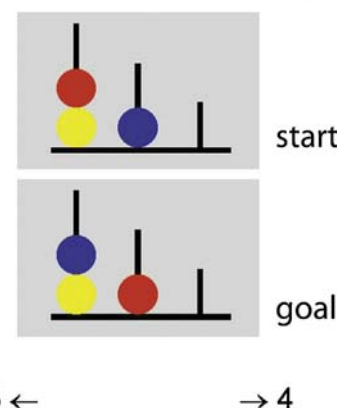


Figure 1 Example of the Tower of London task showing a trial in the planning condition.

Table 1 Sample characteristics and performance data.

Group	<i>n</i>	Age (years) (mean ± SD)	IQ* (mean ± SD)	Tanner stage (mean ± SD)	CBCL scores* (mean ± SD)	Accuracy (%)* (mean ± SD)	RT (s) (mean ± SD)
M	21	14.9 ± 1.5	110.7 ± 15.1	4.2 ± 1.2	48.4 ± 10.5 [■]	88.5 ± 6.8	9.6 ± 2.5
F	24	14.4 ± 1.8	103.0 ± 17.3	4.3 ± 0.9	48.4 ± 10.3 [○]	87.2 ± 11.9	9.0 ± 1.8
MF (total)	18	15.1 ± 2.4	102.6 ± 18.5	3.9 ± 1.1	57.8 ± 9.2	79.1 ± 10.3	10.4 ± 3.5
suppressed	8	15.4 ± 0.7	94.0 ± 10.3	4.1 ± 1.0	57.4 ± 9.8	73.9 ± 9.1	10.9 ± 4.1
untreated	10	14.6 ± 3.2	109.4 ± 21.2	3.8 ± 1.1	58.2 ± 9.3	83.4 ± 9.5	9.9 ± 3.1
FM (total)	22	15.8 ± 1.9	97.1 ± 15.4	4.5 ± 0.9	60.4 ± 10.2	87.1 ± 10.0	10.0 ± 2.6
suppressed	12	16.1 ± 1.7	95.8 ± 15.6	4.1 ± 1.1	57.5 ± 9.4	85.7 ± 10.5	9.9 ± 3.1
untreated	10	15.4 ± 2.3	98.5 ± 15.9	4.9 ± 0.3	63.9 ± 10.5	88.8 ± 9.7	10.0 ± 2.0

n: number of subjects, SD: standard deviation, accuracy: percentage of correct trials, corrected for task load, RT: reaction times in seconds, corrected for task load, CBCL: Child Behavior Checklist.

* Significantly different between groups ($p < .05$, two-sided).

■ $n = 14$.

○ $n = 16$.

M: control boys, F: control girls, MF: male adolescents with GD, FM: female adolescents with GD, suppressed: treated with GnRHa, untreated: without GnRHa treatment.

over ± 12 min using an echo-planar imaging sequence (repetition time [TR] 2.3 s; echo time [TE] 30 ms; field of view: 22 cm $\times$ 22 cm $\times$ 10.5 cm; flip angle: 80 degrees; 96 $\times$ 96 matrix). A sagittal T1-weighted scan was also performed (repetition time [TR] 9 ms; echo time [TE] 3.5 ms; field of view: 25.6 cm $\times$ 23.2 cm $\times$ 17.0 cm; flip angle: 8 degrees; 256 $\times$ 256 matrix, 170 slices).

2.4. Statistical analysis

Subject characteristics and ToL performance data were analyzed with the Statistical Package for the Social Sciences (SPSS), version 21. Accuracy scores (percentage of correct trials) and reaction times (RT) were corrected for task load by multiplying the scores of category 1–5 with increasing weights (1.0, 2.0, 2.5, 3.0 and 3.5, respectively – analogous to the contrast weights for measuring task load activation during first level SPM analysis) and then dividing the sum by 12. Group differences in age, IQ, and accuracy were tested with a one-way analysis of variance (ANOVA) and *post hoc* comparisons were performed using Games–Howell correction. One-way analysis of covariance (ANCOVA) was performed to examine the effect of IQ on group differences in accuracy. Group differences in RT were examined using Kruskal–Wallis test because the assumption of normality was not met. Tanner stage was examined using Kruskal–Wallis tests and a Chi-square test was used to check for group differences in handedness. A Pearson product-moment correlation was computed to determine the relationship between IQ scores and accuracy scores. The relation between IQ and RT was assessed using Spearman's Rank Order correlation.

The fMRI analysis was carried out with Statistical Parametric Mapping 8 (SPM8, Wellcome Department of Imaging Neuroscience, Institute of Neurology at the University College London, UK) implemented in MATLAB R2011b (MathWorks Inc., Natick, MA, USA). Functional images were slice-timed, realigned to the mean image, and co-registered

with the individual anatomical image. Because the participants in this study were adolescents and thus did not have adult-sized brains yet, a DARTEL template of their structural scans was created for optimal spatial normalization into Montreal Neurological Institute (MNI) space (DARTEL: Diffeomorphic Anatomical Registration Through Exponentiated, see [Ashburner, 2007](#)). Functional images were smoothed with a 8 mm FWHM Gaussian filter.

First level contrast images for *planning* were calculated by subtracting the baseline condition from the 5 planning categories. Moreover, to identify brain regions that showed signal intensity variation correlated with increasing planning complexity a *task load* contrast was calculated by giving increasing contrast weights to category 1 to 5 ([Van den Heuvel et al., 2003](#)). Individual head jerks of more than 1 mm were included in every first-level design matrix ([Lemieux et al., 2007](#)) together with the six motion parameters to account for the effects of excessive head motion. Furthermore, error trials were added as regressors of no interest.

Due to the large amount of data, only the results for the *task load* contrast are displayed in Section 3, although analyses were performed for both contrasts. *Task load* was favored because it places a greater emphasis on the more difficult trials and especially those trials (involving 3 or more steps) require EF. The results for *planning* are displayed in the Supplementary Results.

The contrast images for *planning* and *task load* were entered into a second level analysis of variance. IQ scores were added as a covariate because the groups differed in IQ scores. *T*-tests were performed to investigate the activation seen in every group (main effect) and to investigate group differences. The results were examined on whole-brain level first and subsequently region of interest (ROI) analyses were performed. Based on previous ToL neuroimaging studies (see Section 1) the dorsolateral- and rostralateral prefrontal cortex (DLPFC and RLPFC), and precuneus were chosen as ROIs. These areas were selected from the IBASPM116 atlas and separate left and right masks were created using WFU Pick-atlas version 3.0.4. ([Maldjian et al., 2003](#)). Because the

frontal ROI did not distinguish between DLPFC and RLPFC, a functional RLPFC ROI from the BrainMap database (Nielsen and Hansen, 2002) was subtracted from the frontal ROI using MarsBar (version 0.43, MRC Cognition and Brain Sciences Unit, Cambridge, UK). Each set of ROIs was masked with the FWE-corrected ($p=0.05$) main effects for *planning* and *task load* (separately). For examination of the main effect a p -value of 0.05 corrected for multiple comparisons was used (p_{FWE} -corrected = 0.05). For the between group ROI analyses a p_{FWE} -corrected = 0.05 was used as well, corrected for the spatial extent of the ROI.

3. Results

3.1. Sample data

No significant age differences were found between the six groups ($F(5, 79) = 1.52$, NS), but a difference was observed in IQ ($F(5, 79) = 2.32$, $p < .05$). Control boys (M) had significantly higher IQ scores than suppressed MFs ($p = .03$). Tanner stage and handedness did not differ between the groups ($p = 0.207$ and $p = 0.647$, respectively). The means and standard deviations of age, IQ and Tanner stage are presented in Table 1. There was no significant difference in duration of suppression between MFs (mean duration $\pm$ standard deviation: 1.8 ± 0.8 years) and FMs (mean duration $\pm$ standard deviation: 1.4 ± 1.1 years); $T(18) = 1.03$, NS.

3.2. ToL performance data

Accuracy significantly differed between the groups ($F(5, 79) = 3.07$, $p < .05$). *Post hoc* analyses showed that the suppressed MFs had significantly lower accuracy scores than the control groups ($p = .02$ compared to control boys and $p = .04$ compared to control girls) and the untreated FMs ($p = .04$). IQ and accuracy were significantly correlated ($r = 0.31$, $n = 85$, $p < .005$), but even after correcting for IQ, a significant effect of group on accuracy remained ($F(5, 78) = 2.70$, $p < .05$). Additionally, there was a significant negative correlation between IQ and RT ($r_s(85) = -0.31$, $p < .005$). However, RT did not significantly differ between the six groups ($H(5) = 3.92$, NS). No significant correlations between age and the performance scores were found. Means and standard deviations of accuracy and RT are presented in Table 1. For the baseline condition (counting the blue and yellow balls) no significant group differences were found for accuracy ($F(5, 79) = 0.28$, NS) or RT ($F(5, 79) = 1.16$, NS).

3.3. Main effect functional MRI data

The results for the *planning* contrast can be found in the Supplementary Results. *Task load* (Table 2 and Fig. 2) showed a robust activation pattern in the bilateral DLPFC and the left supplementary motor area. The left precentral area was significantly activated as well and activation was seen in the bilateral insular cortices and right pars opercularis. The parietal activation in the left hemisphere was found in the superior gyrus, extending from the precuneus to the more lateral part of the superior parietal cortex. In the right hemisphere significant parietal activation was seen in

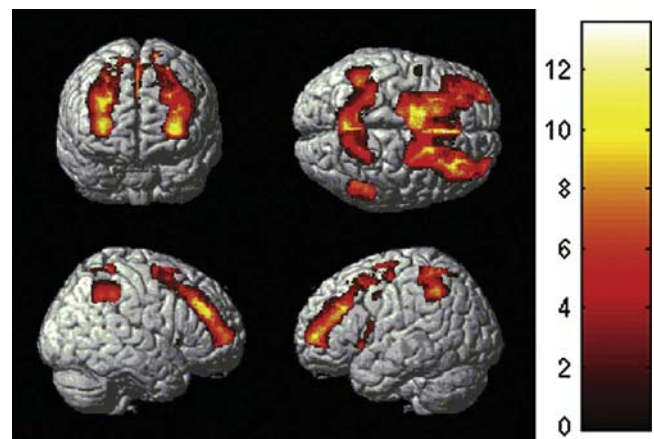


Figure 2 Brain activation pattern in all participants (main effect) for task load, with IQ added as a covariate. P -value (F_{WE} -corrected) = 0.05.

the supramarginal and inferior parietal gyrus. Task load was also associated with significant activation of bilateral basal ganglia (caudate nucleus, putamen and globus pallidus).

3.4. Group effects functional MRI data

3.4.1. Task load activation: sex differences within groups

Whole-brain analyses for *task load* revealed no significant group differences. ROI analyses showed greater activation of the bilateral precuneus and a trend ($p < .10$) for greater activation in the right DLPFC in control boys compared to control girls. In these ROIs similar sex differences were found between the suppressed MFs and FMs. Furthermore, activation in the other ROIs (bilateral RLPFC and left DLPFC) was also greater in suppressed MFs than suppressed FMs. In contrast, no ROIs showed greater activation in the untreated MFs compared to the untreated FMs. The only sex difference between the untreated adolescents with GD was in the opposite direction; the untreated FMs showed a slightly more pronounced ($p < .10$) right DLPFC activation compared to the untreated MFs (An overview of the sex differences reported in this paragraph is given in Table 3.) To explore whether the lack of typical sexual differentiation in untreated adolescents with GD was due to activation levels being in between those of the control groups, we depicted the activation levels of the untreated GD adolescents in those voxels showing the greatest sex difference in controls (Fig. 3). Indeed, plotting effect sizes indicated that activations in untreated GD adolescents were intermediate between the two control groups.

3.4.2. Task load activation in MFs

The suppressed MFs showed greater activation compared to their experienced gender (F) in bilateral DLPFC, left RLPFC, left precuneus and right precuneus (trend), whereas untreated MFs only displayed a trend for greater activation in the right precuneus. The suppressed MFs not only showed a greater left RLPFC activation than Fs, but also relative to their natal sex (M) and untreated MFs. The suppressed MFs

Table 2 Brain regions in main effect of task load.

Brain regions – task load	# Voxels	MNI coordinates			T-value	p (FWE-corrected)
		x	y	z		
<i>Frontal</i>	27,359					
Supp_Motor_Area_L		–14	5	66	13.57	<0.001
Frontal_Mid_R		37	38	31	12.25	<0.001
Frontal_Mid_L		–33	32	31	11.89	<0.001
<i>Parietal_L</i>	7465					
Parietal_Sup_L		–29	–43	66	9.85	<0.001
Precuneus_L		–6	–60	46	9.85	<0.001
Precuneus_L		–11	–57	63	9.64	<0.001
<i>Parietal_R</i>	1213					
Supramarginal_R		54	–42	45	7.81	<0.001
Parietal_Inf_R		52	–54	46	7.14	<0.001
<i>Basal Ganglia_L</i>	421					
Putamen_L		–18	0	12	7.26	<0.001
Pallidum_L		–18	–6	0	5.83	<0.01
<i>Basal Ganglia_R</i>						
Caudate_R	103	15	2	16	6.62	<0.001
<i>Frontal</i>						
Precentral_L	56	–50	–1	45	6.04	<0.01
<i>Frontal Inferior_L</i>	477					
Insula_L		–33	15	1	6.04	<0.01
Frontal_Inf_Oper_L		–53	6	12	5.88	<0.01
Insula_L		–29	23	–3	5.44	<0.05
<i>Insula_R</i>						
Insula_R	23	33	18	3	5.32	<0.05

Results are FWE corrected $p < .05$ and cluster size is > 20 voxels. Bold numbers in column 2 represent the number of voxels in the entire cluster.

showed greater left DLPFC activation than the untreated MFs as well.

3.4.3. Task load activation in FMs

Suppressed FMs differed from their experienced gender (M) by showing less bilateral precuneus activation, corresponding with the activation differences between the control groups. The untreated FMs did not show this resemblance to their natal sex (F). Besides lower right precuneus activation than boys (M), suppressed FMs also showed lower activation of this area than girls (F).

The untreated, but not the suppressed, FMs showed a trend for greater right DLPFC activation than their natal sex (F), thus showing a similarity to their experienced gender (M), who also demonstrated this trend compared to Fs. Untreated FMs displayed greater bilateral precuneus activation than suppressed FMs.

4. Discussion

In this study, we aimed to determine whether puberty suppression affected ToL performance. We found no significant effect of GnRHa on ToL performance scores (reaction times and accuracy) in either MFs or FMs when compared to untreated adolescents with GD. However, suppressed MFs had the lowest accuracy scores, which, as the analysis of covariance pointed out, did not just reflect their IQ scores,

which were the lowest as well. It is possible that this is just a chance finding due to the small size of this subgroup ($n = 8$). No sex differences in performance were found in the control groups.

ROI analysis did reveal sex differences in brain activations associated with ToL performance. Control boys showed significantly greater activation in the bilateral precuneus and right DLPFC (trend) during high task load compared to control girls. In a previous study (Boghi et al., 2006) adults showed similar sex differences in the precuneus, whereas the sex difference in DLPFC activation was reversed; women exhibited greater DLPFC activation than men. A possible explanation for this discrepancy is that the DLPFC is not yet fully developed in our participants. In a Go-No-Go study children displayed greater activation of the DLPFC than adults, this was explained as resulting from greater network efficiency in adults (Casey et al., 1997). Since frontal gray matter starts developing earlier in girls than in boys (Giedd, 2008) network fine-tuning may start earlier as well. During adolescence the DLPFC may still be under the influence of pubertal hormonal effects, either activational or organizational (Romeo, 2003; Sisk and Zehr, 2005) whereas this is no longer the case for the precuneus, since a strong bilateral sex difference is present both in adolescents (present study) and adults (Boghi et al., 2006).

It has been hypothesized that the sexual differentiation of the brain in individuals with GD may be distinct from other members of their natal sex due to organizational effects

Table 3 Voxels showing sex differences for task load activation (corrected for IQ).

Region of interest	Sex difference	MNI coordinates			T-value	p (FWE-corrected)
		x	y	z		
Precuneus L	M > F	-6	-67	51	4.76	<0.01
		-8	-57	46	3.92	<0.05
		-2	-46	46	3.38	<0.10
	MF (s) > FM (s)	-6	-52	48	3.57	<0.05
		-11	-49	46	3.55	<0.05
		-14	-61	60	3.33	<0.10
		-3	-58	48	3.24	<0.10
Precuneus R	M > F	15	-49	60	3.71	<0.05
		15	-43	58	3.63	<0.05
		2	-43	43	3.52	<0.05
		2	-46	48	3.36	<0.10
		8	-43	60	3.31	<0.10
	MF (s) > FM (s)	5	-45	51	3.21	<0.10
		12	-60	45	3.32	<0.10
		8	-54	54	3.30	<0.10
DLPFC L	MF (s) > FM (s)	-18	23	39	5.06	<0.01
		-21	23	51	4.22	<0.05
		-44	38	19	3.96	<0.05
		-17	26	52	3.95	<0.05
		-20	6	49	3.80	<0.10
		-20	18	55	3.65	<0.10
DLPFC R	M > F	27	-1	60	3.76	<0.10
	MF (s) > FM (s)	34	38	25	4.75	<0.01
	FM (u) > MF (u)	18	12	45	3.59	<0.10
RLPFC L	MF (s) > FM (s)	-27	59	7	4.11	<0.01
		-23	51	10	3.68	<0.05
		-23	54	0	3.46	<0.05
		-26	56	19	3.46	<0.05
		-24	53	16	3.32	<0.05
RLPFC R	MF (s) > FM (s)	30	50	-2	3.26	<0.05
		26	50	15	3.02	<0.10

MNI coordinates are given for the voxels showing a sex difference between males and females within the same group, e.g. male *versus* female controls. Indicated in *Italic* is a reversed sex difference. For these comparisons, ROIs were used (indicated in the first column) since no results were obtained at whole-brain level. All sex differences reported are FWE corrected $p < .10$. M: control boys, F: control girls, MF: male adolescents with GD, FM: female adolescents with GD, (s): suppressed by GnRHa, (u): untreated.

of sex hormones (Cohen-Kettenis and Gooren, 1999; Van Goozen et al., 2002; Swaab, 2004). This was based on findings that the development of the sexual organs and the differentiation of the brain follow separate time courses during prenatal development, implying different time windows during which these processes can be affected. Plotting effect sizes in the present study showed that brain activation levels of the untreated adolescents with GD fell in-between those of the two control groups in the areas that showed significant sex differences in the controls (Fig. 3). Hence, untreated MFs and FMs had a closer resemblance to each other than the control groups and no sex differences were found. Similar results were found in the VF study performed by our group (Soleman et al., 2013), where the controls showed a sex difference in right rolandic operculum activation but the untreated adolescents with GD, who showed intermediate activation compared to the control

groups, did not. As proposed by the sexual differentiation hypothesis of GD (Cohen-Kettenis and Gooren, 1999; Van Goozen et al., 2002; Swaab, 2004), the absence of a sex difference in untreated GD might be a result of a different hormonal milieu during prenatal development. However, possible effects of pubertal hormones on establishing atypical differentiation cannot be ruled out based on the results of the untreated participants. To this end, examination of sexual differentiation in puberty suppressed adolescents with GD, as was performed in the present study, provided a useful model. Interestingly, the suppressed MFs showed greater activation than the suppressed FMs in the same ROIs that were more active in control boys than control girls, indicating sex-typical brain activations. This similarity to their natal sex was also observed when comparing the suppressed adolescents with GD to the control groups. Like control boys, suppressed MFs showed greater ROI activation than control

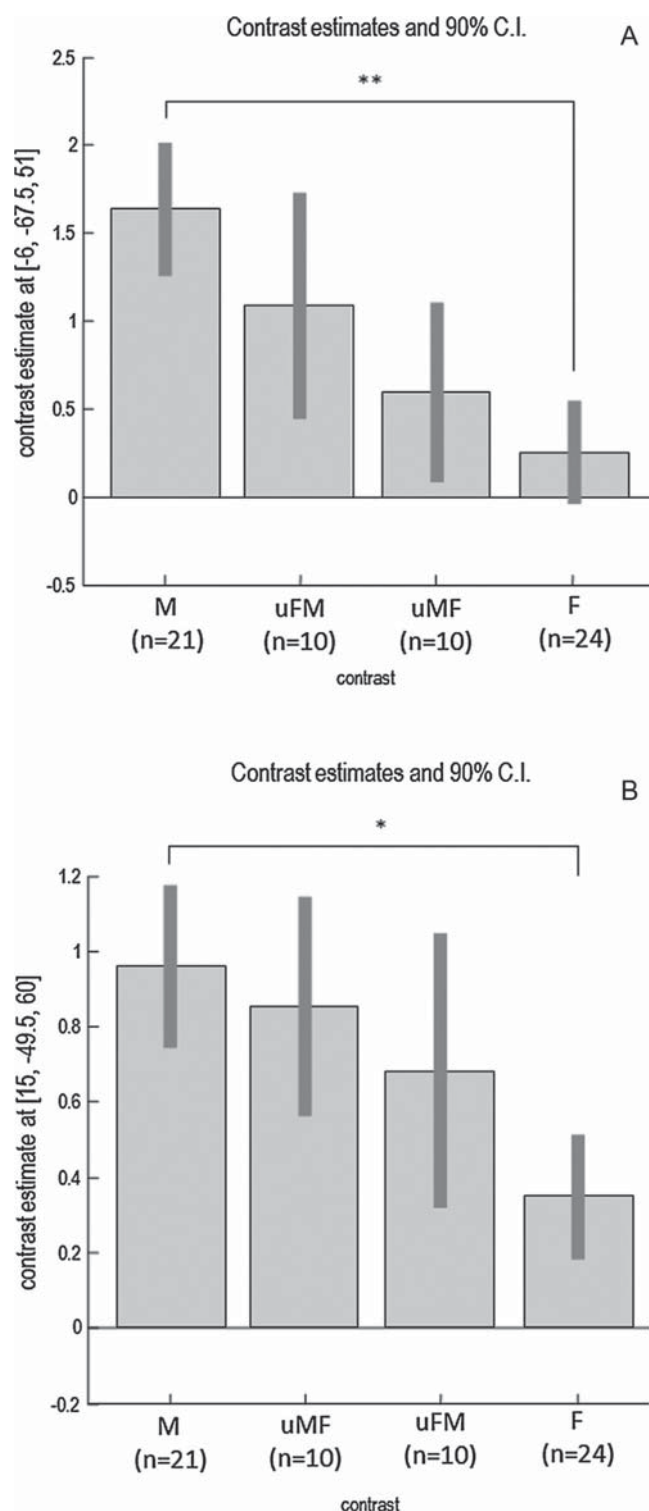


Figure 3 Contrast estimates and 90% confidence intervals (dark gray bars) for task load in the control groups and the untreated adolescents with GD in (A) the left precuneus (MNI coordinates: -6, 67.5, 51) and (B) the right precuneus (MNI coordinates: 15, -49.5, 60). A and B represent the voxels that demonstrated the greatest sex difference in the control groups. * $P(\text{FWE}) < .05$, ** $P(\text{FWE}) < .01$. M = control boys, F = control girls, uMF = untreated male adolescents with GD, uFM = untreated female adolescents with GD.

girls. Likewise, suppressed FMs showed lower ROI activation than control boys. These results were not found in the untreated adolescents with GD.

Thus, the present results indicate that the observed atypical sexual differentiation of ToL related brain activation in the untreated individuals with GD was not (solely) due to pre-natal organizing effects. Interestingly, a recent review by Steensma et al. (2013) suggested that the period of adolescence seems to be crucial for the development of a non-normative gender identity. Pubertal hormones might be needed to activate the sex-atypical ToL related brain activations in adolescents with GD, whereas sex-atypical activations are no longer induced when pubertal hormones are suppressed by GnRHa, leading to sex-typical activation.

The GnRHa treated adolescents with GD even appeared to have *exaggerated* sex-typical activation of the ROIs. The suppressed FMs showed a significantly smaller activation of the right precuneus than Fs and the suppressed MFs showed a greater left RLPFC activation than Ms. Furthermore, the suppressed groups showed significant sex differences in every ROI, including ROIs that were not significantly different in the control groups. Interestingly, pre-pubertally administered GnRHa was also found to modulate the development of cognitive functioning in sheep in a sex-specific manner (Wojniusz et al., 2011). Finally, additional factors might have played a role in the more prominent activation of the RLPFC in suppressed MFs. It is possible that this increase in left RLPFC activity reflects a greater effort of the suppressed MFs in performing the ToL task since they had the lowest IQ scores and made more errors than any other group.

In conclusion, our results suggest that there are no detrimental effects of GnRHa on EF. In addition, we have shed some light on another concern that has been raised among clinicians: whether GnRHa treatment would push adolescents with GD in the direction of their experienced gender. We found no evidence for this and if anything, we found that puberty suppression even seemed to make some aspects of brain functioning more in accordance with the natal sex.

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The funding sources did not play a role in any component of this study.

Conflicts of interest

The authors report no biomedical financial interest or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.psyneuen.2015.03.007>.

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Factors Associated With Desistence and Persistence of Childhood Gender Dysphoria: A Quantitative Follow-Up Study

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Objective: To examine the factors associated with the persistence of childhood gender dysphoria (GD), and to assess the feelings of GD, body image, and sexual orientation in adolescence. **Method:** The sample consisted of 127 adolescents (79 boys, 48 girls), who were referred for GD in childhood (<12 years of age) and followed up in adolescence. We examined childhood differences among persisters and desisters in demographics, psychological functioning, quality of peer relations and childhood GD, and adolescent reports of GD, body image, and sexual orientation. We examined contributions of childhood factors on the probability of persistence of GD into adolescence. **Results:** We found a link between the intensity of GD in childhood and persistence of GD, as well as a higher probability of persistence among natal girls. Psychological functioning and the quality of peer relations did not predict the persistence of childhood GD. Formerly nonsignificant (age at childhood assessment) and unstudied factors (a cognitive and/or affective cross-gender identification and a social role transition) were associated with the persistence of childhood GD, and varied among natal boys and girls. **Conclusion:** Intensity of early GD appears to be an important predictor of persistence of GD. Clinical recommendations for the support of children with GD may need to be developed independently for natal boys and for girls, as the presentation of boys and girls with GD is different, and different factors are predictive for the persistence of GD. *J. Am. Acad. Child Adolesc. Psychiatry*, 2013;52(6):582–590. **Key Words:** childhood gender dysphoria, desistence, persistence, sexual orientation, social role transitioning

Many children who experience gender dysphoria (GD), a sense of discomfort from incongruence between their gender identity and assigned sex, will not continue to experience dysphoria into adolescence and adulthood. However, a substantial minority (2–27% across studies) will continue to report GD and may seek services for gender reassignment later in life. To date, the prospective follow-up studies on children with GD, for whom the majority would meet the *DSM-IV-TR* diagnostic criteria for Gender Identity Disorder (GID)¹ collectively reported on the outcomes of 246 children. At the time of follow-up in adolescence or adulthood, these studies showed that, for the majority of children (84.2%; $n = 207$), the GD

desisted.² These studies were conducted across several decades during which the opportunity and social acceptance for gender reassignment has increased dramatically. The current study focuses on children in a context in which gender reassignment is available, generally socially accepted, and covered by health insurance.

Knowledge of the factors associated with persistence of childhood GD is limited. Prospectively, 1 study by Wallien and Cohen-Kettenis,³ reporting on the outcome in adolescence and early adulthood for 77 clinically referred children with GD (21 persisters and 56 desisters), found that the percentage of a complete childhood GID diagnosis was higher for children with persisting GD than for children with desisting GD. Furthermore, compared to the desisters, the persisters showed more gender-variant behavior and a higher intensity of GD in childhood. In



This article is discussed in an editorial by Dr. Peter T. Daniolos on page 569.

line with these findings, Drummond *et al.*⁴ showed that girls with persisting GD recalled significantly more gender-variant behavior and GD during childhood than the girls classified as having desisting GD. More recently, another study by Singh⁵ in 139 natal boys with GD confirmed the link between the intensity of childhood GD and adolescent and adult persistence of GD. Singh also found that desistence of GD was associated with a higher social class; however other possible indicators, such as psychological functioning or the quality of peer relations, were not different between the persisters and desisters in childhood.

Indications of more subtle childhood differences between persisters and desisters were reported in a qualitative follow-up study of 25 children with GD (14 persisters and 11 desisters) by Steensma *et al.*² They found that both the persisters and desisters reported cross-gender identification from childhood, but their underlying motives appeared to be different. The persisters explicitly indicated that they believed that they *were* the “other” sex. The desisters, however, indicated that they identified as girlish-boys or boyish-girls who only *wished* they were the “other” sex. With regard to the reported bodily discomfort by the persisters as well as by the desisters, the persisters indicated that their discomfort originated from the experience of incongruence between their bodies and their gender identity, whereas the desisters indicated that the discomfort was more likely to be a result of the wish for another body to fulfill the desired social gender role. As the information was based on subjective recollection and was therefore susceptible to biased recall,⁶ these findings should be interpreted with caution. Taken together, the prior research suggests that persistence of childhood GD is most closely linked to the intensity of the GD in childhood, the amount of gender-variant behavior, and possible differences in motives or cognitive constructions of the dysphoria.

Most long-term studies of GD also examined adolescent or adult sexual orientation and found an association between the presence of childhood GD and a heightened report of a sexual orientation directed towards the same natal sex or to both sexes.² In short, childhood GD may predict a later desire for gender reassignment in some, and an increased report of same sex attractions only in others. Remaining children reported desistence of GD and predominately opposite sex attractions. The proportions of children on each

of these 3 developmental pathways have not been fully established.

The present study examined possible factors associated with persistence of childhood GD by comparing a number of childhood variables (e.g., demographic background, GD, gender-variant behavior, psychological functioning, and quality of peer relations) between adolescent persisters and desisters who were clinically referred to our gender identity service in childhood. In addition to this, we examined psychosexual outcomes, body image, and the intensity of GD at the time of follow-up in adolescence.

METHOD

Participants and Procedure

The study sample consisted of 127 adolescents (79 boys, 48 girls), who were referred and diagnosed in childhood (< 12 years of age) at the Center of Expertise on Gender Dysphoria at the Vrije Universiteit (VU) University Medical Center in Amsterdam, the Netherlands. This sample differs from the previous persistence study from the Amsterdam clinic.³ The diagnostic procedure in childhood consisted of several sessions with the child and/or the parents, including an psychodiagnostic assessment of the child. The aim of the diagnostic phase is to determine whether the criteria for a GID diagnosis¹ are met and to evaluate the cognitive, psychological and psychosocial functioning of the child and the functioning of the family, in order to give parents pedagogical advice or advice to treat co-existing problems.⁷

Between 2000 and 2008, 225 children (144 boys, 81 girls) were consecutively referred to the clinic. From this sample, 127 adolescents were selected who were 15 years of age or older during the 4-year period of follow-up between 2008 and 2012. Of these adolescents, 47 adolescents (37%, 23 boys, 24 girls) were identified as persisters. They reapplied to the clinic in adolescence, requested medical treatment, were diagnosed again with GID, and considered eligible for treatment (puberty suppression with GnRH analogues first, cross-sex hormone treatment after the age of 16, and surgery after 18 (details of treatment in de Vries and Cohen-Kettenis⁷). As the Amsterdam clinic is the only gender identity service in the Netherlands where psychological and medical treatment is offered to adolescents with GD, we assumed that for the 80 adolescents (56 boys and 24 girls), who did not return to the clinic, that their GD had desisted, and that they no longer had a desire for gender reassignment. Demographic characteristics of the sample are provided in Table 1.

In this study, information on demographic background, psychological functioning, GD and cross-gender identification in childhood was retrieved from the medical charts for all adolescents. At the time of follow-up, and with approval of the Ethics Committee

TABLE 1 Demographic Characteristics as a Function of Desistence and Persistence and Sex

Characteristic	Persistence (n = 47)		Desistence (n = 80)		Responders ^a (n = 46)		Parents ^a (n = 6)		Nonresponders ^a (n=28)	
	Boys (n = 23)	Girls (n = 24)	Boys (n = 56)	Girls (n = 24)	Boys (n = 31)	Girls (n = 15)	Boys (n = 5)	Girls (n = 1)	Boys (n = 20)	Girls (n = 8)
Age in childhood, y										
Mean	9.33	9.83	8.70	9.35	8.84	9.23	8.92	10.48	8.43	9.44
SD	1.49	1.36	1.52	1.44	1.41	1.54	1.43	—	1.73	1.34
Range	7–12	6–12	6–12	6–12	6–12	6–12	7–12	—	6–12	7–12
Age at follow-up, y										
Mean	16.12	16.33	16.10	16.07	16.05	16.03	15.92	16.32	16.21	16.10
SD	.91	1.25	.92	.82	.93	.80	.74	—	.97	.95
Range	15–18	15–19	15–19	15–18	15–18	15–18	15–17	—	15–19	15–18
Interval, y										
Mean	6.80	6.50	7.39	6.72	7.21	6.81	6.99	5.84	7.78	6.66
SD	1.62	1.42	1.29	1.51	1.18	1.67	1.87	—	1.29	1.33
Childhood diagnosis (%)										
GID	91.3	95.8	39.3	58.3	48.4	66.7	0.0	0.0	35.0	50.0
Subthreshold	8.7	4.2	60.7	41.7	51.6	33.3	100.0	100.0	65.0	50.0
Social role (%)										
No transitioning	56.5	41.7	96.4	54.2	93.5	53.3	100.0	0.0	100.0	62.5
Partial transitioning	30.4	54.2	3.6	45.8	6.5	46.7	0.0	100.0	0.0	37.5
Complete transitioning	13.0	4.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Parents' MS (%)										
Both	82.6	79.2	69.6	54.2	80.6	60.0	80.0	0.0	50.0	50.0
Other ^b	17.4	20.8	30.4	45.8	19.4	40.0	20.0	100.0	50.0	50.0
SES (%) ^b										
I High	17.4	13.0	26.4	29.2	30.0	26.7	0.0	0.0	27.8	37.5
II Med	56.5	56.5	39.6	54.2	33.3	53.3	80.0	100.0	38.9	50.0
III Low	26.1	30.4	34.0	16.7	36.7	20.0	20.0	0.0	33.3	12.5
Full-scale IQ										
Mean	103.30	99.42	101.96	100.55	100.10	102.50	107.20	—	103.61	97.13
SD	12.51	14.34	12.81	15.93	13.07	14.14	9.78	—	13.09	19.22

Note: GID = gender identity disorder; MS = marital status.

^aThis column is a subgroup of the Desistence column.

^bFor parents' MS and socioeconomic status (SES), see text for classification.

of the VU University Medical Center, the adolescents were contacted to participate in the study. Upon agreement, an informed consent form and a set of questionnaires, assessing information on current GD, body image, and sexual orientation was mailed. All 47 persisters participated in the study. Of the 80 desisters, 46 adolescents sent back the questionnaires (57.5%) and 6 (7.5%) adolescents refused to participate, but allowed their parents to fill out the parent questionnaires. Twenty-eight adolescents were classified as nonresponders: 12 (15%) did not send back the questionnaires despite follow-up contacts, another 12 (15.0%) were untraceable. In 4 cases (5.0%), the adolescents and the parents indicated that the GD from the past remitted, but these individuals refused to participate.

Measures: Childhood

Demographics. Seven demographic measures were coded in childhood: natal sex, age at assessment, diagnosis, social role transition, parents' marital status, parents' social class, and Full-Scale IQ.

The diagnosis, made by either a child psychologist or psychiatrist, was categorized as follows: children who met all criteria for a *DSM-IV-TR* GID diagnosis, or children who did not meet all criteria and were subthreshold for a GID diagnosis. Social role transition was determined through 2 questions by 1 of the parents around the time of referral. Parents indicated whether their child had socially transitioned to the preferred gender role on a 3-point scale; no; yes, but not in all situations; or yes, completely. In an open

question, they could give further information on hairstyle, clothing, and in which pronoun and name the child was addressed. Based on this information, the children were categorized as follows: no social transition; partial transition (transition in clothing style and hairstyle, but without a change of name and pronoun change); complete transition (transition in clothing and hairstyle; change of name and use of pronoun). Because of the unequal distribution over the 3 categories for boys and girls (Table 1), the 3-point scale was recoded into a dichotomous scale in which 0 indicated no transitioning (category 1) and 1 indicated some transitioning (categories 2 and 3). Marital status of the parents was categorized as either living with both biological parents (or adoptive parents from birth) or all other categories (e.g., single parent, divorced, blended family, living in a group home). To determine parents' social class, a 5-point scale was used where 1 = university degree and 5 = grade 8 or less, and recoded into an education rating between 1.0 and 2.0 = 1 (high), 2.5 to 3.5 = 2 (medium), and 4.0 to 5.0 = 3 (low). Full-Scale IQ was assessed using the Dutch version of the Wechsler Intelligence Scale for Children.⁸

Gender Identity and Gender Dysphoria. The Dutch version of the Gender Identity Interview for Children (GIIC)⁹ is a 12-item child informant instrument that measures 2 factors: "cognitive gender confusion" and "affective gender confusion." Cognitive gender confusion is assessed by 4 questions asking whether the child identifies as a boy or a girl. Affective gender confusion is assessed by means of 8 questions focusing on affective aspects of gender identity (e.g., "Are there any things that you don't like about being a boy?"). Higher scores on the GIIC reflect more gender-atypical responses.

The Dutch version of the Gender Identity Questionnaire (GIQ)¹⁰ is a 14-item parent-report questionnaire representing 1 factor. The focus of items is on gender-variant behaviors, with higher scores coded in this study to represent a greater frequency of gender-variant behaviors.

Psychological Functioning and the Quality of Peer Relations. Psychological functioning was assessed through parental report, by the Dutch version of the Child Behavior Checklist/ 4-18 (CBCL),¹¹ and through teacher report, by the Dutch version of the Teacher's Report Form (TRF).¹² This study used: the mean Total problem score, i.e., the sum of all items rated 1 or 2; the mean Internalizing behavior score; and the mean Externalizing behavior score.

On the CBCL, there are 2 items related to gender identity: item 5 ("Behaves like the opposite sex") and item 110 ("Wishes to be the opposite sex"). These gender related items were analyzed as separate predictors based on the findings from Cohen-Kettenis *et al.*,¹³ and were not included in the 3 above-mentioned scales of the CBCL and TRF.

We created a Peer Relations Scale from 3 items: "Doesn't get along with other kids" (item 25), "Gets

teased a lot" (item 38), and "Not liked by other kids" (item 48), based on findings from Zucker *et al.*,¹⁴ who used this composite scale from the CBCL in a study and found a Cronbach's alpha of 0.81.

Measures: Adolescence

Gender Identity, Gender Dysphoria, and Body Image. The Gender Identity Interview for Adolescents and Adults (GIAA),^{15,16} is a 27-item adolescent and adult informant instrument with 1 factor. The items measure gender identity problems and GD for the past 12 months (e.g., "In the past 12 months, have you felt satisfied being a boy?"). Lower scores on the GIAA reflect more gender atypical responses.

The Utrecht Gender Dysphoria Scale (UGDS),¹⁷ is a 12-item questionnaire measuring 1 factor. The items measure the intensity of GD (e.g., "I continuously want to be treated like a boy/man."). There are separate versions of the UGDS for males (UGDS-M) and females (UGDS-F). Higher scores indicate more GD.

The Body Image Scale (BIS)¹⁸ is a 30-item questionnaire that measures body satisfaction and consists of 3 scales: Primary sex characteristics (e.g., genitals), secondary sex characteristics (e.g., breasts, body hair), and neutral body characteristics (e.g., hands, legs). Higher scores indicate greater dissatisfaction.

Sexual Orientation. We examined 4 indicators of sexual orientation: "To whom do you feel attracted?" (sexual attraction), "About whom do you fantasize sexually?" (sexual fantasy), "With whom have you kissed?" (sexual behavior), and "How do you identify yourself?" (sexual identity).³ The sexual behavior domain was assessed by asking about kissing because we expected that many of the adolescents would not have had sexual intercourse. The questions were rated on a 7-point Kinsey scale ranging from exclusively heterosexual (0) to exclusively homosexual (6).¹⁹ According to their scores, the adolescents were classified in 3 sexual orientation categories: attracted to other sex (Kinsey rating 0–1); attracted to both sexes (Kinsey rating 2–4); and attracted to same sex (Kinsey rating 5–6).

Parent Report. The questionnaire for parents was used when the adolescent refused to participate, and consisted of 9 questions assessing GD in their offspring. As for sexual orientation, 2 questions assessed sexual attraction ("To whom does your son or daughter feel attracted?") and sexual identity ("How does your son or daughter identify him- or herself?"). Both questions were classified following the same procedure as mentioned above.

Statistical Analysis

The desister subgroups (responders, reports from parents, and nonresponders), were compared in demographics, childhood psychological functioning, the quality of peer relations, and childhood GD using independent-samples Kruskal-Wallis and χ^2 Tests.

Logistic regression analyses examined bivariate and multivariate contributions of demographic variables, psychological functioning, quality of peer relations, and childhood GD on probability of persistence of GD in adolescence.

Analyses of variance, *t* tests, and χ^2 tests compared persisters and desisters on current reports of GD, body image, and sexual orientation.

RESULTS

Combination of Response Groups

For the 3 desister groups, no significant differences were observed between the responders, parents who responded, and nonresponders for the demographic variables, except for childhood diagnosis ($\chi^2[2] = 6.90, p < .05$). The adolescents for whom the parents responded were more likely to have a subthreshold diagnosis for GD than the responders and nonresponders. However, in their scores on the childhood measures of GD and psychological functioning, the 3 groups were not significantly different. Given this information, the 3 groups were combined to 1 group of desisters for further analyses.

Predictors of Persistence

Bivariate logistic regressions estimated the individual contribution of the childhood variables to examine which variables predicted persistence of GD (Table 2). Age and natal sex were the only significant demographic predictors. Older children and girls were more likely to be persisters than younger children and boys. Gender relevant items from the CBCL and TRF, social role transition, responses to the GIIC and GIQ, and receipt of a GD diagnosis in childhood were all significant indicators of adolescent persistence of GD.

To examine the simultaneous contribution of multiple factors, multivariate logistic regressions were run for the combined sample and separately by natal sex. Variables were retained in the model based on their unique contribution to explaining persistence of GD. Variables with very high correlations with other GD measures (e.g., whether or not a diagnosis was given) were not useful for the multivariate model and thus were dropped (Table 3).

In the combined group, the following variables collectively accounted for 58% of the variability in the persistence of GD: age at intake, social role transition, and both cognitive and affective responses to the GIIC. Once these variables were accounted for, responses to the GIQ did

TABLE 2 Childhood Predictors of Persistence of Gender Dysphoria (GD) Into Adolescence (N = 127, n = 47 Persisters, n = 80 Desisters)

Dependent variable: Persistence of GD	Bivariate OR (CI)
Natal boy	.41 (.20–.87)*
Age at intake	1.37 (1.06–1.76)*
Two parents	2.27 (.96–5.37) NS
High socioeconomic status	.30 (.18–1.69) NS
Medium socioeconomic status	.55 (.55–3.04) NS
Full-Scale IQ	1.00 (.97–1.03) NS
CBCL total problem	.99 (.97–1.01) NS
CBCL internalizing	.98 (.93–1.03) NS
CBCL externalizing	.98 (.94–1.03) NS
CBCL peer relations	.99 (.79–1.24) NS
CBCL gender (items 5 and 110)	4.64 (2.28–9.44)**
CBCL item 5	37.56 (4.95–284.87)**
CBCL item 110	5.13 (2.14–12.33)**
TRF total problem score	1.00 (.98–1.01) NS
TRF internalizing	.98 (.93–1.03) NS
TRF externalizing	1.01 (.97–1.06) NS
TRF peer relations	1.05 (.81–1.36) NS
TRF item 5	1.74 (1.05–2.89)*
Childhood role transition	5.38 (2.36–12.27)**
Gender identity disorder diagnosis	17.93 (5.14–62.55)**
Gender identity interview total	1.33 (1.19–1.49)**
GI cognitive items	1.95 (1.46–2.60)**
GI affective items	1.30 (1.15–1.47)**
Gender Identity Questionnaire	5.10 (2.03–12.79)**

Note: CBCL = Child Behavior Checklist; OR = odds ratio;
TRF = Teacher Report Form
p* < .05, *p* < .001.

not predict additional variance in persistence. Cognitive responses to the GIIC were the strongest predictor, accounting for 11% of the unique variability in persistence of GD.

Among natal males, 62% of the variability in the persistence of GD was accounted for by age at intake, social role transition, the cognitive subscale of the GIIC, and the total score of the GIQ. Once these variables were accounted for, responses to the affective component of the GIIC did not predict additional variance in persistence. Social role transition accounted for the largest portion of unique variability (12%), whereas each of the other significant predictors accounted for 6% to 7% of unique variability in persistence of GD. To further examine the effect of childhood social role transitioning on later persistence in natal boys, the boys who transitioned were compared with boys who did not for their scores on the childhood measures of GD. Boys who transitioned had significantly higher scores than those who had not

TABLE 3 Childhood Predictors of Persistence of Gender Dysphoria (GD) Into Adolescence Using Multivariate Logistic Regression (N = 127, n = 47 Persisters, n = 80 Desisters)

Dependent variable: Persistence of GD	Combined Sample OR (95% CI)	Natal boys OR (95% CI)	Natal girls OR (95% CI)
Age at intake	1.65 (1.12–2.44)**	1.90 (1.10–3.30)*	1.98 (.88–4.49) NS
Childhood role transition	5.06 (1.61–15.87)**	22.43 (2.69–187.07)**	1.85 (.27–12.87) NS
GII cognitive	1.68 (1.21–2.34)**	1.55 (1.06–2.28)*	2.04 (1.02–4.09)*
GII affective	1.19 (1.02–1.38)*	1.10 (.91–1.33) NS	1.47 (1.05–2.07)*
GIQ	2.47 (.75–8.16) NS	7.01 (1.17–42.01)*	.40 (.05–3.49) NS

Note: GII = Gender Identity Interview; GIQ = Gender Identity Questionnaire; OR = odds ratio.
* $p < .05$, ** $p < .01$.

transitioned for the 2 gender related CBCL items combined (mean = 3.91 versus mean = 2.88, respectively; $t [61.50] = -6.15$, $p < .001$); the cognitive scale of the GIIC (mean = 2.64 versus mean = 0.95, respectively, $t [74] = -2.74$, $p = .008$), and a borderline significance for the total score of the GIIC (mean = 12.64 versus mean = 9.45, respectively, $t [74] = -1.99$, $p = .051$), but not for the gender related TRF item, the affective scale of the GIIC or the GIQ.

For natal females, 62% of the variability in the persistence of GD was accounted for by cognitive and affective responses to the GIIC. Once these variables were entered, none of the other predictors contributed unique variance to persistence. Cognitive and affective responses to the GIIC explained 15% each of the unique variability in persistence of GD.

Adolescent Reports

Gender Identity and Body Image. Adolescents' reports of GD and body image were compared across persisters and desisters (Table 4), and showed that persisters reported more GD than desisters in the mean total scores of both the GIIC and the UGDS. Clinically, for the GIIC, scores of less than 3 indicate GD;¹⁶ 87.2% of the persisters met the criterion compared to 0% of the desisters. For the UGDS, scores of more than 40.0 indicate GD (Steensma, Kreukels, Jürgensen, Thyen, de Vries, and Cohen-Kettenis, unpublished material, 2013); 97.9% of the persisters met the criterion compared to 2.2% of the desisters (1 bisexual, natal girl). As for body image, the persisters reported more body dissatisfaction for primary and secondary sex characteristics and neutral body characteristics, than the desisters. There were no main effects for sex or significant interactions between sex and persistence for GD or body image.

Sexual Orientation. Table 5 shows sexual orientation percentages for persisters, desisters

and the 2 groups combined. Persisters were more likely to report a sexual orientation toward their natal sex across each of the indicators of sexual orientation: attraction ($\chi^2 [2] = 43.16$, $p < .001$), fantasy ($\chi^2 [2] = 45.95$, $p < .001$), behavior ($\chi^2 [2] = 56.81$, $p < .001$), and identity ($\chi^2 [2] = 47.69$, $p < .001$) compared to the desisters.

Among desisters, natal boys were more likely to report same sex attractions ($\chi^2 [2] = 9.94$, $p < .05$), fantasy ($\chi^2 [2] = 11.76$, $p < .05$), and identity ($\chi^2 [2] = 16.26$, $p < .001$), but not behavior, than natal girls. Within the group of persisters, there were no significant differences between natal boys and girls on any indicator of sexual orientation.

DISCUSSION

The present study aimed to identify associated factors with the persistence of GD into adolescence, and to assess the current feelings of GD, body image, and sexual orientation. Our findings regarding the gender identity of the adolescents were in line with the earlier findings; the persisters reported higher intensities of GD, more body dissatisfaction, and higher reports of a same-sex sexual orientation compared to the desisters.^{3,4} As for the factors associated with the persistence of GD, we replicated the earlier findings on the link between the intensity of GD in childhood and persistence of GD,^{3,4,5} showed that the chance of persisting was greater in natal girls with GD than in boys,³ and that psychological functioning and the quality of peer relations did not predict the persistence of GD.⁵ In addition to this, we found that formerly nonsignificant (age at childhood assessment) and unstudied factors (cognitive and/or affective gender identity responses on the GIIC and a social role transition) were associated with the persistence of GD. Furthermore, our multivariate model revealed that the factors associated with the persistence of GD were different between natal sexes.

TABLE 4 Mean Scores on the Gender Identity Measures and the Body Image Scale (BIS) in Adolescence

Natal Sex	Persistence			Desistence			Persisters vs. Desisters ^b		
	All (n = 47)	Boys (n = 23)	Girls (n = 24)	All (n = 46)	Boys (n = 31)	Girls (n = 15)			
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)			
GI/AA							<i>F</i>	<i>df</i>	<i>p</i>
Total score	2.65 (.33)	2.62 (.34)	2.69 (.32)	4.33 (.35)	4.35 (.34)	4.28 (.39)	510.78	1, 89	.001
BIS ^a									
Primary	3.84 (.66)	3.82 (.65)	3.86 (.68)	2.21 (.70)	2.14 (.66)	2.34 (.78)	117.09	1, 88	.001
Secondary	2.79 (.64)	2.75 (.70)	2.82 (.59)	2.24 (.65)	2.24 (.67)	2.23 (.63)	15.43	1, 88	.001
Neutral	2.56 (.62)	2.71 (.63)	2.42 (.59)	2.09 (.63)	2.05 (.61)	2.16 (.70)	11.53	1, 88	.001
UGDS-M									
Total score	—	52.22 (5.54)	—	—	13.48 (3.11)	—	−30.18	32.18	.001
UGDS-F									
Total score	—	—	53.79 (5.01)	—	—	23.00 (10.23)	−10.87	18.27	.001

Note: UGDS-F = Utrecht Gender Dysphoria Scale for females; UGDS-M = UGDS for males.

^aFor 1 persister, a natal boy, the Body Image Scale was not available, *n* = 46 for persisters and *n* = 22 for persister boys.

^bFor the Gender Identity Interview for Adolescents and Adults (GI/AA) and BIS domains, there were no significant differences between boys and girls, or an interaction for Status (Persistence/Desistence) × Sex.

With regard to the predictive factors for persistence, we expected to observe differences between natal boys and girls. To date, several studies on children with GD showed that girls who are referred to gender identity services generally present a greater level of gender-variant behavior^{9,10,13} and are generally older in age at the time of referral than boys.¹³ Furthermore, visual inspection of the demographic characteristics of our sample (Table 1) indeed indicates that girls had a higher age at referral, a greater percentage who fulfilled a childhood GID diagnosis, and partial transitioning among the majority of girls (irrespective of a later persistence or desistence) at the time of referral, compared to boys. It seems therefore conceivable that the differences in childhood presentation of boys and girls with GD resulted in different factors being associated with persistence of GD, which may have implications for a different approach in the clinical management of boys and girls with GD. For natal boys, gender-variant behaviors, their gender role presentation, and parent reports on the intensity of gender role behaviors provide important indicators of the child's desires and future development. However, because the role of parental report on gender-variant behaviors and surface behaviors such as gender role transitioning, are of less value in predicting a future persistence of GD in girls, it seems important to provide extra focus on girls' own experiences of cross-gender identification and wishes.

Although the relative value of the factors associated with the persistence of GD differed between

the natal boys and girls, a central and shared predictor for persistence for both boys and girls in our model included the cognitive responses to the GIIC. When asked with what sex they identified ("Are you a boy or a girl?"), children who expressed cross-gender identification had a greater chance of persisting GD. This seems to be in concordance with the underlying motives reported by the persisters and desisters in the qualitative study by Steensma *et al.*² Persisters indicated that they believed that they were the "other" sex, and the desisters indicated they wished they were the "other" sex; this difference may also underlie our finding of a higher report of cognitive cross-gender identification in the persisters than in the desisters; either they experience an alternative gender identification, or they interpreted the question differently. Nonetheless, explicitly asking children with GD with which sex they identify seems to be of great value in predicting a future outcome for both boys and girls with GD.

Childhood social transitions were important predictors of persistence, especially among natal boys. Social transitions were associated with more intense GD in childhood, but have never been independently studied regarding the possible impact of the social transition itself on cognitive representation of gender identity or persistence. As we previously indicated, the percentage of transitioned children is increasing and seems to exceed the percentages known from prior literature for the persistence of GD,²⁰ which could result in a larger proportion of children who have to change back to their original gender role, because

TABLE 5 Percentage of Sexual Orientation for Desisters, Persisters, and Combined

Group/Sexual Domain	Attraction		Fantasy		Behavior		Sexual Identity	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
Desistence/natal sex, n	29	14	29	11	22	9	31	15
Other sex, %	34.5	85.7	24.1	81.8	63.6	100.0	22.6	80.0
Both sexes, %	24.1	7.1	37.9	18.2	22.7	0.0	41.9	20.0
Same sex, %	41.4	7.1	37.9	0.0	13.6	0.0	35.5	0.0
Persistence/natal sex, n	23	24	21	24	17	20	23	24
Other sex, %	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Both sexes, %	4.3	4.2	0.0	4.2	0.0	0.0	8.7	4.2
Same sex, %	95.7	95.8	100	95.8	100	100	91.3	95.8
Combined/natal sex, n	52	38	50	35	39	29	54	39
Other sex, %	19.2	31.6	14.0	25.7	35.9	31.0	13.0	30.8
Both sexes, %	15.4	5.2	22.0	8.6	12.8	0.0	27.8	10.2
Same sex, %	65.4	63.2	64.0	65.7	51.3	69.0	59.3	59.0

Note: The domain sexual behavior was assessed by asking about kissing because we expected that many of the adolescents would not have had sexual intercourse.

of desisting GD, accompanied with a possible struggle²; or it may, with the hypothesized link between social transitioning and the cognitive representation of the self, influence the future rates of persistence. Future prospective follow-up studies on children with GD, where cognitive markers and specific indicators of social transitioning are incorporated, may shed more light on this question. Until there is more knowledge about this mechanism, and because the clinical management of children with GD in general should not be aimed to block gender-variant behaviors,²¹ the proposed approach regarding social transitioning in the Standards of Care of the World Professional Association for Transgender Health (WPATH) seems to be best fitting:

Mental health professionals can help families to make decisions regarding the timing and process of any gender role changes for their young children. They should provide information and help parents to weigh the potential benefits and challenges of particular choices ...²²

In conclusion, factors associated with persistence appear to vary among natal boys and girls.

These factors may be indicated by intensity of GD, and may seem to be clinically significant at different ages for boys and girls, but are not associated with psychological health or demographic background factors. In addition, the ways in which GD is managed in the family may be associated with individuals' cognitive representation of their own gender. Finally, clinical recommendations for the support of children with GD may need to be developed independently for natal boys and for girls, as the presentation of boys and girls with GD is different, and different factors are predictive of the persistence of GD. &

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Gender dysphoria in children and adolescents: an inventory of the literature

A systematic scoping review

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DECEMBER 2019 | WWW.SBU.SE/307E

Executive summary

This report was commissioned by the Swedish government and is a scoping review of the literature on gender dysphoria in children and adolescents. The report can be a basis for further evaluation of risk of bias and evidence.

Conclusions

- ▶ We have not found any scientific studies which explains the increase in incidence in children and adolescents who seek the health care because of gender dysphoria.
- ▶ We have not found any studies on changes in prevalence of gender dysphoria over calendar time, nor any studies on factors that can affect the societal acceptance of seeking for gender dysphoria.
- ▶ There are few studies on gender affirming surgery in general in children and adolescents and only single studies on gender affirming genital surgery.
- ▶ Studies on long-term effects of gender affirming treatment in children and adolescents are few, especially for the groups that have appeared during the recent decennium.
- ▶ The scientific activity in the field seems high. A large part of the identified studies are published during 2018 and 2019.
- ▶ Almost all identified studies are observational, some with controls and some with evaluation before and after gender affirming treatment. No relevant randomised controlled trials in children and adolescents were found.

- ▶ We have not found any composed national information from Sweden on:
 - the proportion of those who seek health care for gender dysphoria that get a formal diagnosis
 - the proportion starting endocrine treatment to delay puberty
 - the proportion starting gender affirming hormonal treatment
 - the proportion subjected to different gender affirming surgery

Background

The number of persons below age 18 who seeks the health care for gender dysphoria in Sweden has increased during the last decade. There is a debate as to why this happens and how it should be managed.

Aim

To assess the scientific literature for explanations of the increased number of children and adolescents seeking for gender dysphoria and to make an inventory of the literature on management and long-term effects.

Method

The following questions were assessed.

Are there any scientific studies explaining the increase in numbers seeking for gender dysphoria?

Population: Children and adolescents with gender dysphoria up to 18 years of age.

Intervention: Not applicable.

Control: Not applicable.

Outcome: Studies on incidence and prevalence of gender dysphoria and pattern of self-referral or referral.

Are there any scientific studies on long-term effects of treatment for gender dysphoria?

Population: Persons with gender dysphoria.

Intervention: Treatment for gender dysphoria.

Control: Any.

Outcome: Studies reporting long-term effects such as mental health, suicide attempts, suicide, cardiovascular effects, cancer development, bone health and regrets.

What scientific papers on diagnosis and treatment of gender dysphoria has been published after the National Board of Health and Welfare in Sweden issued its national support for managing children and adolescents with gender dysphoria in 2015?

Population: Children and adolescents with gender dysphoria up to 18 years of age.

Intervention: Diagnosis and treatment for gender dysphoria.

Control: Any.

Outcome: Studies on diagnosis and treatment.

This review is limited to peer reviewed papers with primary data and systematic reviews following PRISMA-standards. Case studies, meeting abstracts and editorials where not included. Only studies written in English or Scandinavian languages were eligible.

A structured systematic literature search in the following databases CINAHL (EBSCO), Cochrane Library (Wiley), EMBASE (Embase.com), PsycINFO (EBSCO), PubMed (NLM), Scopus (Elsevier), SocINDEX (EBSCO). The searches were finalised September 19, 2019.

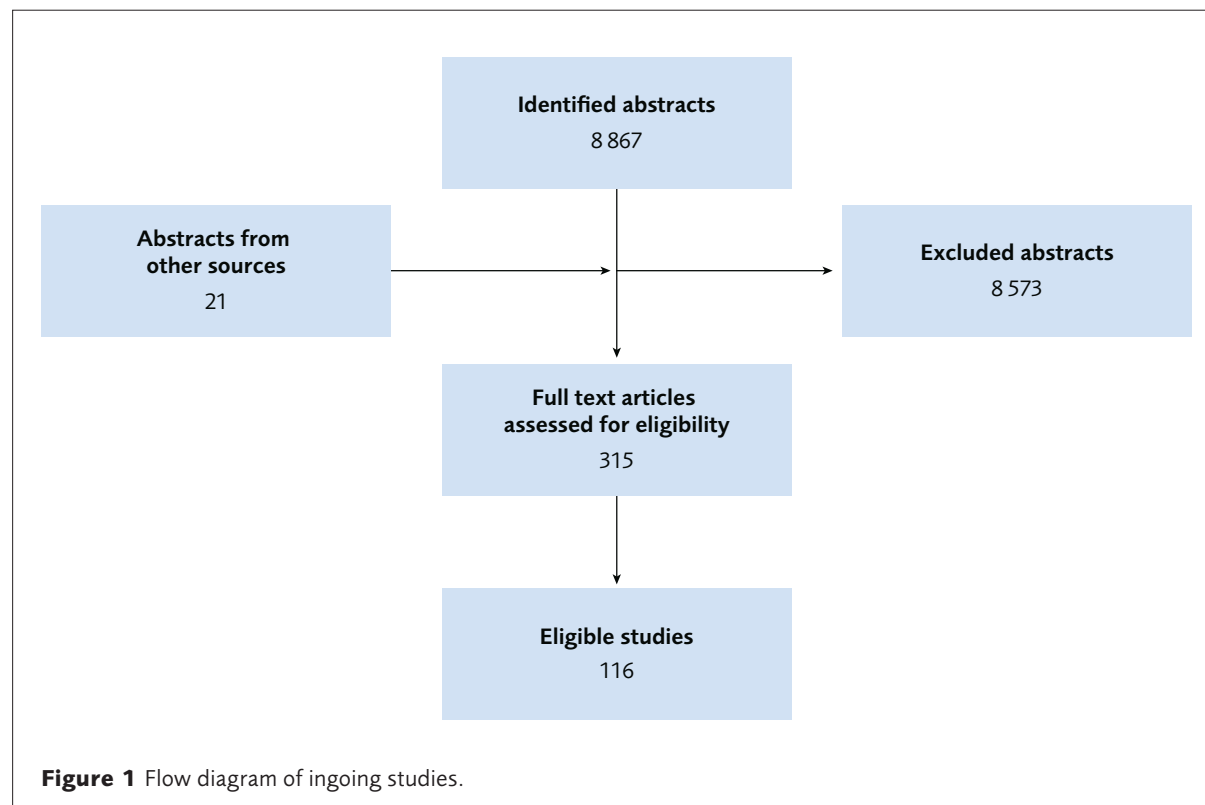
The studies were assessed for their relevance to the questions by two reviewers independently. Assessment of risk of bias, compilation of data or grading of evidence was not done.

Results/discussion

No studies explaining the increase of children and adolescents seeking for gender dysphoria were identified. The literature on management and long-term effects in children and adolescents is sparse, particularly regarding gender affirming surgery. All identified studies are observational, and few are controlled or followed-up over time. Much of the data in the literature are from the University Medical Centre in Amsterdam based on their management tradition. A large part of the literature that was considered relevant was published during 2018 and 2019.

Appendices

For search strategies, excluded articles, references and tables, see www.sbu.se/307e



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Association Between Recalled Exposure to Gender Identity Conversion Efforts and Psychological Distress and Suicide Attempts Among Transgender Adults

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Drafting of the manuscript: Turban, Beckwith, Keuroghlian.

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Key Points

Question

Is recalled exposure to gender identity conversion efforts (ie, psychological interventions that attempt to change one's gender identity from transgender to cisgender) associated with adverse mental health outcomes in adulthood?

Findings

In a cross-sectional study of 27 715 US transgender adults, recalled exposure to gender identity conversion efforts was significantly associated with increased odds of severe psychological distress during the previous month and lifetime suicide attempts compared with transgender adults who had discussed gender identity with a professional but who were not exposed to conversion efforts. For transgender adults who recalled gender identity conversion efforts before age 10 years, exposure was significantly associated with an increase in the lifetime odds of suicide attempts.

Meaning

The findings suggest that lifetime and childhood exposure to gender identity conversion efforts are associated with adverse mental health outcomes.

Abstract

Importance

Gender identity conversion efforts (GICE) have been widely debated as potentially damaging treatment approaches for transgender persons. The association of GICE with mental health outcomes, however, remains largely unknown.

Objective

To evaluate associations between recalled exposure to GICE (by a secular or religious professional) and adult mental health outcomes.

Design, Setting, and Participants

In this cross-sectional study, a survey was distributed through community-based outreach to transgender adults residing in the United States, with representation from all 50 states, the District of Columbia, American Samoa, Guam, Puerto Rico, and US military bases overseas. Data collection occurred during 34 days between August 19 and September 21, 2015. Data analysis was performed from June 8, 2018, to January 2, 2019.

Exposure

Recalled exposure to GICE.

Main Outcomes and Measures

Severe psychological distress during the previous month, measured by the Kessler Psychological Distress Scale (defined as a score ≥ 13). Measures of suicidality during the previous year and lifetime, including ideation, attempts, and attempts requiring inpatient hospitalization.

Results

Of 27 715 transgender survey respondents (mean [SD] age, 31.2 [13.5] years), 11 857 (42.8%) were assigned male sex at birth. Among the 19 741 (71.3%) who had ever spoken to a professional about their gender identity, 3869 (19.6%; 95% CI, 18.7%-20.5%) reported exposure to GICE in their lifetime. Recalled lifetime exposure was associated with severe psychological distress during the previous month (adjusted odds ratio [aOR], 1.56; 95% CI, 1.09-2.24; $P < .001$) compared with non-GICE therapy. Associations were found between recalled lifetime exposure and higher odds of lifetime suicide attempts (aOR, 2.27; 95% CI, 1.60-3.24; $P < .001$) and recalled exposure before the age of 10 years and increased odds of lifetime suicide attempts (aOR, 4.15; 95% CI, 2.44-7.69; $P < .001$). No significant differences were found when comparing exposure to GICE by secular professionals vs religious advisors.

Conclusions and Relevance

The findings suggest that lifetime and childhood exposure to GICE are associated with adverse mental health outcomes in adulthood. These results support policy statements from several professional organizations that have discouraged this practice.

Introduction

Transgender persons are those whose sex assigned at birth differs from their gender identity, the inner sense of their own gender.¹ According to a study by the Williams Institute,¹ approximately 1.4 million (0.6%) adults in the United States identify as transgender. Transgender persons in the United States experience a disproportionately high prevalence of adverse mental health outcomes, including a 41% lifetime prevalence of self-reported suicide attempts.^{2,3,4}

Studies^{5,6,7} have shown that gender-affirming models of care are associated with positive mental health outcomes among transgender people. Gender identity conversion therapy refers to psychological interventions with a predetermined goal to change a person's gender identity to align with their sex assigned at birth.⁸ Several US states have passed legislation banning conversion therapy for gender identity.⁸ Professional organizations including the American Medical Association,⁹ the American Psychiatric Association,¹⁰ the American Academy of Child & Adolescent Psychiatry,¹¹ and the American Academy of Pediatrics¹² have labeled the practice unethical and ineffective. Despite these policy statements, however, the question of whether to ban gender identity conversion therapy remains a contentious policy debate.

State-level conversion therapy bans have been focused on gender identity conversion efforts (GICE) by licensed mental health practitioners. Nonlicensed religious advisors have also advertised GICE, and it is unknown whether GICE by these 2 groups of practitioners are distinct in their effects on mental health.¹³

Because gender identity is thought to be stable after puberty for most transgender persons, few have supported use of GICE after pubertal onset.⁴ Some, however, have supported these efforts for prepubescent children, theorizing that gender identity may be more modifiable at this age.¹⁴ Increasingly, this approach has fallen out of favor, with the growing understanding that gender diversity is not a pathologic finding that requires modification.¹⁴ To our knowledge, there have been no studies evaluating the associations between exposure to GICE during either childhood or adulthood and adult mental health outcomes.

The current study used the largest cross-sectional survey to date of transgender adults living in the United States to assess whether recalled lifetime exposure to GICE is associated with adverse mental health outcomes, including suicide attempts. The study also assessed whether recalled childhood exposure to GICE before the age of 10 years is associated with adverse mental health outcomes in adulthood. We hypothesized that there would be associations between exposure to GICE by both secular and religious professionals and worse mental health outcomes.

Methods

Study Design and Data Source

The 2015 US Transgender Survey¹⁵ is a cross-sectional survey that was conducted by the National Center for Transgender Equality (NCTE) between August 19 and September 21, 2015. It is the largest existing survey of transgender adults and was distributed via community-based outreach.¹⁵ The US Transgender Survey protocol was reviewed and approved by the University of California Los Angeles institutional review board, Los Angeles, California. The US Transgender Survey data set was organized and recoded as described in the NCTE

report on the survey.¹⁵ The protocol for the present study was reviewed by the Fenway Institute institutional review board and was determined not to comprise human subjects research. Data analysis was performed from June 8, 2018, to January 2, 2019.

Study Population

The data set includes responses from 27 715 transgender adults residing in the United States, with representation from all 50 states, the District of Columbia, American Samoa, Guam, Puerto Rico, and US military bases overseas. The NCTE report on the survey further characterizes recruitment strategies and the sample of respondents.¹⁵ Because the organizations that conducted outreach for the survey did not systematically document the number of individuals reached by their outreach efforts, a response rate could not be calculated.

Exposures

The primary exposure of interest was an affirmative response to the binary survey question, “Did any professional (such as a psychologist, counselor, or religious advisor) try to make you identify only with your sex assigned at birth (in other words, try to stop you being trans)?” This recalled exposure is herein referred to as GICE. Endorsement of lifetime exposure to GICE was examined among all those who confirmed having spoken to a professional about gender identity. Outcomes were compared among respondents who reported exposure to GICE before the age of 10 years with outcomes among those who endorsed lifetime exposure to therapy without GICE. Because the data set does not contain age of exposure to non-GICE therapy, participants with any lifetime exposure to non-GICE therapy were selected as the reference group in the analysis of those exposed to GICE before age 10 years. As data regarding ages of pubertal onset among respondents were not available, younger than 10 years was used as a cutoff to approximate a prepubertal population, with the understanding that there is significant individual variability in the age at onset of puberty.^{16,17} Furthermore, we examined whether there was a difference in outcomes between those who reported exposure to GICE from a secular professional compared with those who reported exposure to GICE from a religious advisor.

Outcomes

We compared respondents with and without recalled exposure to GICE with regard to the following binary mental health variables: severe psychological distress during the previous month (defined as a score of ≥ 13 on the Kessler Psychological Distress Scale, a cutoff that has been previously validated in US samples¹⁸); binge drinking during the previous month (defined as ≥ 1 day of consuming ≥ 5 standard alcoholic drinks on the same occasion, a threshold for which the rationale in alcohol research among transgender persons has been discussed in previous reports¹⁹); lifetime cigarette and illicit drug use (not including marijuana); suicidal ideation during the previous year; suicidal ideation with plan during the previous year; suicide attempt during the previous year; suicide attempt requiring inpatient hospitalization during the previous year; lifetime suicidal ideation; and lifetime number of suicide attempts (0, 1, or ≥ 2).

Control Variables

Demographic and socioeconomic variables were collected and analyzed as defined in the US Transgender Survey, including sex assigned at birth, present gender identity, sexual orientation, racial/ethnic identity according to the recoded NCTE categories reflecting those typically reported in the American Community Survey, age (both in integer form and using US census categories to capture cohort effects), family support of

gender identity, relationship status (with *partnered* coded by these authors as binary and inclusive of both open and polyamorous relationships), educational achievement, employment status, and total household income. In supplemental analyses, we also controlled for exposure to sexual orientation conversion efforts undertaken by professionals.

Statistical Analysis

Analyses were conducted using SAS Studio, version 3.71, Basic Edition (SAS Institute). Participants were excluded from analyses if they did not report ever discussing their gender identity with a professional. Control variables were treated as unordered classification variables. Using the sample weights generated by the NCTE¹⁵ to improve generalizability by addressing sampling biases around age, educational level, and race/ethnicity, we generated descriptive statistics for control and outcome variables. Bivariate analyses comparing responses from transgender adults were conducted based on (1) whether or not they had any lifetime exposure to GICE, (2) whether they had experienced GICE before age 10 years vs never, and (3) whether GICE were conducted by a secular vs religious professional. These bivariate analyses were performed to detect potential confounders to control for in subsequent regression analysis. Except for age, all variables were categorical; thus, we used Rao-Scott χ^2 tests for design-adjusted data with 1 *df* for bivariate comparisons. Age as an integer variable was nonnormally distributed; thus, bivariate comparison was performed with the non-parametric Mann-Whitney test. Standard errors and 95% CIs were calculated for the prevalence estimates of exposure to GICE using the aforementioned 1.4 million persons as the total population estimate.¹

Multivariable logistic regression models were conducted to test whether GICE were associated with the outcomes, adjusted for variables with significant differences between groups in the preceding bivariate analyses. These models also used survey weights generated by the NCTE for age, educational level, and race/ethnicity. Adjusted odds ratios (aORs) with 95% CIs and 2-sided *P* values were reported, with a *P* < .001 threshold for significance.

Approximately 66 comparisons (between bivariate tests and logistic regression models) were made in each analysis. To reduce risk of type I error, a modified Bonferroni correction for multiple comparisons was performed, with resulting α = .001 (ie, .05 divided by 50). Using the full number of comparisons yields only a slightly lower α = .0008, which ultimately would not have altered the findings. We therefore selected an α = .001 for both ease of reading and also the statistical consensus that unmodified Bonferroni correction tends to be maximally conservative, thereby unnecessarily inflating type II error.²⁰ Thus, hypothesis tests were 2-sided with corrected significance level *P* < .001 for both primary and secondary analyses, and the 95% CIs reported reflect this correction.

Respondents with missing data for exposure and outcome variables comprised less than 2% of the analytic samples and were therefore excluded without compensatory methods, as is widely considered acceptable for this degree of data completeness.²¹ Data were missing for less than 9% of each control variable, thereby obviating the need for imputation, which can introduce bias, especially when data are nonrandomly missing. There is debate about the degree of incompleteness that is acceptable without compensatory measures, and although individuals with incomplete data may be of particular interest, thresholds for missingness as high as 10% are considered to be acceptable.²²

Results

Of the 27 715 US Transgender Survey respondents (mean [SD] age, 31.2 [13.5] years), 11 857 (42.8%) were assigned male sex at birth, and 3869 (14.0%; 95% CI, 13.3%-14.7%) reported exposure to GICE. Of 19 751 respondents who had discussed their gender identity with a professional, 3869 (19.6%; 95% CI,

18.7%-20.5%) reported exposure to GICE in their lifetime. Of these individuals, 1361 (35.2%; 95% CI, 32.7%-37.7%) who reported exposure to GICE stated that these were enacted by a religious advisor.

Demographic variables among exposed and unexposed respondents are shown in [Table 1](#). After adjusting for statistically significant demographic variables, lifetime exposure to GICE was significantly associated with multiple adverse outcomes, including severe psychological distress during the previous month (aOR, 1.56; 95% CI, 1.09-2.24; $P < .001$) and lifetime suicide attempts (aOR, 2.27; 95% CI, 1.60-3.24; $P < .001$). ([Table 2](#)).

Overall, 206 (1.0%; 95% CI, 0.8%-1.2%) of those who reported discussing their gender identity with a professional also reported exposure to GICE before age 10 years. Demographics are shown in [Table 3](#). After adjusting for statistically significant demographic variables, exposure to GICE before age 10 years was significantly associated with several measures of suicidality, including lifetime suicide attempts (aOR, 4.15; 95% CI, 2.44-7.69; $P < .001$) ([Table 4](#)).

Raw frequencies of outcome variables among exposure groups are shown in the [Figure](#). There were no statistically significant differences in outcomes between those who were exposed to GICE enacted by religious advisors and those exposed to GICE by secular professionals (all aOR, $P > .001$) (eTable 1 and eTable 2 in the [Supplement](#)).

We also repeated all analyses adjusting for lifetime exposure to sexual orientation conversion efforts, defined as a positive response to the survey question, "Did any professional (such as a psychologist, counselor, or religious advisor) ever try to change your sexual orientation or who you are attracted to (such as try to make you straight or heterosexual)?" After this adjustment, both lifetime exposure (aOR, 1.96; 95% CI, 1.38-2.80; $P < .001$) and childhood exposure (aOR, 3.05; 95% CI, 1.55-6.02; $P < .001$) to GICE were associated with increased odds of lifetime suicide attempts but not with the other outcome variables (eTables 3 and 4 in the [Supplement](#)). Because this question was unclear regarding the referent gender (sex assigned at birth vs gender identity) when defining sexual orientation conversion efforts, we refer to the models not adjusted for this variable throughout the article.

Discussion

This study was the first, to our knowledge, to show an association between exposure to GICE (lifetime and childhood) and adverse mental health outcomes among transgender adults in the United States. We found that recalled lifetime exposure to GICE was highly prevalent among adults: 14.0% of all transgender survey respondents and 19.6% of those who had discussed gender identity with a professional reported exposure to GICE.

The Generations Study²³ by the Williams Institute found that 6.7% of sexual minority group adults in the United States reported lifetime exposure to conversion efforts for sexual orientation.²³ Based on the findings of the current study, it appears that transgender people are exposed to GICE at high rates, perhaps even higher than the percentage of cisgender nonheterosexual individuals who are exposed to sexual orientation conversion efforts, although direct comparisons are not possible. One potential explanation for this is that compared with persons in the sexual minority group, many persons in the gender minority group must interact with clinical professionals to be medically and surgically affirmed in their identities. This higher prevalence of interactions with clinical professionals among people in the gender minority group may lead to greater risk of experiencing conversion efforts.

One study²⁴ showed that conversion efforts for sexual orientation were associated with an increased risk of depression and suicidal ideation. The current study was the first, to our knowledge, to find associations between any type of conversion efforts and both suicidal ideation and suicide attempts. A plausible association of these practices with poor mental health outcomes can be conceptualized through the minority stress framework; that is, elevated stigma-related stress from exposure to GICE may increase general emotion dysregulation, interpersonal dysfunction, and maladaptive cognitions.²⁵ Of note, having a lifetime suicide attempt was a more common outcome compared with severe psychological distress during the previous month, a result that was likely attributable to the time frames during which these variables were defined. Although this study suggests that exposure to GICE is associated with increased odds of suicide attempts, GICE are not the only way in which minority group stress manifests, and thus other factors are also likely to be associated with suicidality among gender-diverse people.

Respondents from more socioeconomically disadvantaged backgrounds (eg, low educational attainment or low household income) more commonly reported exposure to GICE. These individuals may have been more likely to receive GICE, or exposure to GICE may have been so damaging that they were impaired in educational, professional, and economic advancement. The cross-sectional nature of this study limits further interpretation. This finding warrants additional attention in the context of nationally representative data showing lower educational attainment and lower income among transgender people in the United States compared with their cisgender counterparts.²⁶

Given the considerable debate surrounding the merits of GICE for prepubertal youth,⁴ we examined recalled early exposure to GICE (ie, before age 10 years) and found this to be less prevalent, with 1% of those who had ever discussed gender identity with a professional reporting that they had been exposed before age 10 years. Many experts have expressed concern that early exposure to GICE may lead to persistent feelings of shame because of physicians and parents defining gender-expansive experience as unacceptable.⁴ A study²⁷ in Canada found a higher prevalence of shame-related feelings among youth treated with GICE. Both family and peer rejection of a child's gender identity have been associated with adverse mental health outcomes.^{27,28,29,30} Extending those findings, the current study showed that recalled early exposure to GICE was associated with adverse mental health outcomes, including lifetime suicide attempts, compared with discussion of gender identity with a professional and no exposure to conversion efforts. Although not compared directly, the aOR of lifetime suicide attempts was higher for those exposed to GICE before age 10 years than the aOR for those with lifetime exposure, suggesting that rejection of gender identity may have more profound consequences at earlier stages of development. Further research is needed to better understand the associations between stage of development at time of exposure to GICE and risk of lifetime suicide attempts.

Our results support the policy positions of the American Academy of Child and Adolescent Psychiatry,¹¹ the American Psychiatric Association,¹⁰ the American Academy of Pediatrics,¹² and the American Medical Association,⁹ which state that gender identity conversion therapy should not be conducted for transgender patients at any age. Our finding of no difference in mental health outcomes between respondents who received GICE from a secular-type professional and those who received it from a religious advisor suggests that any process of intervening to alter gender identity is associated with poorer mental health regardless of whether the intervention occurred within a secular or religious framework.

Strengths and Limitations

Strengths of this study include its sample size, more than 90% completeness in the data set, and participants from a wide geographic area within the United States. Limitations include its cross-sectional study design, which precludes determination of causation. It is possible that those with worse mental health or internalized transphobia may have been more likely to seek out conversion therapy rather than non-GICE therapy,

suggesting that conversion efforts themselves were not causative of these poor mental health outcomes. This interpretation, however, would also imply a mechanism whereby societal rejection leads to internalized transphobia and life-threatening adult mental health outcomes.

We also lack data regarding the degree to which GICE occurred (eg, duration, frequency, and forcefulness of GICE, as well as what specific modalities were used). If a sizable proportion of those reporting exposure to GICE in the current study experienced relatively mild or infrequent conversion efforts, this might suggest the findings of this study are even more concerning (ie, even mild or infrequent conversion efforts were associated with adverse mental health outcomes, including suicide attempts). Because the survey question asked about exposure to GICE from professionals, it is possible that exposures to GICE from other people (eg, family members) were not captured. Although the survey included respondents from a wide geographic distribution across the United States, these participants were not recruited via random sampling. The sample may not be nationally representative. Data are also lacking regarding when respondents entered puberty, making it difficult to define a prepubertal sample; we therefore set an approximate prepubertal cutoff at age 10 years. In this study, we compared exposure to GICE before age 10 years with lifetime exposure to non-GICE therapy. Although it would have been ideal to compare the former group with those who experienced non-GICE therapy before age 10 years, we lacked data on the age at which respondents were exposed to non-GICE therapy.

Conclusions

The findings suggest that recalled exposure to GICE is associated with adverse mental health outcomes in adulthood, including severe psychological distress, lifetime suicidal ideation, and lifetime suicide attempts. In this study, exposure to GICE before age 10 years was associated with adverse mental health outcomes compared with therapy without conversion efforts. Results from this study support past positions taken by leading professional organizations that GICE should be avoided with children and adults.

Notes

Supplement.

eTable 1. Demographics for Those With Exposure to Gender Identity Conversion Efforts by a Secular or Religious Advisor.

eTable 2. Outcomes Comparison for Secular and Religious Gender Identity Conversion Efforts

eTable 3. Outcomes for Those With Lifetime Exposure to Gender Identity Conversion Efforts

eTable 4. Outcomes for Those With Childhood Exposure to Gender Identity Conversion Efforts

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Figures and Tables

Table 1.

Demographics of Participants With and Without Lifetime Exposure to Gender Identity Conversion Efforts^a

Characteristic	Did any professional try to make you identify only with your sex assigned at birth? ^b		
	No. (%)		P Value ^c
	Yes (n = 3869)	No (n = 15 882)	
Sex assigned at birth			
Male	1143 (29.5)	5576 (35.1)	<.001
Female	2726 (70.5)	10 306 (64.9)	
Gender identity			
Cross-dresser	101 (2.6)	721 (4.5)	<.001
Transgender woman (male to female) or woman (birth-assigned male)	2452 (63.4)	8980 (56.5)	<.001
Trangender man (female to male) or man (birth-assigned female)	816 (21.1)	4084 (25.7)	<.001
Nonbinary or genderqueer (birth-assigned female)	327 (8.5)	1454 (9.2)	.11
Nonbinary or genderqueer (birth-assigned male)	173 (4.5)	643 (4.0)	.25
Sexual orientation			
Asexual	339 (8.8)	1034 (6.5)	<.001
Bisexual	753 (19.5)	2570 (16.2)	<.001
Gay, lesbian, or same gender-loving	811 (21.0)	3369 (21.2)	.75
Heterosexual or straight	838 (21.7)	4124 (26.0)	<.001
Pansexual	531 (13.7)	2039 (12.8)	.15
Queer	353 (9.1)	1933 (12.2)	<.001
Other	245 (6.3)	812 (5.1)	.003
Racial/ethnicity			
Alaska Native or American Indian	49 (1.3)	133 (0.8)	.02
Asian, Asian American, Native Hawaiian, or Pacific Islander	62 (1.6)	511 (3.2)	<.001
Biracial, multiracial, or other	79 (2.0)	288 (1.8)	.38
Black or African American	477 (12.3)	1926 (12.1)	.75
Latino, Latina, or Hispanic	609 (15.7)	2219 (14.0)	.005
White, Middle Eastern, or North African	2593 (67.0)	10 805 (68.0)	.23
Census age cohort, y			
18-24	339 (8.8)	1527 (9.6)	.11
25-44	1590 (41.1)	5997 (37.1)	<.001

Abbreviation: GED, general equivalency diploma.

^aDescriptive statistics for transgender adults who reported receiving any therapy regarding gender identity, with bivariate comparisons of those with and without exposure to conversion efforts.

^bProfessionals included psychologists, counselors, or religious advisors.

^cRao-Scott χ^2 tests were used for categorical variables, and the Mann-Whitney test was used for comparison of age because of nonnormality.

Table 2.

Outcomes for Those With Lifetime Exposure to Gender Identity Conversion Efforts^a

Outcome	Adjusted Odds Ratio (95% CI)	P Value
Suicidality in previous 12 mo		
Ideation	1.44 (1.03-2.02)	<.001
Ideation with plan	1.52 (1.09-2.14)	<.001
Attempt	1.49 (0.91-2.46)	.01
Attempt requiring inpatient hospitalization	1.62 (0.75-3.48)	.04
Suicidality in lifetime		
Ideation	1.90 (1.12-3.23)	<.001
Attempts	2.27 (1.60-3.24)	<.001 ^b
Mental health and substance use in previous month		
Severe psychological distress ^c	1.56 (1.09-2.24)	<.001
Binge drinking	0.88 (0.59-1.30)	.27
Mental health and substance use in lifetime		
Cigarette use	1.18 (0.83-1.68)	.12
Illicit drug use	1.08 (0.75-1.54)	.50

^aMental health outcomes among transgender adults exposed to gender identity conversion efforts compared with those who discussed gender identity with a professional without conversion efforts, adjusting for assigned sex at birth, gender identity, sexual orientation, race/ethnicity, age cohort, family support of gender identity, partnership status, educational attainment, employment status, and total household income.

^bOrdinal logistic regression with outcome categories: 0, 1, and 2 or more.

^cKessler Psychological Distress Scale (defined as a score ≥ 13).

Table 3.

Demographics of Those With and Without Childhood Exposure to Gender Identity Conversion Efforts^a

Characteristic	No. (%)		P Value ^c
	Reported Exposure to Conversion Efforts Before Age 10 y (n = 206) ^b	Reported Exposure to Any Lifetime Therapy Without Conversion Efforts (n = 15 882)	
Race/ethnicity			
Alaska Native or American Indian	5 (2.4)	133 (0.8)	.04
Asian, Asian American, Native Hawaiian, or Pacific Islander	3 (1.5)	511 (3.2)	.22
Biracial, multiracial or other	8 (3.9)	288 (1.8)	.05
Black or African American	5 (2.4)	1926 (12.1)	<.001
Latino, Latina, or Hispanic	24 (11.6)	2219 (14.0)	.39
White, Middle Eastern, or North African	161 (78.2)	10 805 (68.0)	.002
Census age cohort, y			
18-24	17 (8.2)	1527 (9.6)	.59
25-44	110 (53.4)	5887 (37.1)	<.001
45-64	76 (36.9)	6141 (38.7)	.65
≥65	3 (1.5)	2326 (14.6)	<.001
Family support of gender identity			
Supportive	59 (28.6)	8287 (52.2)	<.001
Neutral	37 (18.0)	2659 (16.7)	.71
Unsupportive	80 (38.8)	2184 (13.8)	<.001
Not asked	30 (14.6)	2752 (17.3)	.34
Employment status			
Employed	95 (46.1)	9890 (62.3)	<.001
Unemployed	31 (15.0)	1332 (8.4)	<.001
Out of the labor force	77 (37.4)	4578 (28.8)	.01
Unspecified	2 (0.8)	82 (0.5)	.68
Total household income, \$			
No income	10 (4.9)	432 (2.7)	.10
1-9999	47 (22.8)	1608 (10.1)	<.001
10 000-24 999	57 (27.7)	2955 (18.6)	.001
25 000-49 999	32 (15.5)	3692 (23.2)	.01

^aDescriptive statistics for transgender adults who reported receiving any therapy regarding gender identity, with bivariate comparisons for those with and without exposure to conversion efforts before age 10 years.

^bIndividuals with unspecified age of reported exposure to conversion efforts, unspecified exposure to conversion efforts, and unspecified exposure to any therapy (missing data; n = 100) were excluded from this analysis.

^cRao-Scott χ^2 tests were used, and the Mann-Whitney test was used for comparison of age because of nonnormality.

Table 4.

Outcomes for Those With Childhood Exposure to Gender Identity Conversion Efforts^a

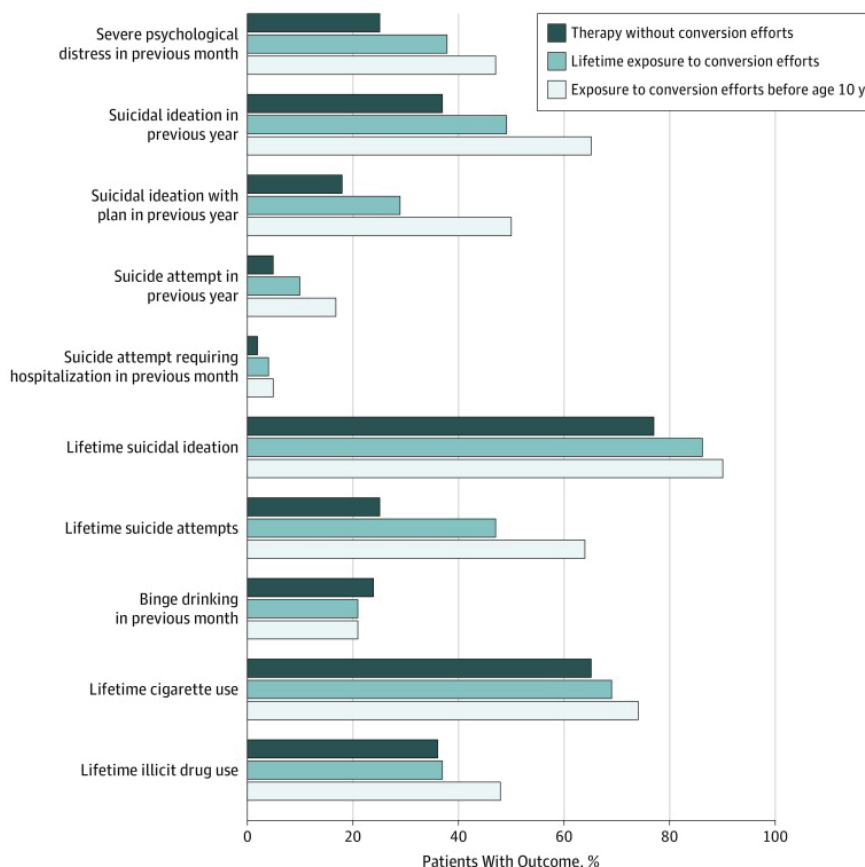
Outcome	Adjusted Odds Ratio (95% CI)	P Value
Suicidality in previous 12 mo		
Ideation	2.03 (1.01-4.07)	<.001
Ideation with plan	2.82 (1.42-5.62)	<.001
Attempt	2.40 (0.87-6.62)	.005
Attempt requiring inpatient hospitalization	1.72 (0.26-11.24)	.34
Suicidality in lifetime		
Ideation	1.90 (0.66-5.52)	.05
Attempts	4.15 (2.44-7.69)	<.001 ^b
Mental health and substance use in previous month		
Severe psychological distress ^c	1.75 (0.72-4.24)	.04
Binge drinking	0.84 (0.33-2.14)	.54
Mental health and substance use in lifetime		
Cigarette use	1.53 (0.66-3.56)	.09
Illicit drug use	1.76 (0.83-3.75)	.01

^aMental health outcomes of transgender adults exposed to gender identity conversion efforts before age 10 years compared with those who discussed gender identity with a professional without conversion efforts in their lifetime, adjusted for age cohort, sex assigned at birth, race/ethnicity, family support of gender identity, employment status, and total household income.

^bOrdinal logistic regression with outcome categories: 0, 1, and 2 or more.

^cKessler Psychological Distress Scale (defined as a score ≥ 13).

Figure.



Mental Health Outcomes Among Those With and Without Exposure to Gender Identity Conversion Efforts

Raw frequencies for outcome variables among those with a lifetime history of non-gender identity conversion efforts therapy, lifetime history of exposure to gender identity conversion efforts, and exposure to conversion efforts before age 10 years. Severe psychological distress in the previous month was defined as a score of 13 or more on the Kessler Psychological Distress Scale, a cutoff that has been previously validated in US samples.¹⁷ Binge drinking was defined as at least 1 or more day of consuming 5 or more standard alcoholic drinks on the same occasion, a threshold for which the rationale in alcohol research among transgender people has been discussed in previous reports.¹⁸ Illicit drug use excludes marijuana use.

Evidence review: Gonadotrophin releasing hormone analogues for children and adolescents with gender dysphoria

This document will help inform Dr Hilary Cass' independent review into gender identity services for children and young people. It was commissioned by NHS England and Improvement who commissioned the Cass review. It aims to assess the evidence for the clinical effectiveness, safety and cost-effectiveness of gonadotrophin releasing hormone (GnRH) analogues for children and adolescents aged 18 years or under with gender dysphoria.

The document was prepared by NICE in October 2020.

The content of this evidence review was up to date on 14 October 2020. See [summaries of product characteristics](#) (SPCs), [British National Formulary](#) (BNF) or the [Medicines and Healthcare products Regulatory Agency](#) (MHRA) or [NICE](#) websites for up-to-date information.

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1. Introduction

This review aims to assess the evidence for the clinical effectiveness, safety and cost-effectiveness of gonadotrophin releasing hormone (GnRH) analogues for children and adolescents aged 18 years or under with gender dysphoria. The review follows the NHS England Specialised Commissioning process and template and is based on the criteria outlined in the PICO framework (see [appendix A](#)). This document will help inform Dr Hilary Cass' independent review into gender identity services for children and young people.

Gender dysphoria in children, also known as gender identity disorder or gender incongruence of childhood ([World Health Organisation 2020](#)), refers to discomfort or distress that is caused by a discrepancy between a person's gender identity (how they see themselves¹ regarding their gender) and that person's sex assigned at birth and the associated gender role, and/or primary and secondary sex characteristics ([Diagnostic and Statistical Manual of Mental Disorders 2013](#)).

GnRH analogues suppress puberty by delaying the development of secondary sexual characteristics. The intention is to alleviate the distress associated with the development of secondary sex characteristics, thereby providing a time for on-going discussion and exploration of gender identity before deciding whether to take less reversible steps. In England, the GnRH analogue triptorelin (a synthetic decapeptide analogue of natural GnRH, which has marketing authorisations for the treatment of prostate cancer, endometriosis and precocious puberty [onset before 8 years in girls and 10 years in boys]) is used for this purpose. The use of triptorelin for children and adolescents with gender dysphoria is [off-label](#).

For children and adolescents with gender dysphoria it is recommended that management plans are tailored to the needs of the individual, and aim to ameliorate the potentially negative impact of gender dysphoria on general developmental processes, support young people and their families in managing the uncertainties inherent in gender identity development and provide on-going opportunities for exploration of gender identity. The plans may also include psychological support and exploration and, for some individuals, the use of GnRH analogues in adolescence to suppress puberty; this may be followed later with gender-affirming hormones of the desired sex ([NHS England 2013](#)).

2. Executive summary of the review

Nine observational studies were included in the evidence review. Five studies were retrospective observational studies ([Brik et al. 2020](#), [Joseph et al. 2019](#), [Khatchadourian et al. 2014](#), [Klink et al. 2015](#), [Vlot et al. 2017](#)), 3 studies were prospective longitudinal observational studies ([Costa et al. 2015](#), [de Vries et al. 2011](#), [Schagen et al. 2016](#)) and 1 study was a cross-sectional study ([Staphorsius et al. 2015](#)). Two studies (Costa et al. 2015

¹ Gender refers to the roles, behaviours, activities, attributes and opportunities that any society considers appropriate for girls and boys, and women and men ([World Health Organisation, Health Topics: Gender](#)).

and Staphorsius et al. 2015) provided comparative evidence and the remaining 7 studies used within-person, before and after comparisons.

The terminology used in this topic area is continually evolving and is different depending on stakeholder perspectives. In this evidence review we have used the phrase 'people's assigned sex at birth' rather than natal or biological sex, gonadotrophin releasing hormone (GnRH) analogues rather than 'puberty blockers' and gender-affirming hormones rather than 'cross sex hormones'. The research studies included in this evidence review may use historical terms which are no longer considered appropriate.

In children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Critical outcomes

The critical outcomes for decision making are the impact on gender dysphoria, mental health and quality of life. The quality of evidence for these outcomes was assessed as very low certainty using modified GRADE.

Impact on gender dysphoria

The study by [de Vries et al. 2011](#) in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones does not affect gender dysphoria (measured using the Utrecht Gender Dysphoria Scale [UGDS]). The mean ($\pm$ SD) gender dysphoria (UGDS) score was not statistically significantly different at baseline compared with follow-up ($n=41$, 53.20 [± 7.91] versus 53.9 [± 17.42], $p=0.333$).

Impact on mental health

The study by [de Vries et al. 2011](#) in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones may reduce depression (measured using the Beck Depression Inventory-II [BDI-II]). The mean ($\pm$ SD) BDI score was statistically significantly lower (improved) from baseline compared with follow-up ($n=41$, 8.31 [± 7.12] versus 4.95 [± 6.72], $p=0.004$).

The study by [de Vries et al. 2011](#) in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones does not affect anger (measured using the Trait Anger Scale [TPI]). The mean ($\pm$ SD) anger (TPI) score was not statistically significantly different at baseline compared with follow-up ($n=41$, 18.29 [± 5.54] versus 17.88 [± 5.24], $p=0.503$).

The study by [de Vries et al. 2011](#) in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones does not affect anxiety (measured using the Trait Anxiety Scale [STAI]). The mean ($\pm$ SD) anxiety (STAI) score was not statistically significantly different at baseline compared with follow-up ($n=41$, 39.43 [± 10.07] versus 37.95 [± 9.38], $p=0.276$).

Impact on quality of life

No evidence was identified.

Important outcomes

The important outcomes for decision making are impact on body image, psychosocial impact, engagement with health care services, impact on extent of and satisfaction with surgery and stopping treatment. The quality of evidence for all these outcomes was assessed as very low certainty using modified GRADE.

Impact on body image

The study by [de Vries et al. 2011](#) in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones does not affect body image (measured using the Body Image Scale [BIS]). The mean [$\pm$ SD] body image (BIS) scores were not statistically significantly different from baseline compared with follow-up for primary sexual characteristics (n=57, 4.10 [$\pm$ 0.56] versus 3.98 [$\pm$ 0.71], p=0.145), secondary sexual characteristics (n=57, 2.74 [$\pm$ 0.65] versus 2.82 [$\pm$ 0.68], p=0.569) or neutral body characteristics (n=57, 2.41 [$\pm$ 0.63] versus 2.47 [$\pm$ 0.56], p=0.620).

Psychosocial impact

The study by [de Vries et al. 2011](#) in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones may improve psychosocial impact over time (measured using the Children's Global Assessment Scale [CGAS]). The mean [$\pm$ SD] CGAS score was statistically significantly higher (improved) from baseline compared with follow-up (n=41, 70.24 [$\pm$ 10.12] versus 73.90 [$\pm$ 9.63], p=0.005).

This study also found that psychosocial functioning may improve over time (measured using the Child Behaviour Checklist [CBCL] and the self-administered Youth Self-Report [YSR]). The mean [$\pm$ SD] CBCL scores were statistically significantly lower (improved) from baseline compared with follow-up for Total T score (n=54, 60.70 [$\pm$ 12.76] versus 54.46 [$\pm$ 11.23], p<0.001), internalising T score (n=54, 61.00 [$\pm$ 12.21] versus 52.17 [$\pm$ 9.81], p<0.001) and externalising T score (n=54, 58.04 [$\pm$ 12.99] versus 53.81 [$\pm$ 11.86], p=0.001). The mean [$\pm$ SD] YSR scores were statistically significantly lower (improved) from baseline compared with follow-up for Total T score (n=54, 55.46 [$\pm$ 11.56] versus 50.00 [$\pm$ 10.56], p<0.001), internalising T score (n=54, 56.04 [$\pm$ 12.49] versus 49.78 [$\pm$ 11.63], p<0.001) and externalising T score (n=54, 53.30 [$\pm$ 11.87] versus 49.98 [$\pm$ 9.35], p=0.009). The proportion of adolescents scoring in the clinical range decreased from baseline to follow up on the CBCL total problem scale (44.4% versus 22.2%, p=0.001) and the internalising scale of the YSR (29.6% versus 11.1%, p=0.017).

The study by [Costa et al. 2015](#) in 201 adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support or continued psychological support only, found that during treatment with GnRH analogues psychosocial impact in terms of global functioning may improve over time (measured using the CGAS). In the group receiving GnRH analogues, the mean [$\pm$ SD] CGAS score was statistically significantly higher (improved) after 6 months (n=60, 64.70 [$\pm$ 13.34]) and 12 months (n=35, 67.40 [$\pm$ 13.39]) compared with baseline (n=101, 58.72 [$\pm$ 11.38], p=0.003 and p<0.001, respectively). However, there was no statistically significant difference in global functioning (CGAS scores) between the group receiving GnRH analogues plus psychological support and the group receiving psychological support only at any time point.

The study by [Staphorsius et al. 2015](#) in 40 adolescents with gender dysphoria (20 of whom were receiving GnRH analogues) gave mean [$\pm$ SD] CBCL scores for each group, but statistical analysis is unclear (transfemales receiving GnRH analogues 57.4 [$\pm$ 9.8], transfemales not receiving GnRH analogues 58.2 [$\pm$ 9.3], transmales receiving GnRH analogues 57.5 [$\pm$ 9.4], transmales not receiving GnRH analogues 63.9 [$\pm$ 10.5]).

Engagement with health care services

The study by [Brik et al. 2018](#) in 143 children and adolescents with gender dysphoria receiving GnRH analogues found that 9 adolescents in the original sampling frame (9/214, 4.2%) were excluded from the study because they stopped attending appointments.

The study by [Costa et al. 2015](#) in 201 adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support or continued psychological support only had a large loss to follow-up over time. The sample size at baseline and 6 months was 201, which dropped by 39.8% to 121 after 12 months and by 64.7% to 71 at 18 months follow-up. No explanation of the reasons for loss to follow-up are reported.

Impact on extent of and satisfaction with surgery

No evidence was identified.

Stopping treatment

The study by [Brik et al. 2018](#) in 143 children and adolescents with gender dysphoria receiving GnRH analogues reported the reasons for stopping GnRH analogues. During the follow-up period 6.2% (9/143) of adolescents had stopped GnRH analogues after a median duration of 0.8 years (range 0.1 to 3.0). Five adolescents stopped treatment because they no longer wished to receive gender-affirming treatment for various reasons. In 4 adolescents (all transmales), GnRH analogues were stopped mainly because of adverse effects (such as mood and emotional lability), although they wanted to continue treatments for gender dysphoria.

The study by [Khatchadourian et al. 2014](#) in 27 adolescents with gender dysphoria who started GnRH analogues reported the reasons for stopping them. Eleven out of 26 where data was available (42%) stopped GnRH analogues during follow up.

In children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Evidence was available for bone density, cognitive development or functioning, and other safety outcomes. The quality of evidence for all these outcomes was assessed as very low certainty using modified GRADE.

Bone density

The study by [Joseph et al. 2019](#) in 70 adolescents with gender dysphoria found that GnRH analogues may reduce the expected increase in lumbar or femoral bone density (measured with the z-score). However, the z-scores were largely within 1 standard deviation of normal,

and actual lumbar or femoral bone density values were not statistically significantly different between baseline and follow-up:

- The mean z-score [$\pm$ SD] for lumbar bone mineral apparent density (BMAD) was statistically significantly lower at 1 year compared with baseline in transfemales (baseline 0.859 [$\pm$ 0.154], 1 year -0.228 [$\pm$ 1.027], $p=0.000$) and transmales (baseline -0.186 [$\pm$ 1.230], 1 year -0.541 [$\pm$ 1.396], $p=0.006$).
- The mean z-score [$\pm$ SD] for lumbar BMAD was statistically significantly lower after receiving GnRH analogues for 2 years compared with baseline in transfemales (baseline 0.486 [$\pm$ 0.809], 2 years -0.279 [$\pm$ 0.930], $p=0.000$) and transmales (baseline -0.361 [$\pm$ 1.439], 2 years -0.913 [$\pm$ 1.318], $p=0.001$).
- The mean z-score [$\pm$ SD] for femoral neck bone mineral density (BMD) was statistically significantly lower after receiving GnRH analogues for 2 years compared with baseline in transfemales (baseline 0.0450 [$\pm$ 0.781], 2 years -0.600 [$\pm$ 1.059], $p=0.002$) and transmales (baseline -1.075 [$\pm$ 1.145], 2 years -1.779 [$\pm$ 0.816], $p=0.001$).

The study by [Klink et al. 2015](#) in 34 adolescents with gender dysphoria found that GnRH analogues may reduce the expected increase in lumbar (transmales only), but not femoral bone density. However, the z-scores are largely within 1 standard deviation of normal. Actual lumbar or femoral bone density values were not statistically significantly different between baseline and follow-up (apart from BMD measurements in transmales):

- The mean z-score [$\pm$ SD] for lumbar BMAD was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales, but was statistically significantly lower when starting gender-affirming hormones in transmales (GnRH analogues 0.28 [$\pm$ 0.90], gender-affirming hormones -0.50 [$\pm$ 0.81], $p=0.004$).

The study by [Vlot et al. 2017](#) in 70 adolescents with gender dysphoria found that GnRH analogues may reduce the expected increase in lumbar or femoral bone density. However, the z-scores were largely within 1 standard deviation of normal. Actual lumbar or femoral bone density values were not statistically significantly different between baseline and follow-up (apart from in transmales with a bone age ≥ 14 years). This study reported change in bone density from starting GnRH analogues to starting gender-affirming hormones by bone age:

- The median z-score [range] for lumbar BMAD in transfemales with a bone age of <15 years was statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (GnRH analogues -0.20 [-1.82 to 1.18], gender-affirming hormones -1.52 [-2.36 to 0.42], $p=0.001$) but was not statistically significantly different in transfemales with a bone age ≥ 15 years.
- The median z-score [range] for lumbar BMAD in transmales with a bone age of <14 years was statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (GnRH analogues -0.05 [-0.78 to 2.94], gender-affirming hormones -0.84 [-2.20 to 0.87], $p=0.003$) and in transmales with a bone age ≥ 14 years (GnRH analogues 0.27 [-1.60 to 1.80], gender-affirming hormones -0.29 [-2.28 to 0.90], $p\leq 0.0001$).

- The median z-score [range] for femoral neck BMAD in transfemales with a bone age of <15 years was not statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (GnRH analogues -0.71 [-3.35 to 0.37], gender-affirming hormones -1.32 [-3.39 to 0.21], $p \leq 0.1$) or in transfemales with a bone age ≥ 15 years (GnRH analogues -0.44 [-1.37 to 0.93], gender-affirming hormones -0.36 [-1.50 to 0.46]).
- The z-score for femoral neck BMAD in transmales with a bone age of <14 years was not statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (GnRH analogues -0.01 [-1.30 to 0.91], gender-affirming hormone -0.37 [-2.28 to 0.47]) but was statistically significantly lower in transmales with a bone age ≥ 14 years (GnRH analogues 0.27 [-1.39 to 1.32], gender-affirming hormones -0.27 [-1.91 to 1.29], $p=0.002$).

Cognitive development or functioning

The study by [Staphorsius et al. 2015](#) in 40 adolescents with gender dysphoria (20 of whom were receiving GnRH analogues) measured cognitive development or functioning (using an IQ test, and reaction time and accuracy measured using the Tower of London task):

- The mean ($\pm$ SD) IQ in transfemales receiving GnRH analogues was 94.0 (± 10.3) and 109.4 (± 21.2) in the control group. In transmales receiving GnRH analogues the mean ($\pm$ SD) IQ was 95.8 (± 15.6) and 98.5 (± 15.9) in the control group.
- The mean ($\pm$ SD) reaction time in transfemales receiving GnRH analogues was 10.9 (± 4.1) and 9.9 (± 3.1) in the control group. In transmales receiving GnRH analogue it was 9.9 (± 3.1) and 10.0 (± 2.0) in the control group.
- The mean ($\pm$ SD) accuracy score in transfemales receiving GnRH analogues was 73.9 (± 9.1) and 83.4 (± 9.5) in the control group. In transmales receiving GnRH analogues it was 85.7 (± 10.5) and 88.8 (± 9.7) in the control group.

No statistical analyses or interpretation of the results was reported.

Other safety outcomes

The study by [Schagen et al. 2016](#) in 116 adolescents with gender dysphoria found that GnRH analogues do not affect renal or liver function:

- There was no statistically significant difference between baseline and 1 year results for serum creatinine in transfemales, but there was a statistically significant decrease between baseline and 1 year in transmales ($p=0.01$).
- Glutamyl transferase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels did not significantly change from baseline to 12 months of treatment.

The study by [Khatchadourian et al. 2014](#) in 27 adolescents with gender dysphoria who started GnRH analogues narratively reported adverse effects from GnRH analogues in 26 adolescents:

- 1 transmale developed sterile abscesses; they were switched from leuprolide acetate to triptorelin, and this was well tolerated
- 1 transmale developed leg pains and headaches, which eventually resolved
- 1 participant gained 19 kg within 9 months of starting GnRH analogues.

In children and adolescents with gender dysphoria, what is the cost-effectiveness of GnRH analogues compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?

No cost-effectiveness evidence was found for GnRH analogues in children and adolescents with gender dysphoria.

From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may benefit from GnRH analogues more than the wider population of interest?

Some studies reported data separately for the following subgroups of children and adolescents with gender dysphoria: sex assigned at birth males (transfemales) and sex assigned at birth females (transmales). This included some direct comparisons of these subgroups, and differences were largely seen at baseline as well as follow up. No evidence was found for other specified subgroups.

Sex assigned at birth males (transfemales)

Impact on gender dysphoria

The study by [Costa et al. 2015](#) in 201 adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support or continued psychological support only, found that gender dysphoria (measured using the UGDS) in sex assigned at birth males is lower than in sex assigned at birth females. Sex assigned at birth males had a statistically significantly lower (improved) mean [$\pm$ SD] UGDS score of 51.6 [$\pm$ 9.7] compared with sex assigned at birth females (56.1 [$\pm$ 4.3], $p < 0.001$), but it was not reported if this was at baseline or follow-up.

The study by [de Vries et al. 2011](#) in 70 adolescents with gender dysphoria found that gender dysphoria (measured using the UGDS) in sex assigned at birth males is lower than in sex assigned at birth females at baseline and follow up. The mean [$\pm$ SD] UGDS score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n =not reported, mean UGDS score: 47.95 [$\pm$ 9.70] versus 56.57 [$\pm$ 3.89]) and follow up (n =not reported, 49.67 [$\pm$ 9.47] versus 56.62 [$\pm$ 4.00]); between sex difference $p < 0.001$).

Impact on mental health

The study by [de Vries et al. 2011](#) in 70 adolescents with gender dysphoria found that the impact on mental health (depression, anger and anxiety) may be different in sex assigned at birth males compared with sex assigned at birth females. Over time there was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for depression, but sex assigned at birth males had statistically significantly lower levels of anger and anxiety than sex assigned at birth females at baseline and follow up.

- The mean [$\pm$ SD] depression (BDI-II) score was not statistically significantly different in sex assigned at birth males compared with sex assigned at birth females at baseline (n =not reported, mean BDI score [$\pm$ SD]: 5.71 [$\pm$ 4.31] versus 10.34 [$\pm$ 8.24]) and follow-up (n =not reported, 3.50 [$\pm$ 4.58] versus 6.09 [$\pm$ 7.93]), between sex difference $p = 0.057$

- The mean [$\pm$ SD] anger (TPI) score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean TPI score [$\pm$ SD]: 5.22 [$\pm$ 2.76] versus 6.43 [$\pm$ 2.78]) and follow-up (n=not reported, 5.00 [$\pm$ 3.07] versus 6.39 [$\pm$ 2.59]), between sex difference $p=0.022$
- The mean [$\pm$ SD] anxiety (STAI) score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean STAI score [$\pm$ SD]: 4.33 [$\pm$ 2.68] versus 7.00 [$\pm$ 2.36]) and follow-up (n=not reported, 4.39 [$\pm$ 2.64] versus 6.17 [$\pm$ 2.69]), between sex difference $p<0.001$.

Impact on body image

The study by [de Vries et al. 2011](#) in 70 adolescents with gender dysphoria found that the impact on body image may be different in sex assigned at birth males compared with sex assigned at birth females. Sex assigned at birth males are less dissatisfied with their primary and secondary sex characteristics than sex assigned at birth females at both baseline and follow up, but the satisfaction with neutral body characteristics is not different.

- The mean [$\pm$ SD] BIS score for primary sex characteristics was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean BIS score [$\pm$ SD]: 4.02 [$\pm$ 0.61] versus 4.16 [$\pm$ 0.52]) and follow up (n=not reported, 3.74 [$\pm$ 0.78] versus 4.17 [$\pm$ 0.58]) between sex difference $p=0.047$.
- The mean [$\pm$ SD] BIS score for secondary sex was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean BIS score [$\pm$ SD]: 2.66 [$\pm$ 0.50] versus 2.81 [$\pm$ 0.76]) and follow up (n=not reported, 2.39 [$\pm$ 0.69] versus 3.18 [$\pm$ 0.42]), between sex difference $p=0.001$.
- The mean [$\pm$ SD] BIS score for neutral body characteristics was not statistically significantly different in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, 2.60 [$\pm$ 0.58] versus 2.24 [$\pm$ 0.62], between sex difference $p=0.777$).

Psychosocial impact

The study by [Costa et al. 2015](#) in 201 adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support or continued psychological support only, found that sex assigned at birth males had statistically significant lower mean [$\pm$ SD] CGAS scores at baseline compared with sex assigned at birth females (n=201, 55.4 [$\pm$ 12.7] versus 59.2 [$\pm$ 11.8], $p=0.03$), but no conclusions could be drawn.

The study by [de Vries et al. 2011](#) in 70 adolescents with gender dysphoria found that psychosocial impact in terms of global functioning (CGAS) and psychosocial functioning (CBCL and YSR) may be different in sex assigned at birth males compared with sex assigned at birth females, but no conclusions could be drawn.

- There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females (at baseline or follow up) for the CBCL Total T

score, the CBCL internalising T score, the YSR Total T score or the YSR internalising T score.

- Sex assigned at birth males had statistically higher mean [$\pm$ SD] CGAS scores compared with sex assigned at birth females at baseline (n=54, 73.10 [$\pm$ 8.44] versus 67.25 [$\pm$ 11.06]) and follow up (n=54, 77.33 [$\pm$ 8.69] versus 70.30 [$\pm$ 9.44]), between sex difference p=0.021.
- Sex assigned at birth males had statistically lower mean [$\pm$ SD] CBCL externalising T scores compared with sex assigned at birth females at baseline (n=54, 54.71 [$\pm$ 12.91] versus 60.70 [$\pm$ 12.64]) and follow up (n=54, 48.75 [$\pm$ 10.22] versus 57.87 [$\pm$ 11.66]), between sex difference p=0.015.
- Sex assigned at birth males had statistically lower mean [$\pm$ SD] YSR externalising T scores compared with sex assigned at birth females at both baseline (n=54, 48.72 [$\pm$ 11.38] versus 57.24 [$\pm$ 10.59]) and follow up (n=54, 46.52 [$\pm$ 9.23] versus 52.97 [$\pm$ 8.51]), between sex difference p=0.004.

Bone density

The studies by [Joseph et al. 2019](#), [Klink et al. 2015](#) and [Vlot et al. 2017](#) provided evidence on bone density in sex assigned at birth males (see above for details).

Cognitive development or functioning

The study by [Staphorsius et al. 2015](#) provided evidence on cognitive development or functioning in sex assigned at birth males (see above for details).

Other safety outcomes

The study by [Schagen et al. 2016](#) provided evidence on renal function in sex assigned at birth males (see above).

Sex assigned at birth females (transmales)

Impact on gender dysphoria

The studies by [de Vries et al. 2011](#) and [Costa et al. 2015](#) found that gender dysphoria (measured using the UGDS) in sex assigned at birth females is higher than in sex assigned at birth males at baseline and follow up (see above for details).

Impact on mental health

The study by [de Vries et al. 2011](#) found that the impact on mental health (depression, anger and anxiety) may be different in sex assigned at birth females compared with sex assigned at birth males. Over time there was no statistically significant difference between sex assigned at birth females and sex assigned at birth males for depression, but sex assigned at birth females had statistically significantly greater levels of anger and anxiety than sex assigned at birth males at both baseline and follow up (see above for details).

Impact on body image

The study by [de Vries et al. 2011](#) found that the impact on body image may be different in sex assigned at birth females compared with sex assigned at birth males. Sex assigned at birth females are more dissatisfied with their primary and secondary sex characteristics than sex assigned at birth males at both baseline and follow up, but the satisfaction with neutral body characteristics is not different (see above for details).

Psychosocial impact

The studies by [de Vries et al. 2011](#) and [Costa et al. 2015](#) found that psychosocial impact in terms of global functioning (CGAS) and psychosocial functioning (CBCL and YSR) may be different in sex assigned at birth females compared with sex assigned at birth males, but no conclusions could be drawn (see above for details).

Bone density

The studies by [Joseph et al. 2019](#), [Klink et al. 2015](#) and [Vlot et al. 2017](#) provided evidence on bone density in sex assigned at birth females (see above for details).

Cognitive development or functioning

The study by [Staphorsius et al. 2015](#) provided evidence on cognitive development or functioning in sex assigned at birth females (see above for details).

Other safety outcomes

The study by [Schagen et al. 2016](#) provided evidence on renal function in sex assigned at birth females (see above for details).

From the evidence selected:

- (a) **what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?**
- (b) **what were the ages at which participants commenced treatment with GnRH analogues?**
- (c) **what was the duration of treatment with GnRH analogues?**

All studies that reported diagnostic criteria for gender dysphoria (6/9 studies) used the version of the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria that was in use at the time. In 5 studies ([Costa et al. 2015](#), [Klink et al. 2015](#), [Schagen et al. 2016](#), [Staphorsius et al. 2015](#) and [Vlot et al. 2017](#)) the DSM-fourth edition, text revision (IV-TR) criteria were used. The study by [Brik et al. 2020](#) used DSM-V criteria. It was not reported how gender dysphoria was defined in the remaining 3 studies.

The studies show variation in the age (11 to 18 years old) at which children and adolescents with gender dysphoria started GnRH analogues.

Most studies did not report the duration of treatment with GnRH analogues ([Joseph et al. 2019](#), [Khatchadourian et al. 2014](#), [Vlot et al. 2017](#), [Costa et al. 2015](#), [de Vries et al. 2011](#), [Schagen et al. 2016](#)), but where this was reported ([Brik et al. 2020](#), [Klink et al. 2015](#), [Staphorsius et al. 2015](#)) there was a wide variation ranging from a few months to about 5 years.

Discussion

A key limitation to identifying the effectiveness and safety of GnRH analogues for children and adolescents with gender dysphoria is the lack of reliable comparative studies. The lack of clear, expected outcomes from treatment with a GnRH analogue (the purpose of which is to suppress secondary sexual characteristics which may cause distress from unwanted pubertal changes) also makes interpreting the evidence difficult.

The studies included in this evidence review are all small, uncontrolled observational studies, which are subject to bias and confounding, and all the results are of very low certainty using modified GRADE. They all reported physical and mental health comorbidities and concomitant treatments very poorly. All the studies are from a limited number of, mainly European, care facilities. They are described as either tertiary referral or expert services but the low number of services providing such care and publishing evidence may bias the results towards the outcomes in these services only and limit extrapolation.

Many of the studies did not report statistical significance or confidence intervals. Changes in outcome scores for clinical effectiveness and bone density were assessed with regards to statistical significance. However, there is relatively little interpretation of whether the changes in outcomes are clinically meaningful.

In the observational, retrospective studies providing evidence on bone density, participants acted as their own controls and change in bone density was determined between starting GnRH analogues and follow up. Observational studies such as these can only show an association with GnRH analogues and bone density; they cannot show that GnRH analogues caused any differences in bone density seen. Because there was no comparator group and participants acted as their own controls, it is not known whether the findings are associated with GnRH analogues or due to changes over time.

Conclusion

The results of the studies that reported impact on the critical outcomes of gender dysphoria and mental health (depression, anger and anxiety), and the important outcomes of body image and psychosocial impact (global and psychosocial functioning), in children and adolescents with gender dysphoria are of very low certainty using modified GRADE. They suggest little change with GnRH analogues from baseline to follow-up.

Studies that found differences in outcomes could represent changes that are either of questionable clinical value, or the studies themselves are not reliable and changes could be due to confounding, bias or chance. It is plausible, however, that a lack of difference in scores from baseline to follow-up is the effect of GnRH analogues in children and adolescents with gender dysphoria, in whom the development of secondary sexual characteristics might be expected to be associated with an increased impact on gender dysphoria, depression, anxiety, anger and distress over time without treatment. The study by [de Vries et al. 2011](#) reported statistically significant reductions in the Child Behaviour Checklist (CBCL) and Youth Self-Report (YSR) scores from baseline to follow up, which include measures of distress. As the aim of GnRH analogues is to reduce distress caused by the development of secondary sexual characteristics, this may be an important finding. However, as the studies all lack appropriate controls who were not receiving GnRH analogues, any positive changes could be a regression to mean.

The results of the studies that reported bone density outcomes suggest that GnRH analogues may reduce the expected increase in bone density (which is expected during puberty). However, as the studies themselves are not reliable, the results could be due to confounding, bias or chance. While controlled trials may not be possible, comparative studies are needed to understand this association and whether the effects of GnRH analogues on bone density are seen after they are stopped. All the studies that reported safety outcomes provided very low certainty evidence.

No cost-effectiveness evidence was found to determine whether or not GnRH analogues are cost-effective for children and adolescents with gender dysphoria.

The results of the studies that reported outcomes for subgroups of children and adolescents with gender dysphoria, suggest there may be differences between sex assigned at birth males (transfemales) and sex assigned at birth females (transmales).

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
2. For children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
3. For children and adolescents with gender dysphoria, what is the cost-effectiveness of GnRH analogues compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?
4. From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may derive more (or less) advantage from treatment with GnRH analogues than the wider population of children and adolescents with gender dysphoria?
5. From the evidence selected,
 - a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?
 - b) what were the ages at which participants commenced treatment with GnRH analogues?
 - c) what was the duration of treatment with GnRH analogues?

See [appendix A](#) for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 23 July 2020.

See [appendix B](#) for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO framework. Full text references of potentially

relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See [appendix C](#) for evidence selection details and [appendix D](#) for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See appendices [E](#) and [F](#) for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See [appendix G](#) for GRADE Profiles.

4. Summary of included studies

Nine observational studies were identified for inclusion. Five studies were retrospective observational studies ([Brik et al. 2020](#), [Joseph et al. 2019](#), [Khatchadourian et al. 2014](#), [Klink et al. 2015](#), [Vlot et al. 2017](#)), 3 studies were prospective longitudinal observational studies ([Costa et al. 2015](#), [de Vries et al. 2011](#), [Schagen et al. 2016](#)) and 1 study was a cross-sectional study ([Staphorsius et al. 2015](#)).

The terminology used in this topic area is continually evolving and is different depending on stakeholder perspectives. In this evidence review we have used the phrase 'people's assigned sex at birth' rather than natal or biological sex, gonadotrophin releasing hormone (GnRH) analogues rather than 'puberty blockers' and gender-affirming hormones rather than 'cross sex hormones'. The research studies included in this evidence review may use historical terms which are no longer considered appropriate.

Table 1 provides a summary of these included studies and full details are given in [appendix E](#).

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Brik et al. 2020 Retrospective observational single-centre study Netherlands	The study was conducted at the Curium-Leiden University Medical Centre gender clinic in Leiden, the Netherlands and involved adolescents with gender dysphoria. The sample size was 143 adolescents (median age at start of treatment was 15.0 years, range 11.1 to 18.6 years in transfemales; 16.1 years, range 10.1 to 17.9 years in transmales) from a sampling frame of 269 children and adolescents registered at the clinic between November 2010 and January 2018.	Intervention 143 children and adolescents receiving GnRH analogues (no specific treatment, dose, route or frequency of administration reported). The median duration was 2.1 years (range 1.6–2.8 years). Comparison No comparator.	Critical Outcomes - No critical outcomes reported Important outcomes - Stopping treatment

Study	Population	Intervention and comparison	Outcomes reported
	Participants were included in the study if they were diagnosed with gender dysphoria according to the DSM-5 criteria, registered at the clinic, were prepubertal and within the appropriate age range, and had started GnRH analogues. No concomitant treatments were reported.		
Costa et al. 2015 Prospective longitudinal observational single centre cohort study United Kingdom	The study was conducted at the Gender Identity Development Service in London and involved adolescents with gender dysphoria. The sample size was 201 adolescents (mean [±SD] age 15.52±1.41 years, range 12 to 17 years) from a sampling frame of 436 consecutive adolescents referred to the service between 2010 and 2014. The mean [±SD] age at the start of GnRH analogues was 16.48 [±1.26] years, range 13 to 17 years. Participants were invited to participate following a 6-month diagnostic process using DSM-IV-TR criteria. No concomitant treatments were reported.	Intervention 101 adolescents assessed as being immediately eligible for GnRH analogues (no specific treatment, dose or route of administration reported) plus psychological support. The average duration of treatment was approximately 12 months (no exact figure given). Comparison 100 adolescents assessed as not immediately eligible for GnRH analogues (more time needed to make the decision to start GnRH analogues) who had psychological support only. None received GnRH analogues throughout the study.	Critical Outcomes - No critical outcomes reported Important outcomes - Psychosocial impact
de Vries et al. 2011 Prospective longitudinal observational single centre before and after study Netherlands	The study was conducted at the Amsterdam gender identity clinic of the VU University Medical Centre and involved adolescents who were defined as “transsexual”. The sample size was 70 adolescents receiving GnRH analogues (mean age [±SD] at assessment 13.6±1.8 years) from a sampling frame of 196 consecutive adolescents referred to the service between 2000 and 2008. Participants were invited to participate if they subsequently started gender-affirming hormones between 2003 and 2009. No diagnostic criteria or concomitant treatments were reported.	Intervention 70 individuals assessed at baseline (T0) before the start of GnRH analogues (no specific treatment, dose or route of administration reported). Comparison No comparator.	Critical Outcomes - Gender dysphoria - Mental health (depression, anger and anxiety) Important outcomes - Body image - Psychosocial impact

Study	Population	Intervention and comparison	Outcomes reported
Joseph et al. 2019 Retrospective longitudinal observational single centre study United Kingdom	This study was conducted at the Early intervention clinic at University College London Hospital (all participants had been seen at the Gender Identity Development Service in London) and involved adolescents with gender dysphoria. The sample size was 70 adolescents with gender dysphoria (no diagnostic criteria described) all offered GnRH analogues. The mean age at the start of treatment was 13.2 years (SD ± 1.4) for transfemales and 12.6 years (SD ± 1.0) for transmales. Details of the sampling frame were not reported. Further details of how the sample was drawn are not reported. No concomitant treatments were reported.	Intervention GnRH analogues. No specific treatment, duration, dose or route of administration reported. Comparison No comparator.	Critical Outcomes - No critical outcomes reported Important outcomes - Safety: bone density
Khatchadourian et al. 2014 Retrospective observational chart review single centre study Canada	This study was conducted at the Endocrinology and Diabetes Unit at British Columbia Children's Hospital, Canada and involved youths with gender dysphoria. The sample size was 27 young people with gender dysphoria who started GnRH analogues (at mean age 14.7 [SD ± 1.9] years) out of 84 young people seen at the unit between 1998 and 2011. Diagnostic criteria and concomitant treatments were not reported.	Intervention 84 young people with gender dysphoria. For GnRH analogues no specific treatment, duration, dose or route of administration reported. Comparison No comparator.	Critical Outcomes - No critical outcomes reported Important outcomes - Stopping treatment - Safety: adverse effects
Klink et al. 2015 Retrospective longitudinal observational single centre study Netherlands	This study was conducted in the Netherlands at a tertiary referral centre. It is unclear which centre this was. The sample size was 34 adolescents (mean age 14.9 [SD ± 1.9] years for transfemales and 15.0 [SD ± 2.0] years for transmales at start of GnRH analogues). Details of the sampling frame are not reported. Participants were included if they met DSM-IV-TR criteria for gender identity disorder of adolescence and had been treated with GnRH analogues and gender-affirming hormones during their pubertal years. No concomitant treatments were reported.	Intervention The intervention was GnRH analogue monotherapy (triptorelin 3.75 mg subcutaneously every 4 weeks) followed by gender-affirming hormones with discontinuation of GnRH analogues after gonadectomy. Duration of GnRH analogues was 1.3 years (range 0.5 to 3.8 years) in transfemales and 1.5 years (0.25 to 5.2 years) in transmales. Comparison No comparator.	Critical Outcomes - No critical outcomes reported Important outcomes - Safety: bone density

Study	Population	Intervention and comparison	Outcomes reported
Schagen et al. 2016 Prospective longitudinal study Netherlands	This study was conducted at the Centre of Expertise on Gender Dysphoria at the VU University Medical Centre (Amsterdam, Netherlands) and involved adolescents with gender dysphoria. The sample size was 116 adolescents (median age [range] 13.6 years [11.6 to 17.9] in transfemales and 14.2 years [11.1 to 18.6] in transmales during first year of GnRH analogues) out of 128 adolescents who started GnRH analogues. Participants were included if they met DSM-IV-TR criteria for gender dysphoria, had lifelong extreme gender dysphoria, were psychologically stable and were living in a supportive environment. No concomitant treatments were reported.	Intervention The intervention was GnRH analogue monotherapy (triptorelin 3.75 mg at 0, 2 and 4 weeks followed by intramuscular injections every 4 weeks, for at least 3 months). Comparison No comparator.	Critical Outcomes - No critical outcomes reported Important outcomes - Safety: liver and renal function.
Staphorsius et al. 2015 Cross-sectional (single time point) assessment single centre study Netherlands	This study was conducted at the VU University Medical Centre (Amsterdam, Netherlands) and involved adolescents with gender dysphoria. The sample size was 85, of whom 40 were adolescents with gender dysphoria (20 of whom were being treated with GnRH analogues) and 45 were controls without gender dysphoria (not further reported here). Mean ($\pm$SD) age 15.1 ($\pm$2.4) years in transfemales and 15.8 ($\pm$1.9) years in transmales. Details of the sampling frame are not reported. Participants were included if they were diagnosed with Gender Identity Disorder according to the DSM-IV-TR and at least 12 years old and Tanner stage of at least B2 or G2 to G3 with measurable oestradiol and testosterone levels in girls and boys, respectively. No concomitant treatments were reported.	Intervention The intervention was a GnRH analogue (triptorelin 3.75 mg every 4 weeks subcutaneously or intramuscularly). The mean duration of treatment was 1.6 years (SD $\pm$1.0). Comparison Adolescents with gender dysphoria not treated with GnRH analogues.	Critical Outcomes - No critical outcomes reported Important outcomes - Psychosocial impact - Safety: cognitive functioning
Vlot et al. 2017 Retrospective observational data analysis study	This study was conducted at the VU University Medical Centre (Amsterdam, Netherlands) and involved adolescents with gender dysphoria. The sample size was 70 adolescents (median age [range] 15.1 years [11.7 to 18.6] for	Intervention The intervention was a GnRH analogue (triptorelin 3.75 mg every 4 weeks subcutaneously). Comparison No comparator.	Critical Outcomes No critical outcomes reported Important outcomes

Study	Population	Intervention and comparison	Outcomes reported
Netherlands	transmales and 13.5 years [11.5 to 18.3] for transfemales at start of GnRH analogues). Details of the sampling frame are not reported. Participants were included if they had a diagnosis of gender dysphoria according to DSM-IV-TR criteria who were receiving GnRH analogues and then gender-affirming hormones. No concomitant treatments were reported.		Safety: bone density
Abbreviations: DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision; GnRH, Gonadotrophin releasing hormone; SD, Standard deviation.			

5. Results

In children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Impact on gender dysphoria Certainty of evidence: very low	This is a critical outcome because gender dysphoria in children and adolescents is associated with significant distress and problems with functioning. One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on gender dysphoria in adolescents, measured using the Utrecht Gender Dysphoria Scale (UGDS). The UGDS is a validated screening tool for both adolescents and adults to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. The higher the UGDS score the greater the gender dysphoria. The study measured the impact on gender dysphoria at 2 time points: - before starting a GnRH analogue (mean [$\pm$SD] age: 14.75 [$\pm$1.92] years), and - shortly before starting gender-affirming hormones (mean [$\pm$SD] age: 16.64 [$\pm$1.90] years). The mean ($\pm$SD) UGDS score was not statistically significantly different at baseline compared with follow-up (n=41, 53.20 [$\pm$7.91] versus 53.9 [$\pm$17.42], p=0.333) (VERY LOW).

	This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, does not affect gender dysphoria.
Impact on mental health: depression Certainty of evidence: very low	This is a critical outcome because self-harm and thoughts of suicide have the potential to result in significant physical harm and, for completed suicides, the death of the young person. One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on depression in children and adolescents with gender dysphoria. Depression was measured using the Beck Depression Inventory-II (BDI-II). The BDI-II is a valid, reliable, and widely used tool for assessing depressive symptoms. There are no specific scores to categorise depression severity, but it is suggested that 0 to 13 is minimal symptoms, 14 to 19 is mild depression, 20 to 28 is moderate depression, and severe depression is 29 to 63. The study provided evidence for depression measured at 2 time points: • before starting a GnRH analogue (mean [$\pm$SD] age: 14.75 [$\pm$1.92] years), and • shortly before starting gender-affirming hormones (mean [$\pm$SD] age: 16.64 [$\pm$1.90] years). The mean ($\pm$SD) depression (BDI) score was statistically significantly lower (improved) from baseline compared with follow-up (n=41, 8.31 [$\pm$7.12] versus 4.95 [$\pm$6.72], p=0.004) (VERY LOW). This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, may reduce depression.
Impact on mental health: anger Certainty of evidence: very low	This is a critical outcome because self-harm and thoughts of suicide have the potential to result in significant physical harm and, for completed suicides, the death of the young person. One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on anger in children and adolescents with gender dysphoria. Anger was measured using the Trait Anger Scale of the State-Trait Personality Inventory (TPI). This is a validated 20-item inventory tool which measures the intensity of anger as the disposition to experience angry feelings as a personality trait. Higher scores indicate greater anger. The study provided evidence for anger measured at 2 time points: • before starting a GnRH analogue (mean [$\pm$SD] age: 14.75 [$\pm$1.92] years), and • shortly before starting gender-affirming hormones (mean [$\pm$SD] age: 16.64 [$\pm$1.90] years). The mean ($\pm$SD) anger (TPI) score was not statistically significantly different at baseline compared with follow-up (n=41, 18.29 [$\pm$5.54] versus 17.88 [$\pm$5.24], p=0.503) (VERY LOW). This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, does not affect anger.

Impact on mental health: anxiety Certainty of evidence: very low	This is a critical outcome because self-harm and thoughts of suicide have the potential to result in significant physical harm and, for completed suicides, the death of the young person. One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on anxiety in children and adolescents with gender dysphoria. Anxiety was measured using the Trait Anxiety Scale of the State-Trait Personality Inventory (STAI). This is a validated and commonly used measure of trait and state anxiety. It has 20 items and can be used in clinical settings to diagnose anxiety and to distinguish it from depressive illness. Higher scores indicate greater anxiety. The study provided evidence for anxiety at 2 time points: • before starting a GnRH analogue (mean [$\pm$SD] age: 14.75 [$\pm$1.92] years), and • shortly before starting gender-affirming hormones (mean [$\pm$SD] age: 16.64 [$\pm$1.90] years). The mean ($\pm$SD) anxiety (STAI) score was not statistically significantly different at baseline compared with follow-up (n=41, 39.43 [$\pm$10.07] versus 37.95 [$\pm$9.38], p=0.276) (VERY LOW). This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, does not affect levels of anxiety.
Quality of life	This is a critical outcome because gender dysphoria in children and adolescents may be associated with a significant reduction in health-related quality of life. No evidence was identified.
Important outcomes	
Impact on body image Certainty of evidence: very low	This is an important outcome because some children and adolescents with gender dysphoria may want to take steps to suppress features of their physical appearance associated with their sex assigned at birth or accentuate physical features of their desired gender. One uncontrolled, prospective observational longitudinal study provided evidence relating to the impact on body image (de Vries et al. 2011). Body image was measured using the Body Image Scale (BIS) which is a validated 30-item scale covering 3 aspects: primary, secondary and neutral body characteristics. Higher scores represent a higher degree of body dissatisfaction. The study (de Vries et al. 2011) provided evidence for body image measured at 2 time points: • before starting a GnRH analogue (mean [$\pm$SD] age: 14.75 [$\pm$1.92] years), and • shortly before starting gender-affirming hormones (mean [$\pm$SD] age: 16.64 [$\pm$1.90] years). The mean ($\pm$SD) body image (BIS) scores for were not statistically significantly different from baseline compared with follow-up for:

	• primary sexual characteristics (n=57, 4.10 [$\pm$0.56] versus 3.98 [$\pm$0.71], p=0.145) • secondary sexual characteristics (n=57, 2.74 [$\pm$0.65] versus 2.82 [$\pm$0.68], p=0.569) • neutral body characteristics (n=57, 2.41 [$\pm$0.63] versus 2.47 [$\pm$0.56], p=0.620) (VERY LOW). This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender affirming hormones, does not affect body image.
Psychosocial impact: global functioning Certainty of evidence: very low	This is an important outcome because gender dysphoria in children and adolescents is associated with internalising and externalising behaviours, and emotional and behavioural problems which may impact on social and occupational functioning. One uncontrolled, observational, prospective cohort study (de Vries et al 2011) and one prospective cross-sectional cohort study (Costa et al. 2015) provided evidence relating to psychosocial impact in terms of global functioning. Global functioning was measured using the Children's Global Assessment Scale (CGAS). The CGAS tool is a validated measure of global functioning on a single rating scale from 1 to 100. Lower scores indicate poorer functioning. One study (de Vries et al. 2011) provided evidence for global functioning (CGAS) at 2 time points: • before starting a GnRH analogue (mean [$\pm$SD] age: 14.75 [$\pm$1.92] years), and • shortly before starting gender-affirming hormones (mean [$\pm$SD] age: 16.64 [$\pm$1.90] years). The mean ($\pm$SD) CGAS score was statistically significantly higher (improved) from baseline compared with follow-up (n=41, 70.24 [$\pm$10.12] versus 73.90 [$\pm$9.63], p=0.005) (VERY LOW). One study (Costa et al. 2015) in adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support (the immediately eligible group) or continued psychological support only (the delayed eligible group who did not receive GnRH analogues) provided evidence for global functioning (CGAS) measured at 4 time points: • at baseline (T0) in both groups, • after 6 months of psychological support in both groups (T1), • after 6 months of GnRH analogues and 12 months of psychological support in the immediately eligible group and 12 months of psychological support only in the delayed eligible group (T2), and • after 18 months of psychological support and 12 months of GnRH analogues in the immediately eligible group and after 18 months of psychological support only in the delayed eligible group (T3). The mean [$\pm$SD] CGAS score was statistically significantly higher (improved) for all adolescents (including those not receiving GnRH analogues) at T1, T2 or T3 compared with baseline (T0).

	For the immediately eligible group (who received GnRH analogues) versus the delayed eligible group (who did not receive GnRH analogues) there were no statistically significant differences in CGAS scores between the 2 groups at baseline T0 (n=201, p=0.23), T1 (n=201, p=0.73), T2 (n=121, p=0.49) or T3 (n=71, p=0.14) time points. For the immediately eligible group (who received GnRH analogues), the mean ($\pm$SD) CGAS score was not statistically significantly different at: • T1 compared with T0 • T2 compared with T1 • T3 compared with T2. The mean ($\pm$SD) CGAS score was statistically significantly higher (improved) at: • T2 compared with T0 (n=60, 64.70 [$\pm$13.34] versus n=101, 58.72 [$\pm$11.38], p=0.003) • T3 compared with T0 (n=35, 67.40 [$\pm$13.39] versus n=101, 58.72 [$\pm$11.38], p<0.001) • T3 compared with T1 (n=35, 67.40 [$\pm$13.93] versus n=101, 60.89 [$\pm$12.17], p<0.001) (VERY LOW). These studies provide very low certainty evidence that during treatment with GnRH analogues, global functioning may improve over time. However, there was no statistically significant difference in global functioning between GnRH analogues plus psychological support compared with psychological support only at any time point.
Psychosocial impact: psychosocial functioning Certainty of evidence: very low	This is an important outcome because gender dysphoria in children and adolescents is associated with internalising and externalising behaviours, and emotional and behavioural problems which may impact on social and occupational functioning. Two studies provided evidence for this outcome. One uncontrolled, observational, prospective cohort study (de Vries et al. 2011) and 1 cross-sectional observational study (Staphorsius et al. 2015) assessed psychosocial functioning using the Child Behaviour Checklist (CBCL) and the self-administered Youth Self-Report (YSR). The CBCL is a checklist parents complete to detect emotional and behavioural problems in children and adolescents. YSR is similar but is self-completed by the child or adolescent. The scales consist of a Total problems score, which is the sum of the scores of all the problem items. An internalising problem scale sums the anxious/depressed, withdrawn-depressed, and somatic complaints scores while the externalising problem scale combines rule-breaking and aggressive behaviour. The standard scores are scaled so that 50 is average for the child or adolescent's age and gender, with a SD of 10 points. Higher scores indicate greater problems, with a T-score above 63 considered to be in the clinical range. One study (de Vries et al. 2011) provided evidence for psychosocial functioning (CBCL and YSR scores) at 2 time points: • before starting a GnRH analogue (mean [$\pm$SD] age: 14.75 [$\pm$1.92] years), and

	• shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). At follow up, the mean (±SD) CBCL scores were statistically significantly lower (improved) compared with baseline for: • Total T score (n=54, 60.70 [±12.76] versus 54.46 [±11.23], p<0.001 • Internalising T score (n=54, 61.00 [±12.21] versus 52.17 [±9.81], p<0.001) • Externalising T score (n=54, 58.04 [±12.99] versus 53.81 [±11.86], p=0.001). At follow up, the mean (±SD) YSR scores were statistically significantly lower (improved) compared with baseline for: • Total T score (n=54, 55.46 [±11.56] versus 50.00 [±10.56], p<0.001) • Internalising T score (n=54, 56.04 [±12.49] versus 49.78 [±11.63], p<0.001) • Externalising T score (n=54, 53.30 [±11.87] versus 49.98 [±9.35], p=0.009). The proportion of adolescents scoring in the clinical range decreased from baseline to follow up on the CBCL total problem scale (44.4% versus 22.2%, p=0.001) and the internalising scale of the YSR (29.6% versus 11.1%, p=0.017) (VERY LOW). One study (Staphorsius et al. 2015) assessed CBCL in a cohort of adolescents with gender dysphoria (transfemale: n=18, mean [±SD] age 15.1 [±2.4] years and transmale: n=22, mean [±SD] age 15.8 [±1.9] years) either receiving GnRH analogues (transfemale, n=8 and transmale, n=12), or not receiving GnRH analogues (transfemale, n=10 and transmale, n=10). The mean (±SD) CBCL scores for each group were (statistical analysis unclear): • transfemales (total) 57.8 [±9.2] • transfemales receiving GnRH analogues 57.4 [±9.8] • transfemales not receiving GnRH analogues 58.2 [±9.3] • transmales (total) 60.4 [±10.2] • transmales receiving GnRH analogues 57.5 [±9.4] • transmales not receiving GnRH analogues 63.9 [±10.5] (VERY LOW). These studies provide very low certainty evidence that during treatment with GnRH analogues psychosocial functioning may improve, with the proportion of adolescents in the clinical range for some CBCL and YSR scores decreasing over time.
Engagement with health care services Certainty of evidence: very low	This is an important outcome because patient engagement with health care services will impact on their clinical outcomes. Two uncontrolled observational cohort studies provided evidence relating to loss to follow up, which could be a marker of engagement with health care services (Brik et al. 2018 and Costa et al. 2015).

	In one retrospective study (Brik et al. 2018), 9 adolescents (9/214, 4.2%) who had stopped attending appointments were excluded from the study between November 2010 and July 2019 (VERY LOW). One prospective study (Costa et al. 2015) had evidence for a large loss to follow-up over time. The sample size at baseline (T0) and 6 months (T1) was 201, which dropped by 39.8% to 121 after 12 months (T2) and by 64.7% to 71 at 18 months follow-up (T3). No explanation of the reasons for loss to follow-up are reported (VERY LOW). Due to their design there was no reported loss to follow-up in the other 3 effectiveness studies (de Vries et al 2011; Khatchadourian et al. 2014; Staphorsius et al. 2015). These studies provide very low certainty evidence about loss to follow up, which could be a marker of engagement with health care services, during treatment with GnRH analogues. Due to the large variation in rates between studies no conclusions could be drawn.
Impact on extent of and satisfaction with surgery	This is an important outcome because some children and adolescents with gender dysphoria may proceed to transitioning surgery. No evidence was identified.
Stopping treatment Certainty of evidence: very low	This is an important outcome because there is uncertainty about the short- and long-term safety and adverse effects of GnRH analogues in children and adolescents with gender dysphoria. Two uncontrolled, retrospective, observational cohort studies provided evidence relating to stopping GnRH analogues. One study had complete reporting of the cohort (Brik et al. 2018), the other (Khatchadourian et al. 2014) had incomplete reporting of its cohort, particularly for transfemales where outcomes for only 4/11 were reported. Brik et al. 2018 narratively reported the reasons for stopping GnRH analogues in a cohort of 143 adolescents (38 transfemales and 105 transmales). Median age at the start of GnRH analogues was 15.0 years (range, 11.1–18.6 years) in transfemales and 16.1 years (range, 10.1–17.9 years) in transmales. Of these adolescents, 125 (87%, 36 transfemales, 89 transmales) subsequently started gender-affirming hormones after 1.0 (0.5–3.8) and 0.8 (0.3–3.7) years of GnRH analogues. At the time of data collection, the median duration of GnRH analogue use was 2.1 years (1.6–2.8). During the follow-up period 6.3% (9/143) of adolescents had discontinued GnRH analogues after a median duration of 0.8 years (range 0.1 to 3.0). The percentages and reasons for stopping were: • 2.8% (4/143) stopped GnRH analogues although they wanted to continue endocrine treatments for gender dysphoria: - o 1 transmale stopped due to increase in mood problems, suicidal thoughts and confusion attributed to GnRH analogues - o 1 transmale had hot flushes, increased migraines, fear of injections, stress at school and unrelated medical issues, and temporarily stopped treatment (after 4 months) and restarted 5 months later.

	- o 1 transmale had mood swings 4 months after starting GnRH analogues. After 2.2 years had unexplained severe nausea and rapid weight loss and discontinued GnRH analogues after 2.4 years - o 1 transmale stopped GnRH analogues because of inability to regularly collect medication and attend appointments for injections. • 3.5% (5/143) stopped treatment because they no longer wished to receive gender-affirming treatment for various reasons (VERY LOW). Khatchadourian et al. 2014 narratively reported the reasons for stopping GnRH analogues in a cohort of 26 adolescents (15 transmales and 11 transfemales), 42% (11/26) discontinued GnRH analogues during follow-up between 1998 and 2011. Of 15 transmales receiving GnRH analogues, 14 received testosterone during the observation period, of which: • 7 continued GnRH analogues after starting testosterone • 7 stopped GnRH analogues after a median of 3.0 years (range 0.2 to 9.2 years), of which: - o 5 stopped after hysterectomy and salpingo-oophorectomy - o 1 stopped after 2.2 years (transitioned to gender-affirming hormones) - o 1 stopped after <2 months due to mood and emotional lability (VERY LOW). Of 11 transfemales receiving GnRH analogues, 5 received oestrogen during the observation period, of which: • 4 continued GnRH analogues after starting oestrogen • 1 stopped GnRH analogues when taking oestrogen (no reason reported) (VERY LOW). Of the remaining 6 transfemales taking GnRH analogues: • 1 stopped GnRH analogues after a few months due to emotional lability • 1 stopped GnRH analogues before taking oestrogen (the following year delayed due to heavy smoking) • 1 stopped GnRH analogues after 13 months due not to pursuing transition (VERY LOW). These studies provide very low certainty evidence for the number of adolescents who stop GnRH analogues and the reasons for this.

Abbreviations: GnRH, gonadotrophin releasing hormone; SD, standard deviation.

In children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Outcome	Evidence statement

Safety	
Change in bone density: lumbar Certainty of evidence: very low	This is an important outcome because puberty is an important time for bone development and puberty suppression may affect bone development, as shown by changes in lumbar bone density. Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on bone density (based on lumbar BMAD) between starting with a GnRH analogue and at 1 and 2 year intervals (Joseph et al. 2019), and between starting GnRH analogues and starting gender-affirming hormones (Klink et al. 2015 and Vlot et al. 2017). All outcomes were reported separately for transfemales and transmales; also see subgroups table below. BMAD is a size adjusted value of BMD incorporating body size measurements using UK norms in growing adolescents. It was reported as g/cm³ and as z-scores. Z-scores report how many standard deviations from the mean a measurement sits. A z-score of 0 is equal to the mean, a z-score of -1 is equal to 1 standard deviation below the mean, and a z-score of +1 is equal to 1 standard deviation above the mean. One retrospective observational study (Joseph et al. 2019, n=70) provided non-comparative evidence on change in lumbar BMAD increase using z-scores. • The z-score for lumbar BMAD was statistically significantly lower at 2 years compared with baseline in transfemales (z-score [±SD]: baseline 0.486 [0.809], 2 years -0.279 [0.930], p=0.000) and transmales (baseline -0.361 [1.439], 2 years -0.913 [1.318], p=0.001) (VERY LOW). • The z-score for lumbar BMAD was statistically significantly lower at 1 year compared with baseline in transfemales (baseline 0.859 [0.154], 1 year -0.228 [1.027], p=0.000) and transmales (baseline -0.186 [1.230], 1 year -0.541 [1.396], p=0.006) (VERY LOW). • Actual lumbar BMAD values in g/cm³ were not statistically significantly different between baseline and 1 or 2 years in transfemales or transmales (VERY LOW). Two retrospective observational studies (Klink et al. 2015 and Vlot et al. 2017, n=104 in total) provided non-comparative evidence on change in lumbar BMAD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. In Klink et al. 2015 the z-score for lumbar BMAD was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales but was statistically significantly lower when starting gender-affirming hormones in transmales (z-score mean [±SD]: GnRH analogue 0.28 [±0.90], gender-affirming hormone -0.50 [±0.81], p=0.004). Actual lumbar BMAD values in g/cm³ were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales or transmales (VERY LOW).

	Vlot et al. 2017 reported change from starting GnRH analogues to starting gender-affirming hormones in lumbar BMAD by bone age. • The z-score for lumbar BMAD in transfemales with a bone age of <15 years was statistically significantly lower at starting gender-affirming hormone treatment than at starting GnRH analogues (z-score median [range]: GnRH analogue -0.20 [-1.82 to 1.18], gender-affirming hormone -1.52 [-2.36 to 0.42], p=0.001) but was not statistically significantly different in transfemales with a bone age ≥15 years (VERY LOW). • The z-score for lumbar BMAD in transmales with a bone age of <14 years was statistically significantly lower at starting gender-affirming hormone treatment than at starting GnRH analogues (z-score median [range]: GnRH analogue -0.05 [-0.78 to 2.94], gender-affirming hormone -0.84 [-2.20 to 0.87], p=0.003) and in transmales with a bone age ≥14 years (GnRH analogue 0.27 [-1.60 to 1.80], gender-affirming hormone -0.29 [-2.28 to 0.90], p≤0.0001) (VERY LOW). • Actual lumbar BMAD values in g/cm³ were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales or transmales with young or old bone age (VERY LOW). Two uncontrolled, observational, retrospective studies provided evidence for the effect of GnRH analogues on bone density (based on lumbar BMD) between starting GnRH analogues and either at 1 or 2 year intervals (Joseph et al. 2019), or starting gender-affirming hormones (Klink et al. 2015). All outcomes were reported separately for transfemales and transmales; also see subgroups table below. One retrospective observational study (Joseph et al. 2019, n=70) provided non-comparative evidence on change in lumbar BMD increase using z-scores. • The z-score for lumbar BMD was statistically significantly lower at 2 years compared with baseline in transfemales (z-score mean [±SD]: baseline 0.130 [0.972], 2 years -0.890 [±1.075], p=0.000) and transmales (baseline -0.715 [±1.406], 2 years -2.000 [1.384], p=0.000) (VERY LOW). • The z-score for lumbar BMD was statistically significantly lower at 1 year compared with baseline in transfemales (z-score mean [±SD]: baseline -0.016 [±1.106], 1 year -0.461 [±1.121], p=0.003) and transmales (baseline -0.395 [±1.428], 1 year -1.276 [±1.410], p=0.000) (VERY LOW). • With the exception of transmales, where lumbar BMD in kg/m² increased between baseline and 1 year (mean [±SD]: baseline 0.694 [±0.149], 1 year 0.718 [±0.124], p=0.006), actual lumbar BMD values were not statistically significantly different between baseline and 1 or 2 years in transfemales or between 0 and 2 years in transmales (VERY LOW). One retrospective observational study (Klink et al. 2015, n=34) provided non-comparative evidence on change in lumbar BMD between starting GnRH analogues and starting gender-affirming hormones. • The z-score for lumbar BMD was not statistically significantly different between starting GnRH analogue and starting gender-affirming hormone treatment in transfemales, but was

	statistically significantly lower when starting gender-affirming hormones in transmales (z-score mean [$\pm$SD]: GnRH analogue 0.17 [$\pm$1.18], gender-affirming hormone -0.72 [$\pm$0.99], $p < 0.001$) (VERY LOW). Actual lumbar BMD in g/cm² was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales but was statistically significantly lower when starting gender-affirming hormones in transmales (mean [$\pm$SD]: GnRH analogues 0.95 [$\pm$0.12], gender-affirming hormones 0.91 [$\pm$0.10], $p = 0.006$) (VERY LOW). These studies provide very low certainty evidence that GnRH analogues reduce the expected increase in lumbar bone density (BMAD or BMD) compared with baseline (although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual lumbar bone density (BMAD or BMD).
Change in bone density: femoral Certainty of evidence: very low	This is an important outcome because puberty is an important time for bone development and puberty suppression may affect bone development, as shown by changes in femoral bone density. Two uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on bone density (based on femoral BMAD) between starting treatment with a GnRH analogue and starting gender-affirming hormones (Klink et al. 2015 and Vlot et al. 2017). All outcomes were reported separately for transfemales and transmales; also see subgroups table below. One retrospective observational study (Klink et al. 2015, $n = 34$) provided non-comparative evidence on change in femoral area BMAD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales. - The z-score for femoral area BMAD was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales or transmales (VERY LOW). - Actual femoral area BMAD values were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transmales or transfemales (VERY LOW). One retrospective observational study (Vlot et al. 2017, $n = 70$) provided non-comparative evidence on change in femoral neck (hip) BMAD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. - The z-score for femoral neck BMAD in transfemales with a bone age of < 15 years was not statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (z-score median [range]: GnRH analogue -0.71 [-3.35 to 0.37], gender-affirming hormone -1.32 [-3.39 to 0.21], $p \leq 0.1$) or in transfemales with a bone age ≥ 15 years (GnRH analogue -0.44 [-1.37 to 0.93], gender-affirming hormone -0.36 [-1.50 to 0.46]) (VERY LOW).

- The z-score for femoral neck BMAD in transmales with a bone age of <14 years was not statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (z-score median [range]: GnRH analogue -0.01 [-1.30 to 0.91], gender-affirming hormone -0.37 [-2.28 to 0.47]) but was statistically significantly lower in transmales with a bone age ≥14 years (GnRH analogue 0.27 [-1.39 to 1.32], gender-affirming hormone -0.27 [-1.91 to 1.29], p=0.002) **(VERY LOW)**.
- Actual femoral neck BMAD values were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales or in transmales with a young bone age, but were statistically significantly lower in transmales with a bone age ≥14 years (GnRH analogue 0.33 [0.25 to 0.39], gender-affirming hormone 0.30 [0.23 to 0.41], p≤0.01) **(VERY LOW)**.

Two uncontrolled, observational, retrospective studies provided evidence for the effect of GnRH analogues on bone density (based on femoral BMD) between starting GnRH analogues and either at 1 or 2 year intervals (Joseph et al. 2019), or starting gender-affirming hormones (Klink et al. 2015). All outcomes were reported separately for transfemales and transmales; also see subgroups table below.

One retrospective observational study ([Joseph et al. 2019](#), n=70) provided non-comparative evidence on change in femoral neck BMD increase using z-scores. All outcomes were reported separately for transfemales and transmales.

- The z-score for femoral neck BMD was statistically significantly lower at 2 years compared with baseline in transfemales (z-score mean [±SD]: baseline 0.0450 [±0.781], 2 years -0.600 [±1.059], p=0.002) and transmales (baseline -1.075 [±1.145], 2 years -1.779 [±0.816], p=0.001) **(VERY LOW)**.
- The z-score for femoral neck BMD was statistically significantly lower at 1 year compared with baseline in transfemales (z-score mean [±SD]: baseline 0.157 [±0.905], 1 year -0.340 [±0.816], p=0.002) and transmales (baseline -0.863 [±1.215], 1 year -1.440 [±1.075], p=0.000) **(VERY LOW)**.
- Actual femoral neck BMD values in kg/m² were not statistically significantly different between baseline and 1 or 2 years in transmales or transfemales **(VERY LOW)**.

One retrospective observational study ([Klink et al. 2015](#), n=34) provided non-comparative evidence on change in femoral area BMD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales.

- The z-score for femoral area BMD was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales, but was statistically significantly lower in transmales (z-score mean [±SD]: GnRH analogue 0.36 [±0.88], gender-affirming hormone -0.35 [±0.79], p=0.001) **(VERY LOW)**.
- Actual femoral area BMD values were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales, but were

	statistically significantly lower in transmales (mean [$\pm$SD] GnRH analogue 0.92 [$\pm$0.10], gender-affirming hormone 0.88 [$\pm$0.09], $p=0.005$) (VERY LOW). These studies provide very low certainty evidence that GnRH analogues may reduce the expected increase in femoral bone density (femoral neck or area BMAD or BMD) compared with baseline (although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual femoral bone density (femoral area BMAD or femoral neck BMD), apart from actual femoral area BMD in transmales.
Cognitive development or functioning Certainty of evidence: very low	This is an important outcome because puberty is an important time for cognitive development and puberty suppression may affect cognitive development or functioning. One cross-sectional observational study (Staphorsius et al. 2015, $n=70$) provided comparative evidence on cognitive development or functioning in adolescents with gender dysphoria on GnRH analogues compared with adolescents with gender dysphoria not on GnRH analogues. Cognitive functioning was measured using an IQ test. Reaction time (in seconds) and accuracy (percentage of correct trials) were measured using the Tower of London (ToL) task. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. No statistical analyses or interpretation of the results in these groups were reported: • IQ in transfemales (mean [$\pm$SD] GnRH analogue 94.0 [$\pm$10.3], control 109.4 [$\pm$21.2]). IQ transmales (GnRH analogue 95.8 [$\pm$15.6], control 98.5 [$\pm$15.9]). • Reaction time in transfemales (mean [$\pm$SD] GnRH analogue 10.9 [$\pm$4.1], control: 9.9 [$\pm$3.1]). Reaction time transmales (GnRH analogue 9.9 [$\pm$3.1], control 10.0 [$\pm$2.0]). • Accuracy score in transfemales (GnRH analogue 73.9 [$\pm$9.1], control 83.4 [$\pm$9.5]). Accuracy score in transmales (GnRH analogue 85.7 [$\pm$10.5], control 88.8 [$\pm$9.7]). This study provides very low certainty evidence (with no statistical analysis) on the effects of GnRH analogues on cognitive development or functioning. No conclusions could be drawn.
Other safety outcomes: kidney function Certainty of evidence: very low	This is an important outcome because if renal damage (raised serum creatinine is a marker of this) is suspected, GnRH analogues may need to be stopped. One prospective observational study (Schagen et al. 2016, $n=116$) provided non-comparative evidence on change in serum creatinine between starting GnRH analogues and at 1 year. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. • There was no statistically significant difference between baseline and 1 year for serum creatinine in transfemales (mean [$\pm$SD] baseline 70 [$\pm$12], 1 year 66 [$\pm$13], $p=0.20$). • There was a statistically significant decrease between baseline and 1 year for serum creatinine in transmales (baseline 73 [$\pm$8], 1 year 68 [$\pm$13], $p=0.01$).

	This study provides very low certainty evidence that GnRH analogues do not affect renal function.
Other safety outcomes: liver function Certainty of evidence: very low	This is an important outcome because if treatment-induced liver injury (raised liver enzymes are a marker of this) is suspected, GnRH analogues may need to be stopped. One prospective observational study (Schagen et al. 2016, n=116) provided non-comparative evidence on elevated liver enzymes between starting GnRH analogues and during use. No comparative values or statistical analyses were reported. • Glutamyl transferase was not elevated at baseline or during use in any person. • Mild elevations of AST and ALT above the reference range were present at baseline but were not more prevalent during use than at baseline. • Glutamyl transferase, AST, and ALT levels did not significantly change from baseline to 12 months of use. This study provides very low certainty evidence (with no statistical analysis) that GnRH analogues do not affect liver function.
Other safety outcomes: adverse effects Certainty of evidence: very low	This is an important outcome because if there are adverse effects, GnRH analogues may need to be stopped. One uncontrolled, retrospective, observational cohort study (Khatchadourian et al. 2014) provided evidence relating to adverse effects from GnRH analogues. It had incomplete reporting of its cohort, particularly for transfemales where outcomes for only 4/11 were reported. Khatchadourian et al. 2014 reported adverse effects in a cohort of 26 adolescents (15 transmales and 11 transfemales) receiving GnRH analogues. Of these: • 1 transmale developed sterile abscesses; they were switched from leuprolide acetate to triptorelin, and this was well tolerated. • 1 transmale developed leg pains and headaches, which eventually resolved • 1 participant gained 19 kg within 9 months of starting GnRH analogues. This study provides very low certainty evidence about potential adverse effects of GnRH analogues. No conclusions could be drawn.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMAD, bone mineral apparent density; BMD, bone mineral density; GnRH, gonadotrophin releasing hormone; IQ, intelligence quotient; NS, not significant; SD, standard deviation.

In children and adolescents with gender dysphoria, what is the cost-effectiveness of GnRH analogues compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Outcome	Evidence statement

Cost-effectiveness	No studies were identified to assess the cost-effectiveness of GnRH analogues for children and adolescents with gender dysphoria.

From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may benefit from GnRH analogues more than the wider population of interest?

Subgroup	Evidence statement
Sex assigned at birth males (transfemales) Certainty of evidence: Very low	Some studies reported data separately for sex assigned at birth males (transfemales). This included some direct comparisons with sex assigned at birth females (transmales). Impact on gender dysphoria One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence for gender dysphoria in sex assigned at birth males. See the clinical effectiveness results table above for a full description of the study. The mean ($\pm$SD) UGDS score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean UGDS score [$\pm$SD]: 47.95 [$\pm$9.70] versus 56.57 [$\pm$3.89]) and T1 (n=not reported, 49.67 [$\pm$9.47] versus 56.62 [$\pm$4.00]); between sex difference $p < 0.001$ (VERY LOW). One further prospective observational longitudinal study (Costa et al. 2015) provided evidence for the impact on gender dysphoria in sex assigned at birth males. See the clinical effectiveness results table above for a full description of the study. Sex assigned at birth males had a statistically significantly lower (improved) mean ($\pm$SD) UGDS score of 51.6 [$\pm$9.7] compared with sex assigned at birth females (56.1 [$\pm$4.3], $p < 0.001$). However, it was not reported if this was baseline or follow-up (VERY LOW). These studies provide very low certainty evidence that in sex assigned at birth males (transfemales), gender dysphoria is lower than in sex assigned at birth females (transmales). Impact on mental health One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence for the impact on mental health (depression, anger and anxiety) in sex assigned at birth males. See the clinical effectiveness results table above for a full description of the study. - The mean ($\pm$SD) depression (BDI-II) score was not statistically significantly different in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean BDI score [$\pm$SD]: 5.71 [$\pm$4.31] versus 10.34 [$\pm$8.24]) and T1 (n=not reported, 3.50 [$\pm$4.58] versus 6.09 [$\pm$7.93]), between sex difference $p = 0.057$ - The mean ($\pm$SD) anger (TPI) score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean TPI score [$\pm$SD]: 5.22 [$\pm$2.76]

versus 6.43 [± 2.78]) and T1 (n=not reported, 5.00 [± 3.07] versus 6.39 [± 2.59]), between sex difference $p=0.022$

- The mean ($\pm$ SD) anxiety (STAI) score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean STAI score [$\pm$ SD]: 4.33 [± 2.68] versus 7.00 [± 2.36]) and T1 (n=not reported, 4.39 [± 2.64] versus 6.17 [± 2.69]), between sex difference $p<0.001$ (**VERY LOW**).

This study provides very low certainty evidence that the impact on mental health (depression, anger and anxiety) may be different in sex assigned at birth males (transfemales) compared with sex assigned at birth females (transmales). Over time there was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for depression. However, sex assigned at birth males had statistically significantly lower levels of anger and anxiety than sex assigned at birth females at both baseline and follow up.

Impact on body image

One uncontrolled prospective observational longitudinal study ([de Vries et al. 2011](#)) provided evidence relating to the impact on body image in sex assigned at birth males.

- The mean ($\pm$ SD) BIS score for primary sex characteristics was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean BIS score [$\pm$ SD]: 4.02 [± 0.61] versus 4.16 [± 0.52]) and T1 (n=not reported, 3.74 [± 0.78] versus 4.17 [± 0.58]), between sex difference $p=0.047$
- The mean ($\pm$ SD) BIS score for secondary sex was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean BIS score [$\pm$ SD]: 2.66 [± 0.50] versus 2.81 [± 0.76]) and T1 (n=not reported, 2.39 [± 0.69] versus 3.18 [± 0.42]), between sex difference $p=0.001$
- The mean ($\pm$ SD) BIS score for neutral body characteristics was not statistically significantly different in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean BIS score [$\pm$ SD]: 2.60 [± 0.58] versus 2.24 [± 0.62]) and T1 (n=not reported, 2.32 [± 0.59] versus 2.61 [± 0.50]), between sex difference $p=0.777$ (**VERY LOW**).

This study provides very low certainty evidence that the impact on body image may be different in sex assigned at birth males (transfemales) compared with sex assigned at birth females (transmales). Sex assigned at birth males are less dissatisfied with their primary and secondary sex characteristics than sex assigned at birth females at both baseline and follow up, but the satisfaction with neutral body characteristics is not different.

Psychosocial impact

One uncontrolled prospective observational longitudinal study ([de Vries et al. 2011](#)) provided evidence for psychosocial impact in terms

of global functioning (CGAS) and psychosocial functioning (CBCL and YSR) in sex assigned at birth males.

- Sex assigned at birth males had statistically higher mean ($\pm$ SD) CGAS scores compared with sex assigned at birth females at both baseline (T0) (n=54, 73.10 [$\pm$ 8.44] versus 67.25 [$\pm$ 11.06]) and T1 (n=54, 77.33 [$\pm$ 8.69] versus 70.30 [$\pm$ 9.44]), between sex difference p=0.021
- There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the CBCL Total T score at T0 or T1 (n=54, p=0.110)
- There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the CBCL internalising T score at T0 or T1 (n=54, p=0.286)
- Sex assigned at birth males had statistically lower mean ($\pm$ SD) CBCL externalising T scores compared with sex assigned at birth females at both T0 (n=54, 54.71 [$\pm$ 12.91] versus 60.70 [$\pm$ 12.64]) and T1 (n=54, 48.75 [$\pm$ 10.22] versus 57.87 [$\pm$ 11.66]), between sex difference p=0.015
- There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the YSR Total T score at T0 or T1 (n=54, p=0.164)
- There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the YSR internalising T score at T0 or T1 (n=54, p=0.825)
- Sex assigned at birth males had statistically lower mean ($\pm$ SD) YSR externalising T scores compared with sex assigned at birth females at both T0 (n=54, 48.72 [$\pm$ 11.38] versus 57.24 [$\pm$ 10.59]) and T1 (n=54, 46.52 [$\pm$ 9.23] versus 52.97 [$\pm$ 8.51]), between sex difference p=0.004 (**VERY LOW**).

One uncontrolled, observational, prospective cohort study ([Costa et al. 2015](#)) provided evidence for psychosocial impact in terms of global functioning (CGAS) in sex assigned at birth males.

- Sex assigned at birth males had statistically significant lower mean ($\pm$ SD CGAS scores at baseline) compared with sex assigned at birth females (n=201, 55.4 [$\pm$ 12.7] versus 59.2 [$\pm$ 11.8], p=0.03) (**VERY LOW**).

These studies provide very low certainty evidence that psychosocial impact may be different in sex assigned at birth males (transfemales) compared with sex assigned at birth females (transmales). However, no conclusions could be drawn.

Change in bone density: lumbar

Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on lumbar bone density in sex assigned at birth males ([Joseph et al. 2019](#), [Klink et al. 2015](#) and [Vlot et al. 2017](#)). See the safety results table above for a full description of the results.

These studies provide very low certainty evidence that GnRH analogues reduce the expected increase in lumbar bone density (BMAD or BMD) in sex assigned at birth males (transfemales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically

	significantly decrease actual lumbar bone density (BMAD or BMD) in sex assigned at birth males (transfemales). Change in bone density: femoral Three uncontrolled, observational, retrospective studies provided evidence for the effect of GnRH analogues on femoral bone density in sex assigned at birth males (Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017). See the safety results table above for a full description of the results. These studies provide very low certainty evidence that GnRH analogues may reduce the expected increase in femoral bone density (femoral neck or area BMAD or BMD) in sex assigned at birth males (transfemales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual femoral bone density (femoral area BMAD or femoral neck BMD) in sex assigned at birth males (transfemales). Cognitive development or functioning One cross-sectional observational study (Staphorsius et al. 2015) provided comparative evidence on cognitive development or functioning in sex assigned at birth males. See the safety results table above for a full description of the results. This study provides very low certainty evidence (with no statistical analysis) on the effects of GnRH analogues on cognitive development or functioning in sex assigned at birth males (transfemales). No conclusions could be drawn. Other safety outcomes: kidney function One prospective observational study (Schagen et al. 2016) provided non-comparative evidence on change in serum creatinine in sex assigned at birth males. See the safety results table above for a full description of the results. This study provides very low certainty evidence that GnRH analogues do not affect renal function in sex assigned at birth males (transfemales).
Sex assigned at birth females (transmales) Certainty of evidence: Very low	Some studies reported data separately for sex assigned at birth females (transmales). This included some direct comparisons with sex assigned at birth males (transfemales). Impact on gender dysphoria One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) and one prospective observational longitudinal study (Costa et al. 2015) provided evidence for gender dysphoria in sex assigned at birth females. See the sex assigned at birth males (transfemales) row above for a full description of the results. These studies provide very low certainty evidence that in sex assigned at birth females (transmales), gender dysphoria is higher than in sex assigned at birth males (transfemales) at both baseline and follow up.

	Impact on mental health One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on mental health (depression, anger and anxiety) in sex assigned at birth females. See the sex assigned at birth males (transfemales) row above for a full description of the results. This study provides very low certainty evidence that the impact on mental health (depression, anger and anxiety) may be different in sex assigned at birth females (transmales) compared with sex assigned at birth males (transfemales). Over time there was no statistically significant difference between sex assigned at birth females and sex assigned at birth males for depression. However, sex assigned at birth females had statistically significantly greater levels of anger and anxiety than sex assigned at birth males at baseline and follow up. Impact on body image One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on body image in sex assigned at birth females. See the sex assigned at birth males (transfemales) row above for a full description of the results. This study provides very low certainty evidence that the impact on body image may be different in sex assigned at birth females (transmales) compared with sex assigned at birth males (transfemales). Sex assigned at birth females are more dissatisfied with their primary and secondary sex characteristics than sex assigned at birth males at both baseline and follow up, but the satisfaction with neutral body characteristics is not different. Psychosocial impact One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence for psychosocial impact in terms of global functioning (CGAS) and psychosocial functioning (CBCL and YSR) in sex assigned at birth females. One uncontrolled, observational, prospective cohort study (Costa et al. 2015) provided evidence for psychosocial impact in terms of global functioning (CGAS) in sex assigned at birth females. See the sex assigned at birth males (transfemales) row above for a full description of the results. These studies provide very low certainty evidence that psychosocial impact may be different in sex assigned at birth females (transmales) compared with sex assigned at birth males (transfemales). However, no conclusions could be drawn. Change in bone density: lumbar Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on lumbar bone density in sex assigned at birth females (Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017). See the safety results table above for a full description of the results.

	These studies provide very low certainty evidence that GnRH analogues reduce the expected increase in lumbar bone density (BMAD or BMD) in sex assigned at birth females (transmales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual lumbar bone density (BMAD or BMD) in sex assigned at birth females (transmales). Change in bone density: femoral Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on femoral bone density in sex assigned at birth females (Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017). See the safety results table above for a full description of the results. These studies provide very low certainty evidence that GnRH analogues may reduce the expected increase in femoral bone density (femoral neck or area BMAD or BMD) in sex assigned at birth females (transmales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual femoral bone density (femoral area BMAD or femoral neck BMD) in sex assigned at birth females (transmales), apart from actual femoral area. Cognitive development or functioning One cross-sectional observational study (Staphorsius et al. 2015) provided comparative evidence on cognitive development or functioning in sex assigned at birth females. See the safety results table above for a full description of the results. This study provides very low certainty evidence (with no statistical analysis) on the effects of GnRH analogues on cognitive development or functioning in sex assigned at birth females (transmales). No conclusions could be drawn. Other safety outcomes: kidney function One prospective observational study (Schagen et al. 2016) provided non-comparative evidence on change in serum creatinine in sex assigned at birth females (transmales). See the safety results table above for a full description of the results. This study provides very low certainty evidence that GnRH analogues do not affect renal function in sex assigned at birth females (transmales).
Duration of gender dysphoria	No evidence was identified.
Age at onset of gender dysphoria	No evidence was identified.
Age at which GnRH analogue started	No evidence was identified.
Age at onset of puberty	No evidence was identified.

Tanner stage at which GnRH analogue started	No evidence was identified.
Diagnosis of autistic spectrum disorder	No evidence was identified.
Diagnosis of mental health condition	No evidence was identified.

Abbreviations: BDI-II, Beck Depression Inventory-II; BIS, Body Image Scale; CBCL, Child Behaviour Checklist; CGAS, Children's Global Assessment Scale; SD, standard deviation; STAI, Trait Anxiety Scale of the State-Trait Personality Inventory; TPI, Trait Anger Scale of the State-Trait Personality Inventory; UGDS, Utrecht Gender Dysphoria Scale; YSR, Youth Self-Report

From the evidence selected,

- (a) **what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?**
- (b) **what were the ages at which participants commenced treatment with GnRH analogues?**
- (c) **what was the duration of treatment with GnRH analogues?**

Outcome	Evidence statement										
Diagnostic criteria	In 5 studies (Costa et al. 2015, Klink et al. 2015, Schagen et al. 2016, Staphorsius et al. 2015 and Vlot et al. 2017) the DSM-IV-TR criteria of gender identity disorder was used. The study by Brik et al. 2020 used DSM-V criteria. The DSM-V has one overarching definition of gender dysphoria with separate specific criteria for children and for adolescents and adults. The general definition describes a conflict associated with significant distress and/or problems functioning associated with this conflict between the way they feel and the way they think of themselves which must have lasted at least 6 months. It was not reported how gender dysphoria was defined in the remaining 3 studies (VERY LOW). From the evidence selected, all studies that reported diagnostic criteria for gender dysphoria (6/9 studies) used the DSM criteria in use at the time the study was conducted.										
Age when GnRH analogues started	8/9 studies reported the age at which participants started GnRH analogues, either as the mean age (with SD) or median age (with the range): <table border="1"> <thead> <tr> <th>Study</th><th>Mean age (±SD)</th></tr> </thead> <tbody> <tr> <td>Costa et al. 2015</td><td>16.5 years (±1.3)</td></tr> <tr> <td>de Vries et al. 2011</td><td>13.6 years (±1.8)</td></tr> <tr> <td>Joseph et al. 2019</td><td>13.2 years (±1.4) in transfemales 12.6 years (±1.0) in transmales</td></tr> <tr> <td>Khatchadourian et al. 2014</td><td>14.7 years (±1.9)</td></tr> </tbody> </table>	Study	Mean age (±SD)	Costa et al. 2015	16.5 years (±1.3)	de Vries et al. 2011	13.6 years (±1.8)	Joseph et al. 2019	13.2 years (±1.4) in transfemales 12.6 years (±1.0) in transmales	Khatchadourian et al. 2014	14.7 years (±1.9)
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Khatchadourian et al. 2014	14.7 years (±1.9)										

	Klink et al. 2015	14.9 years (± 1.9) in transfemales 15.0 years (± 2.0) in transmales
	Study	Median age (range)
	Brik et al. 2020	15.5 years (11.1–18.6) in transfemales 16.1 years (10.1–17.9) in transmales
	Schagen et al. 2016	13.6 years (11.6–17.9) in transfemales 14.2 years (11.1–18.6) in transmales
	Vlot et al. 2017	13.5 years (11.5–18.3) in transfemales 15.1 years (11.7–18.6) in transmales
Age at the start of GnRH analogues was not reported in Staphorsius et al. 2015, but participants were required to be at least 12 years (VERY LOW). The evidence included showed wide variation in the age (11 to 18 years old) at which children and adolescents with gender dysphoria started GnRH analogues.		
Duration of treatment	The duration of treatment with GnRH analogues was reported in 3/9 studies. The median duration was: 2.1 years (range 1.6–2.8) in Brik et al. 2020. 1.3 years (range 0.5–3.8) in transfemales and 1.5 years (range 0.25–5.2) in transmales in Klink et al. 2015. In Staphorsius et al. 2015, the mean duration was 1.6 years (SD ± 1.0). In de Vries et al. 2011, the mean duration of time between starting GnRH analogues and gender-affirming hormones was 1.88 years (SD ± 1.05). The evidence included showed wide variation in the duration of treatment with GnRH analogues, but most studies did not report this information. Treatment duration ranged from a few months up to about 5 years.	

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders criteria; SD, standard deviation.

6. Discussion

A key limitation to identifying the effectiveness and safety of GnRH analogues for children and adolescents with gender dysphoria is the lack of reliable comparative studies. The lack of clear, expected outcomes from treatment with a GnRH analogue (the purpose of which is to suppress secondary sexual characteristics which may cause distress from unwanted pubertal changes) also makes interpreting the evidence difficult. The size of the population with gender dysphoria means conducting a prospective trial may be unrealistic, at least on a single centre basis. There may also be ethical issues with a 'no treatment arm' in comparative trials of GnRH analogues, where there may be poor mental health outcomes if treatment is withheld. However, the use of an active comparator such as close psychological support may reduce ethical concerns in future trials.

The studies included in this evidence review are all small, uncontrolled observational studies, which are subject to bias and confounding, and are of very low certainty as

assessed using modified GRADE. All the included studies reported physical and mental health comorbidities and concomitant treatments very poorly. For example, very little data are reported on how many children and adolescents needed additional mental health support, and for what reasons, or whether additional interventions, and what form and duration (for example drug treatment or counselling) that took. This is a possible confounder for the treatment outcomes in the studies because changes in critical and important outcomes may be attributable to external care rather than the psychological support or GnRH analogues used in the studies.

The studies that reported diagnostic criteria for gender dysphoria (6/9 studies) used the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria in use at the time the study was conducted (either DSM-IV-TR or DSM-V). The definition was unclear in the remaining studies. There was wide variation in the ages at which participants started a GnRH analogue, typically ranging from about 11 to 18 years. Similarly, there was a wide variation in the duration of use, but few studies reported this.

Changes in outcome scores for clinical effectiveness were assessed for statistical significance in the 3 studies reporting these outcomes ([Costa et al. 2015](#); [de Vries et al. 2011](#); [Staphorsius et al. 2015](#)). However, there is relatively little interpretation of whether the changes in outcome scores seen in these studies are clinically meaningful.

For some outcomes there was no statistically significant difference from before starting GnRH analogues until just before starting gender-affirming hormones. These were the Utrecht Gender Dysphoria Scale (UGDS) (which was assessed in 1 study [de Vries et al. 2011](#)), the Trait Anger (TPI) and Trait Anxiety (STAI) Scales (which were assessed in 1 study [de Vries et al. 2011](#)), and Body Image Scale (BIS) which was assessed in 1 study ([de Vries et al. 2011](#)).

The Beck Depression Inventory (BDI-II) was used in 1 study ([de Vries et al. 2011](#)) to assess change in depression from before starting GnRH analogues to just before starting gender-affirming hormones. The result is statistically significant, with the mean ($\pm$ SD) BDI-II score decreasing from 8.31 ($\pm$ 7.12) at baseline to 4.95 ($\pm$ 6.27) at follow up ($p=0.004$). However, both scores fall into the minimal range using the general guidelines for interpretation of BDI-II (0 to 13 minimal, 14 to 19 mild depression, 20 to 28 moderate depression and 29 to 63 severe depression), suggesting that while statistically significant, it is unclear if this is a clinically meaningful change.

Psychosocial outcomes were assessed in 3 studies ([Costa et al. 2015](#); [de Vries et al. 2011](#); [Staphorsius et al. 2015](#)) using the Children's Global Assessment Scale (CGAS) and Child Behavior Checklist/Youth Self-Report (CBCL/YSR). The CGAS score was assessed in 2 studies ([Costa et al. 2015](#); [de Vries et al. 2011](#)). In [de Vries et al. 2011](#) the mean ($\pm$ SD) CGAS score statistically significantly increased over time from 70.24 [$\pm$ 10.12] at baseline to 73.90 [$\pm$ 9.63] at follow up. CGAS scores are clinically categorised into 10 categories (10 to 1, 20 to 11 and so on until 100 to 91) and both scores reported were in a single category (71 to 80, no more than slight impairment) suggesting that while statistically significant, it is unclear if this is a clinically meaningful change. The [Costa et al. 2015](#) study does highlight a larger change in CGAS scores from baseline to follow-up (mean [$\pm$ SD] 58.72 [$\pm$ 11.38] compared with 67.40 [$\pm$ 13.39]), but whether this is clinically meaningful is unclear. The average score moved from the clinical category of 60 to 51 (variable functioning with sporadic difficulties) at baseline to 70 to 61 (some difficulty in a single area, but generally

functioning pretty well) at follow up, but the large standard deviations suggest clinically significant overlaps between the scores from baseline to follow-up.

Psychosocial functioning using the CBCL/YSR was assessed in 2 studies ([de Vries et al. 2011](#); [Staphorsius et al. 2015](#)). In de Vries et al. 2011 there was a statistically significant reduction in both CBCL and YSR scores from before starting GnRH analogues to just before starting gender-affirming hormones. The study interpreted the CBCL/YSR with a proportion of adolescents who scored in the clinical range (a T-score above 63), which allows changes in clinically meaningful scores to be assessed, and proportions of adolescents in the clinical range for some CBCL and YSR scores decreased over time. One cross-sectional study ([Staphorsius et al. 2015](#)) assessed CBCL scores only, but it was unclear if this was the Total T score, or whether subscales of internalising or externalising scores were also assessed, and whether the results were statistically significant.

The 2 prospective observational studies ([Costa et al. 2015](#); [de Vries et al. 2011](#)) are confounded by a number of common factors. Firstly, the single assessment of scores at baseline means it is unclear if scores were stable, already improving or declining before starting treatment. Secondly, in an uncontrolled study any changes in scores from baseline to follow-up could be attributed to a regression-to-mean, for example getting older has been positively associated with maturity and wellbeing. The studies use mean and standard deviations in the descriptive statistics and analyses; however, they do not report testing the normality of data which would support the use of parametric measures. The study by de Vries et al. 2011 used general linear models (regression) to examine between and within group variances (changes in outcomes). In using such models, the data is assumed to be balanced (measured at regular intervals and without missing data), but the large ranges in ages at which participants were assessed and started on various interventions suggests that ascertainment of outcome was unlikely to be regular and missing data was likely. Missing data was handled through listwise deletion (omits those cases with the missing data and analyses the remaining data) which is acceptable if data loss is completely random but for some outcomes where there was incomplete data for individual items this was not random (items were introduced by the authors after the first eligible adolescents had started GnRH analogues). The study provided no detail on whether these assumptions for the modeling were met, they also provided no adequate assessment of whether any regression diagnostics (analysis that seek to assess the validity of a model) or model fit (how much of the variance in outcome is explained by the between and within group variance) were undertaken.

The 2 retrospective observational studies ([Brik et al. 2020](#); [Khatchadourian et al. 2014](#)) both only report absolute numbers for each trajectory along with reasons for stopping GnRH analogues. It is difficult to assess outcomes from such single centre studies because there is little comparative data for outcomes from other such services. A lack of any critical or other important outcomes also means the success of the treatment across all the participants is difficult to judge.

Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on bone density ([Joseph et al. 2019](#); [Klink et al. 2015](#); [Vlot et al. 2017](#)). In all 3 studies, the participants acted as their own controls and change in bone density was determined between starting GnRH analogues and either after 1 and 2 year follow-up timepoints (Joseph et al. 2019) or when gender-affirming hormones were started

(Klink et al. 2015 and Vlot et al. 2017). Observational studies such as these can only show an association with GnRH analogues and bone density; they cannot show that GnRH analogues caused any differences in bone density seen. Because there was no comparator group and participants acted as their own controls, it is unclear whether the findings are associated with GnRH analogues or due to changes over time. The authors reported z-scores which allows for comparison with the expected increase in bone density in the general population. However, because no concomitant treatments or comorbidities were reported it is possible that the findings may not be because of GnRH analogues and there is another way in which the study population differs from the general population.

All the studies are from a limited number of, mainly European, care facilities. They are described as either tertiary referral or expert services but the low number of services providing such care and publishing evidence may bias the results towards the outcomes in these services only and limit extrapolation.

The first study ([Brik et al. 2020](#)) was an uncontrolled, retrospective, observational study that assessed the outcome trajectories of adolescents receiving GnRH analogues for gender dysphoria. This study followed-up 143 individuals who had received GnRH analogues (38 transfemales and 105 transmales) using clinical records to show outcomes for up to 9 years (continuing use of GnRH analogues, reasons for stopping GnRH analogues and onward care such as gender-affirming hormone use). The methods and results are well reported, but no analysis of data was undertaken. The views of adolescents and their parents are particularly difficult to interpret because no data on how many responded to each question and in what ways are reported.

The second study ([Costa et al. 2015](#)) was an uncontrolled, prospective observational study which assessed global functioning in adolescents with gender dysphoria using CGAS every 6 months, including during the first 6 months where statistically significant improvements were seen without GnRH analogues. The study is confounded by significant unexplained loss to follow-up (64.7%: from n=201 adolescents to n=71 after 18 months). Missing data for those lost to follow-up maybe more than sufficient to change the direction of effects seen in the study if the reasons for loss to follow-up are systematic (such as deriving little or no benefit from treatment). The study uses clustered data in its analysis, a single outcome (CGAS) measured in clusters (at different visits), and the analysis does not take account of the correlation of scores (data at different time points are not independent) as a significant change in scores early in the study means the successive changes measured against baseline were also significant. The study relies on multiple (>20) pairwise independent *t*-tests to examine change in CGAS between the 4 time points, increasing the possibility of type-I error (a false positive which occurs when a researcher incorrectly rejects a true null hypothesis) because the more tests performed the more likely a statistically significant result will be observed by chance alone.

The [Costa et al. 2015](#) study compares immediately eligible and delayed eligible cohorts, however, it is highly likely that they are non-comparable groups because the immediately eligible group were those able to start GnRH analogues straight away whilst those in the delayed eligible group were either not ready to make a decision about starting treatment (no age comparison was made between the 2 groups so it is unclear if they were a younger cohort than the immediately eligible group) or had comorbid mental health or psychological difficulties. The authors report that those with concomitant problems (such as mental health

problems, substantial problems with peers, or conflicts with parents or siblings) were referred to local mental health services but no details are provided.

The third study ([de Vries et al. 2011](#)) was an uncontrolled, prospective observational study which assessed gender dysphoria and psychological functioning before and after puberty suppression in adolescents with gender dysphoria. Although the study mentions the DSM-IV-TR there is no explicit discussion of this, or any other criteria, being used as the diagnostic criteria for study entry. There are no details reported for how the outcomes in the study were assessed, and by whom. The length of follow-up for the outcomes in the model are questionable in relation to whether there was sufficient time for GnRH analogues to have a measurable effect. The time points used are start of GnRH analogues and start of gender-affirming hormones. Overall, the mean time between starting GnRH analogues and gender-affirming hormones was 1.88 (± 1.05) years, but the range is as low as just 5 months between the 2 time points, which may be insufficient for any difference in outcome to have occurred in some individuals.

The fourth study ([Joseph et al. 2019](#)) was a retrospective, longitudinal observational single centre study which assessed bone mineral density in adolescents with gender dysphoria in the UK. For inclusion in the study, participants had to have been assessed by the Gender Identity Development Service multi-disciplinary psychosocial health team for at least 4 assessments over a minimum of 6 months. No other diagnostic criteria, such as the DSM-IV-TR, are discussed. Bone density was assessed using dual energy X-ray absorptiometry (DAXA) scan of the lumbar spine (L1-L4) and the femoral neck at baseline (n=70), 1 year (n=70) and 2 years after starting GnRH analogues (n=39). The results suggest a possible association between GnRH analogues and bone mineral apparent density. However, the evidence is of poor quality, and the results could be due to bias or chance. No concomitant treatments or comorbidities were reported.

The fifth study ([Khatchadourian et al. 2014](#)) was an uncontrolled retrospective observational study which describes patient characteristics at presentation, treatment, and response to treatment in 84 adolescents with gender dysphoria, of whom 27 received GnRH analogues. The study used clinical records to show outcomes for up to 13 years (continuing use of GnRH analogues, reasons for stopping GnRH analogues and onward care such as gender-affirming hormone use). The methods are well reported but the results for those taking GnRH analogues are poorly and incompletely reported, particularly for transfemales, and no analysis of data was undertaken. It is difficult to assess the results for stopping GnRH analogues due to incomplete reporting of this outcome.

The sixth study ([Klink et al. 2015](#)) was a retrospective longitudinal observational single centre study which assessed bone mineral density in adolescents with gender dysphoria, diagnosed with the DSM-IV-TR criteria. Bone density was assessed when starting GnRH analogues and then when starting gender-affirming hormones. Results are reported for transmales and transfemales separately and no results for the whole cohort are given. Statistical analyses were reported for all outcomes of interest but, because there was no comparator group and participants acted as their own controls, it is not known whether the findings are associated with GnRH analogues or due to changes over time. The authors reported z-scores which allows for comparison with the expected increase in bone density in the general population. However, because no concomitant treatments or comorbidities were

reported it is possible that the findings may not be because of GnRH analogues and there is another way in which the study population differs from the general population.

The seventh study ([Schagen et al. 2016](#)) was a prospective observational study of 116 adolescents which provided very low certainty non-comparative evidence on change in serum creatinine between starting GnRH analogues and 1 year, and liver function during treatment. Statistical analyses were reported for changes in serum creatinine but not for liver function. Because there was no comparator group and participants acted as their own controls, it is not known whether the findings are associated with GnRH analogues or due to changes over time, or concomitant treatments.

The eighth study ([Staphorsius et al. 2015](#)) was a cross-sectional study of 85 adolescents, 40 with gender dysphoria (of whom 20 were receiving GnRH analogues) and 45 matched controls (not further reported in this evidence review). The study includes 1 outcome of interest for clinical effectiveness (CBCL) and 1 outcome of interest for safety (cognitive development or functioning). The mean ($\pm$ SD) CBCL, IQ test, reaction time and accuracy scores were given for each group, but the statistical analysis is unclear. It is not reported what analysis was used or which of the groups were compared, therefore it is difficult to interpret the results.

The ninth study ([Vlot et al. 2017](#)) was a retrospective observational study which assessed bone mineral apparent density in adolescents with DSM-IV-TR gender dysphoria. Measurements were taken at the start of GnRH analogues and at the start of gender-affirming hormones. Results are reported for young bone age and old bone age in transmales and transfemales separately, and no results for the whole cohort are given. Statistical analyses were reported for all outcomes of interest but, because there was no comparator group and participants acted as their own controls, it is not known whether the findings are associated with GnRH analogues or due to changes over time. The authors reported z-scores which allows for comparison with the expected increase in bone density in the general population. However, because no concomitant treatments or comorbidities were reported it is possible that the findings may not be because of GnRH analogues and there is another way in which the study population differs from the general population.

7. Conclusion

The results of the studies that reported impact on the critical outcomes of gender dysphoria and mental health (depression, anger and anxiety), and the important outcomes of body image and psychosocial impact (global and psychosocial functioning) in children and adolescents with gender dysphoria are of very low certainty using modified GRADE. They suggest little change with GnRH analogues from baseline to follow-up.

Studies that found differences in outcomes could represent changes that are either of questionable clinical value, or the studies themselves are not reliable and changes could be due to confounding, bias or chance. It is plausible, however, that a lack of difference in scores from baseline to follow-up is the effect of GnRH analogues in children and adolescents with gender dysphoria, in whom the development of secondary sexual characteristics might be expected to be associated with an increased impact on gender dysphoria, depression, anxiety, anger and distress over time without treatment. One study reported statistically significant reductions in the Child Behaviour Checklist/Youth Self-Report (CBCL/YSR) scores from

baseline to follow up, and given that the purpose of GnRH analogues is to reduce distress caused by the development of secondary sexual characteristics and the CBCL/YSR in part measures distress, this could be an important finding. However, as the studies all lack reasonable controls not receiving GnRH analogues, the natural history of the outcomes measured in the studies is not known and any positive changes could be a regression to mean.

The results of the studies that reported bone density outcomes suggest that GnRH analogues may reduce the increase in bone density which is expected during puberty. However, as the studies themselves are not reliable, the results could be due to confounding, bias or chance. While controlled trials may not be possible, comparative studies are needed to understand this association and whether the effects of GnRH analogues on bone density are seen after treatment is stopped. All the studies that reported safety outcomes provided very low certainty evidence.

No cost-effectiveness evidence was found to determine whether or not GnRH analogues are cost-effective for children and adolescents with gender dysphoria.

The results of the studies that reported outcomes for subgroups of children and adolescents with gender dysphoria, suggest there may be differences between sex assigned at birth males (transfemales) and sex assigned at birth females (transmales).

Appendix A PICO document

The review questions for this evidence review are:

1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
2. For children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
3. For children and adolescents with gender dysphoria, what is the cost-effectiveness of GnRH analogues compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?
4. From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may derive more (or less) advantage from treatment with GnRH analogues than the wider population of children and adolescents with gender dysphoria?
5. From the evidence selected,
 - a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?
 - b) what were the ages at which participants commenced treatment with GnRH analogues?
 - c) what was the duration of treatment with GnRH analogues?

PICO table

P – Population and Indication	Children and adolescents aged 18 years or less who have gender dysphoria, gender identity disorder or gender incongruence of childhood as defined by study: The following subgroups of children and adolescents with gender dysphoria, gender identity disorder or gender incongruence of childhood need to be considered: • Sex assigned at birth males. • Sex assigned at birth females. • The duration of gender dysphoria: less than 6 months, 6-24 months, and more than 24 months. • The age of onset of gender dysphoria. • The age at which treatment was initiated. • The age of onset of puberty. • Tanner stage at which treatment was initiated. • Children and adolescents with gender dysphoria who have a pre-existing diagnosis of autistic spectrum disorder. • Children and adolescents with gender dysphoria who had a significant mental health symptom load at diagnosis including anxiety, depression (with or without a history of self-harm and suicidality), suicide attempts, psychosis, personality disorder, Attention Deficit Hyperactivity Disorder and eating disorders.
I – Intervention	Any GnRH analogue including: triptorelin*; buserelin; histrelin; goserelin (Zoladex); leuporelin/leuprolide (Prostap); nafarelin.

	* Triptorelin (brand names Gonapeptyl and Decapeptyl) are used in Leeds Hospital, England. The search should include brand names as well as generic names.
C – Comparator(s)	One or a combination of: • Psychological support. • Social transitioning to the gender with which the individual identifies. • No intervention.
O – Outcomes	There are no known minimal clinically important differences and there are no preferred timepoints for the outcome measures selected. All outcomes should be stratified by: • The age at which treatment with GnRH analogues was initiated. • The length of treatment with GnRH analogues where possible. <u>A: Clinical Effectiveness</u> <i>Critical to decision making</i> • Impact on Gender Dysphoria This outcome is critical because gender dysphoria in adolescents and children is associated with significant distress and problems functioning. Impact on gender dysphoria may be measured by the Utrecht Gender Dysphoria Scale. Other measures as reported in studies may be used as an alternative to the stated measure. • Impact on mental health Examples of mental health problems include self-harm, thoughts of suicide, suicide attempts, eating disorders, depression/low mood and anxiety. These outcomes are critical because self-harm and thoughts of suicide have the potential to result in significant physical harm and for completed suicides the death of the young person. Disordered eating habits may cause significant morbidity in young people. Depression and anxiety are also critical outcomes because they may impact on social, occupational, or other areas of functioning of children and adolescents. The Child and Adolescent Psychiatric Assessment (CAPA) may be used to measure depression and anxiety. The impact on self-harm and suicidality (ideation and behaviour) may be measured using the Suicide Ideation Questionnaire Junior. Other measures may be used as an alternative to the stated measures. • Impact on Quality of Life This outcome is critical because gender dysphoria in children and adolescents may be associated with a significant reduction in health-related quality of life. Quality of Life may be measured by the KINDL questionnaire, Kidscreen 52. Other measures as reported in studies may be used as an alternative to the stated measure. <i>Important to decision making</i> • Impact on body Image This outcome is important because some transgender young people may desire to take steps to suppress features of their physical appearance associated with their sex assigned at birth or accentuate physical features of their desired gender. The Body Image Scale could be used as a measure. Other measures

	as reported in studies may also be used as an alternative to the stated measure. Psychosocial Impact Examples of psychosocial impact are: coping mechanisms which may impact on substance misuse; family relationships; peer relationships. This outcome is important because gender dysphoria in adolescents and children is associated with internalising and externalising behaviours and emotional and behavioural problems which may impact on social and occupational functioning. The child behavioural check list (CBCL) may be used to measure the impact on psychosocial functioning. Other measures as reported in studies may be used as an alternative to the stated measure. Engagement with health care services This outcome is important because patient engagement with healthcare services will impact on their clinical outcomes. Engagement with health care services may be measured using the Youth Health Care measure-satisfaction, utilization, and needs (YHC-SUN) questionnaire. Loss to follow up should also be ascertained as part of this outcome. Alternative measures to the YHC-SUN questionnaire may be used as reported in studies. Transitioning surgery – Impact on extent of and satisfaction with surgery This outcome is important because some children and adolescents with gender dysphoria may proceed to transitioning surgery. Stated measures of the extent of transitioning surgery and satisfaction with surgery in studies may be reported. Stopping treatment The proportion of patients who stop treatment with GnRH analogues and the reasons why. This outcome is important to patients because there is uncertainty about the short- and long-term safety and adverse effects of GnRH analogues in children and adolescents being treated for gender dysphoria. <u>B: Safety</u> - Short and long-term safety and adverse effects of taking GnRH analogues are important because GnRH analogues are not licensed for the treatment of adolescents and children with gender dysphoria. Aspects to be reported on should include: - Impact of the drug use such as its impact on bone density, arterial hypertension, cognitive development/functioning - Impact of withdrawing the drug such as, slipped upper femoral epiphysis, reversibility on the reproductive system, and any others as reported. <u>C: Cost effectiveness</u> Cost effectiveness studies should be reported.
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.

Language	English only
Patients	Human studies only
Age	18 years or less
Date limits	2000-2020
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines and pre-publication prints
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, the Cochrane Library, HTA and APA PsycInfo were searched on 23 July 2020, limiting the search to papers published in English language in the last 20 years. Conference abstracts and letters were excluded.

Database: Medline

Platform: Ovid

Version: Ovid MEDLINE(R) <1946 to July 21, 2020>

Search date: 23/7/2020

Number of results retrieved: 144

Search strategy:

- 1 Gender Dysphoria/ (485)
- 2 Gender Identity/ (18452)
- 3 "Sexual and Gender Disorders"/ (75)
- 4 Transsexualism/ (3758)
- 5 Transgender Persons/ (3143)
- 6 Health Services for Transgender Persons/ (136)
- 7 exp Sex Reassignment Procedures/ (836)
- 8 (gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw. (7435)
- 9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (12678)
- 10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (102343)
- 11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (6974)
- 12 (male-to-female or m2f or female-to-male or f2m).tw. (114841)
- 13 or/1-12 (252702)
- 14 exp Infant/ or Infant Health/ or Infant Welfare/ (1137479)
- 15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (852400)
- 16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1913257)

17 Minors/ (2574)
 18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (2361686)
 19 exp pediatrics/ (58118)
 20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (836269)
 21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2024207)
 22 Puberty/ (13278)
 23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert*
 or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn.
 (424246)
 24 Schools/ (38104)
 25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (7199)
 26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or
 pupil* or student*).ti,ab,jn. (468992)
 27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or
 "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or
 aged)).ti,ab. (89353)
 28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19")
 adj2 (year or years or age or ages or aged)).ti,ab. (887838)
 29 or/14-28 (5534171)
 30 13 and 29 (79263)
 31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (7)
 32 30 or 31 (79263)
 33 Gonadotropin-Releasing Hormone/ (27588)
 34 (pubert* adj3 block*).ti,ab. (78)
 35 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (17299)
 36 (GnRH adj2 analog*).ti,ab. (2541)
 37 GnRH*.ti,ab. (20991)
 38 "GnRH agonist*".ti,ab. (4040)
 39 Triptorelin Pamoate/ (1906)
 40 triptorelin.ti,ab. (677)
 41 arvekap.ti,ab. (1)
 42 ("AY 25650" or AY25650).ti,ab. (1)
 43 ("BIM 21003" or BIM21003).ti,ab. (0)
 44 ("BN 52014" or BN52014).ti,ab. (0)
 45 ("CL 118532" or CL118532).ti,ab. (0)
 46 Debio.ti,ab. (83)
 47 diphereline.ti,ab. (17)
 48 moapar.ti,ab. (0)
 49 pamorelin.ti,ab. (0)
 50 trelstar.ti,ab. (3)
 51 triptodur.ti,ab. (1)
 52 ("WY 42422" or WY42422).ti,ab. (0)
 53 ("WY 42462" or WY42462).ti,ab. (0)
 54 gonapeptyl.ti,ab. (0)
 55 decapeptyl.ti,ab. (210)
 56 salvacyl.ti,ab. (0)
 57 Buserelin/ (2119)
 58 buserelin.ti,ab. (1304)

59 bigonist.ti,ab. (0)
 60 ("hoe 766" or hoe-766 or hoe766).ti,ab. (69)
 61 profact.ti,ab. (2)
 62 receptal.ti,ab. (30)
 63 suprecur.ti,ab. (4)
 64 suprefact.ti,ab. (22)
 65 tiloryth.ti,ab. (0)
 66 histrelin.ti,ab. (55)
 67 "LHRH-hydrogel implant".ti,ab. (1)
 68 ("RL 0903" or RL0903).ti,ab. (1)
 69 ("SPD 424" or SPD424).ti,ab. (1)
 70 goserelin.ti,ab. (875)
 71 Goserelin/ (1612)
 72 ("ici 118630" or ici118630).ti,ab. (51)
 73 ("ZD-9393" or ZD9393).ti,ab. (0)
 74 zoladex.ti,ab. (379)
 75 leuprorelin.ti,ab. (413)
 76 carcinil.ti,ab. (0)
 77 enanton*.ti,ab. (23)
 78 ginecrin.ti,ab. (0)
 79 leuplin.ti,ab. (13)
 80 Leuprolide/ (2900)
 81 leuprolide.ti,ab. (1743)
 82 lucrin.ti,ab. (11)
 83 lupron.ti,ab. (162)
 84 provren.ti,ab. (0)
 85 procrin.ti,ab. (3)
 86 ("tap 144" or tap144).ti,ab. (40)
 87 (a-43818 or a43818).ti,ab. (3)
 88 Trenantone.ti,ab. (1)
 89 staladex.ti,ab. (0)
 90 prostap.ti,ab. (6)
 91 Nafarelin/ (327)
 92 nafarelin.ti,ab. (251)
 93 ("76932-56-4" or "76932564").ti,ab. (0)
 94 ("76932-60-0" or "76932600").ti,ab. (0)
 95 ("86220-42-0" or "86220420").ti,ab. (0)
 96 ("rs 94991 298" or rs94991298).ti,ab. (0)
 97 synarel.ti,ab. (12)
 98 deslorelin.ti,ab. (263)
 99 gonadorelin.ti,ab. (201)
 100 ("33515-09-2" or "33515092").ti,ab. (0)
 101 ("51952-41-1" or "51952411").ti,ab. (0)
 102 ("52699-48-6" or "52699486").ti,ab. (0)
 103 cetrotorelix.ti,ab. (463)
 104 cetrotide.ti,ab. (41)
 105 ("NS 75A" or NS75A).ti,ab. (0)
 106 ("NS 75B" or NS75B).ti,ab. (0)

107 ("SB 075" or SB075).ti,ab. (0)
 108 ("SB 75" or SB75).ti,ab. (63)
 109 gonadoliberin.ti,ab. (143)
 110 kryptocur.ti,ab. (6)
 111 cetorelix.ti,ab. (463)
 112 cetrotide.ti,ab. (41)
 113 antagon.ti,ab. (17)
 114 ganirelix.ti,ab. (138)
 115 ("ORG 37462" or ORG37462).ti,ab. (3)
 116 orgalutran.ti,ab. (20)
 117 ("RS 26306" or RS26306).ti,ab. (5)
 118 ("AY 24031" or AY24031).ti,ab. (0)
 119 factrel.ti,ab. (11)
 120 fertagyl.ti,ab. (11)
 121 lutrelef.ti,ab. (5)
 122 lutrepulse.ti,ab. (3)
 123 relefact.ti,ab. (10)
 124 fertiral.ti,ab. (0)
 125 (hoe471 or "hoe 471").ti,ab. (6)
 126 relisorm.ti,ab. (4)
 127 cystorelin.ti,ab. (18)
 128 dirigestran.ti,ab. (5)
 129 or/33-128 (42216)
 130 32 and 129 (416)
 131 limit 130 to english language (393)
 132 limit 131 to (letter or historical article or comment or editorial or news or case reports)
 (36)
 133 131 not 132 (357)
 134 animals/ not humans/ (4686361)
 135 133 not 134 (181)
 136 limit 135 to yr="2000 -Current" (144)

Database: Medline in-process

Platform: Ovid

Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to July 21, 2020>

Search date: 23/7/2020

Number of results retrieved:

Search strategy: 42

1 Gender Dysphoria/ (0)
 2 Gender Identity/ (0)
 3 "Sexual and Gender Disorders"/ (0)
 4 Transsexualism/ (0)
 5 Transgender Persons/ (0)
 6 Health Services for Transgender Persons/ (0)
 7 exp Sex Reassignment Procedures/ (0)

8 (gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or
 9 minorit* or queer*)).tw. (1645)
 10 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen*
 11 or transperson* or transpeopl*).tw. (2333)
 12 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw.
 13 (20884)
 14 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (968)
 15 (male-to-female or m2f or female-to-male or f2m).tw. (15513)
 16 or/1-12 (39905)
 17 exp Infant/ or Infant Health/ or Infant Welfare/ (0)
 18 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or
 19 perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (80723)
 20 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
 21 Minors/ (0)
 22 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (321871)
 23 exp pediatrics/ (0)
 24 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (119783)
 25 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
 26 Puberty/ (0)
 27 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert*
 28 or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn.
 29 (60264)
 30 Schools/ (0)
 31 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
 32 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or
 33 pupil* or student*).ti,ab,jn. (69233)
 34 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or
 35 "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or
 36 aged)).ti,ab. (10319)
 37 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19")
 38 adj2 (year or years or age or ages or aged)).ti,ab. (112800)
 39 or/14-28 (525529)
 40 13 and 29 (9196)
 41 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (3)
 42 30 or 31 (9197)
 43 Gonadotropin-Releasing Hormone/ (0)
 44 (pubert* adj3 block*).ti,ab. (19)
 45 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (1425)
 (GnRH adj2 analog*).ti,ab. (183)
 GnRH*.ti,ab. (1695)
 "GnRH agonist".ti,ab. (379)
 Triptorelin Pamoate/ (0)
 triptorelin.ti,ab. (72)
 arvekap.ti,ab. (0)
 ("AY 25650" or AY25650).ti,ab. (0)
 ("BIM 21003" or BIM21003).ti,ab. (0)
 ("BN 52014" or BN52014).ti,ab. (0)
 ("CL 118532" or CL118532).ti,ab. (0)

46 Debio.ti,ab. (11)
 47 diphereline.ti,ab. (6)
 48 moapar.ti,ab. (0)
 49 pamorelin.ti,ab. (0)
 50 trelstar.ti,ab. (0)
 51 triptodur.ti,ab. (0)
 52 ("WY 42422" or WY42422).ti,ab. (0)
 53 ("WY 42462" or WY42462).ti,ab. (0)
 54 gonapeptyl.ti,ab. (0)
 55 decapeptyl.ti,ab. (8)
 56 salvacyl.ti,ab. (0)
 57 Buserelin/ (0)
 58 buserelin.ti,ab. (59)
 59 bigonist.ti,ab. (0)
 60 ("hoe 766" or hoe-766 or hoe766).ti,ab. (3)
 61 profact.ti,ab. (0)
 62 receptal.ti,ab. (0)
 63 suprecur.ti,ab. (1)
 64 suprefact.ti,ab. (2)
 65 tiloryth.ti,ab. (0)
 66 histrelin.ti,ab. (9)
 67 "LHRH-hydrogel implant".ti,ab. (0)
 68 ("RL 0903" or RL0903).ti,ab. (0)
 69 ("SPD 424" or SPD424).ti,ab. (0)
 70 goserelin.ti,ab. (68)
 71 Goserelin/ (0)
 72 ("ici 118630" or ici118630).ti,ab. (0)
 73 ("ZD-9393" or ZD9393).ti,ab. (0)
 74 zoladex.ti,ab. (6)
 75 leuprorelin.ti,ab. (47)
 76 carcinil.ti,ab. (0)
 77 enanton*.ti,ab. (1)
 78 ginecrin.ti,ab. (0)
 79 leuplin.ti,ab. (1)
 80 Leuprolide/ (0)
 81 leuprolide.ti,ab. (121)
 82 lucrin.ti,ab. (4)
 83 lupron.ti,ab. (10)
 84 provren.ti,ab. (0)
 85 procrin.ti,ab. (0)
 86 ("tap 144" or tap144).ti,ab. (0)
 87 (a-43818 or a43818).ti,ab. (0)
 88 Trenantone.ti,ab. (1)
 89 staladex.ti,ab. (0)
 90 prostap.ti,ab. (0)
 91 Nafarelin/ (0)
 92 nafarelin.ti,ab. (5)
 93 ("76932-56-4" or "76932564").ti,ab. (0)

94 ("76932-60-0" or "76932600").ti,ab. (0)
 95 ("86220-42-0" or "86220420").ti,ab. (0)
 96 ("rs 94991 298" or rs94991298).ti,ab. (0)
 97 synarel.ti,ab. (0)
 98 deslorelin.ti,ab. (14)
 99 gonadorelin.ti,ab. (13)
 100 ("33515-09-2" or "33515092").ti,ab. (0)
 101 ("51952-41-1" or "51952411").ti,ab. (0)
 102 ("52699-48-6" or "52699486").ti,ab. (0)
 103 cetorelix.ti,ab. (31)
 104 cetrotide.ti,ab. (5)
 105 ("NS 75A" or NS75A).ti,ab. (0)
 106 ("NS 75B" or NS75B).ti,ab. (0)
 107 ("SB 075" or SB075).ti,ab. (0)
 108 ("SB 75" or SB75).ti,ab. (2)
 109 gonadoliberin.ti,ab. (4)
 110 kryptocur.ti,ab. (1)
 111 cetorelix.ti,ab. (31)
 112 cetrotide.ti,ab. (5)
 113 antagonist.ti,ab. (0)
 114 ganirelix.ti,ab. (8)
 115 ("ORG 37462" or ORG37462).ti,ab. (0)
 116 orgalutran.ti,ab. (3)
 117 ("RS 26306" or RS26306).ti,ab. (0)
 118 ("AY 24031" or AY24031).ti,ab. (0)
 119 factrel.ti,ab. (2)
 120 fertagyl.ti,ab. (1)
 121 lutrelef.ti,ab. (0)
 122 lutrepulse.ti,ab. (0)
 123 relefact.ti,ab. (0)
 124 fertiral.ti,ab. (0)
 125 (hoe471 or "hoe 471").ti,ab. (0)
 126 relisorm.ti,ab. (0)
 127 cystorelin.ti,ab. (1)
 128 dirigestran.ti,ab. (0)
 129 or/33-128 (2332)
 130 32 and 129 (45)
 131 limit 130 to english language (45)
 132 limit 131 to yr="2000 -Current" (42)

Database: Medline epubs ahead of print

Platform: Ovid

Version: Ovid MEDLINE(R) Epub Ahead of Print <July 21, 2020>

Search date: 23/7/2020

Number of results retrieved: 8

Search strategy:

1 Gender Dysphoria/ (0)

2 Gender Identity/ (0)
 3 "Sexual and Gender Disorders"/ (0)
 4 Transsexualism/ (0)
 5 Transgender Persons/ (0)
 6 Health Services for Transgender Persons/ (0)
 7 exp Sex Reassignment Procedures/ (0)
 8 (gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or
 9 minorit* or queer*)).tw. (486)
 10 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen*
 11 or transperson* or transpeopl*).tw. (640)
 12 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw.
 13 (1505)
 14 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (178)
 15 (male-to-female or m2f or female-to-male or f2m).tw. (2480)
 16 or/1-12 (4929)
 17 exp Infant/ or Infant Health/ or Infant Welfare/ (0)
 18 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or
 19 perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (15496)
 20 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
 21 Minors/ (0)
 22 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (53563)
 23 exp pediatrics/ (0)
 24 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (22796)
 25 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
 26 Puberty/ (0)
 27 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert*
 28 or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn.
 29 (13087)
 30 Schools/ (0)
 31 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
 32 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or
 33 pupil* or student*).ti,ab,jn. (12443)
 34 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or
 35 "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or
 36 aged)).ti,ab. (1416)
 37 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19")
 38 adj2 (year or years or age or ages or aged)).ti,ab. (20166)
 39 or/14-28 (88366)
 40 13 and 29 (1638)
 41 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (1)
 42 30 or 31 (1638)
 43 Gonadotropin-Releasing Hormone/ (0)
 44 (pubert* adj3 block*).ti,ab. (2)
 45 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (176)
 46 (GnRH adj2 analog*).ti,ab. (30)
 47 GnRH*.ti,ab. (223)
 48 "GnRH agonist".ti,ab. (49)
 49 Triptorelin Pamoate/ (0)

40 triptorelin.ti,ab. (12)
 41 arvekap.ti,ab. (0)
 42 ("AY 25650" or AY25650).ti,ab. (0)
 43 ("BIM 21003" or BIM21003).ti,ab. (0)
 44 ("BN 52014" or BN52014).ti,ab. (0)
 45 ("CL 118532" or CL118532).ti,ab. (0)
 46 Debio.ti,ab. (2)
 47 diphereline.ti,ab. (1)
 48 moapar.ti,ab. (0)
 49 pamorelin.ti,ab. (0)
 50 trelstar.ti,ab. (0)
 51 triptodur.ti,ab. (0)
 52 ("WY 42422" or WY42422).ti,ab. (0)
 53 ("WY 42462" or WY42462).ti,ab. (0)
 54 gonapeptyl.ti,ab. (0)
 55 decapeptyl.ti,ab. (0)
 56 salvacyl.ti,ab. (0)
 57 Buserelin/ (0)
 58 buserelin.ti,ab. (7)
 59 bigonist.ti,ab. (0)
 60 ("hoe 766" or hoe-766 or hoe766).ti,ab. (0)
 61 profact.ti,ab. (0)
 62 receptal.ti,ab. (0)
 63 suprecur.ti,ab. (0)
 64 suprefact.ti,ab. (1)
 65 tiloryth.ti,ab. (0)
 66 histrelin.ti,ab. (2)
 67 "LHRH-hydrogel implant".ti,ab. (0)
 68 ("RL 0903" or RL0903).ti,ab. (0)
 69 ("SPD 424" or SPD424).ti,ab. (0)
 70 goserelin.ti,ab. (11)
 71 Goserelin/ (0)
 72 ("ici 118630" or ici118630).ti,ab. (0)
 73 ("ZD-9393" or ZD9393).ti,ab. (0)
 74 zoladex.ti,ab. (1)
 75 leuprorelin.ti,ab. (13)
 76 carcinil.ti,ab. (0)
 77 enanton*.ti,ab. (1)
 78 ginecrin.ti,ab. (0)
 79 leuplin.ti,ab. (0)
 80 Leuprolide/ (0)
 81 leuprolide.ti,ab. (22)
 82 lucrin.ti,ab. (0)
 83 lupron.ti,ab. (2)
 84 provren.ti,ab. (0)
 85 procrin.ti,ab. (0)
 86 ("tap 144" or tap144).ti,ab. (1)
 87 (a-43818 or a43818).ti,ab. (0)

88 Trenantone.ti,ab. (0)
 89 staladex.ti,ab. (0)
 90 prostap.ti,ab. (0)
 91 Nafarelin/ (0)
 92 nafarelin.ti,ab. (4)
 93 ("76932-56-4" or "76932564").ti,ab. (0)
 94 ("76932-60-0" or "76932600").ti,ab. (0)
 95 ("86220-42-0" or "86220420").ti,ab. (0)
 96 ("rs 94991 298" or rs94991298).ti,ab. (0)
 97 synarel.ti,ab. (0)
 98 deslorelin.ti,ab. (3)
 99 gonadorelin.ti,ab. (3)
 100 ("33515-09-2" or "33515092").ti,ab. (0)
 101 ("51952-41-1" or "51952411").ti,ab. (0)
 102 ("52699-48-6" or "52699486").ti,ab. (0)
 103 cetorelix.ti,ab. (6)
 104 cetrotide.ti,ab. (2)
 105 ("NS 75A" or NS75A).ti,ab. (0)
 106 ("NS 75B" or NS75B).ti,ab. (0)
 107 ("SB 075" or SB075).ti,ab. (0)
 108 ("SB 75" or SB75).ti,ab. (0)
 109 gonadoliberin.ti,ab. (0)
 110 kryptocur.ti,ab. (0)
 111 cetorelix.ti,ab. (6)
 112 cetrotide.ti,ab. (2)
 113 antagon.ti,ab. (1)
 114 ganirelix.ti,ab. (1)
 115 ("ORG 37462" or ORG37462).ti,ab. (0)
 116 orgalutran.ti,ab. (0)
 117 ("RS 26306" or RS26306).ti,ab. (0)
 118 ("AY 24031" or AY24031).ti,ab. (0)
 119 factrel.ti,ab. (0)
 120 fertagyl.ti,ab. (0)
 121 lutrelef.ti,ab. (0)
 122 lutrepulse.ti,ab. (0)
 123 relefact.ti,ab. (0)
 124 fertiral.ti,ab. (0)
 125 (hoe471 or "hoe 471").ti,ab. (0)
 126 relisorm.ti,ab. (0)
 127 cystorelin.ti,ab. (0)
 128 dirigestran.ti,ab. (0)
 129 or/33-128 (310)
 130 32 and 129 (8)
 131 limit 130 to english language (8)
 132 limit 131 to yr="2000 -Current" (8)

Database: Medline daily update

Platform: Ovid

Version: Ovid MEDLINE(R) Daily Update <July 21, 2020>

Search date: 23/7/2020

Number of results retrieved: 1

Search strategy

- 1 Gender Dysphoria/ (4)
- 2 Gender Identity/ (38)
- 3 "Sexual and Gender Disorders"/ (0)
- 4 Transsexualism/ (2)
- 5 Transgender Persons/ (26)
- 6 Health Services for Transgender Persons/ (1)
- 7 exp Sex Reassignment Procedures/ (3)
- 8 (gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*).tw. (24)
- 9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (39)
- 10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (87)
- 11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*).tw. (15)
- 12 (male-to-female or m2f or female-to-male or f2m).tw. (181)
- 13 or/1-12 (358)
- 14 exp Infant/ or Infant Health/ or Infant Welfare/ (932)
- 15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (981)
- 16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1756)
- 17 Minors/ (3)
- 18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3672)
- 19 exp pediatrics/ (75)
- 20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1658)
- 21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2006)
- 22 Puberty/ (8)
- 23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (732)
- 24 Schools/ (56)
- 25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (5)
- 26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (622)
- 27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (98)
- 28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (1301)
- 29 or/14-28 (6705)
- 30 13 and 29 (130)
- 31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (0)
- 32 30 or 31 (130)
- 33 Gonadotropin-Releasing Hormone/ (11)

34 (pubert* adj3 block*).ti,ab. (0)
 35 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (10)
 36 (GnRH adj2 analog*).ti,ab. (2)
 37 GnRH*.ti,ab. (14)
 38 "GnRH agonist*".ti,ab. (4)
 39 Triptorelin Pamoate/ (1)
 40 triptorelin.ti,ab. (1)
 41 arvekap.ti,ab. (0)
 42 ("AY 25650" or AY25650).ti,ab. (0)
 43 ("BIM 21003" or BIM21003).ti,ab. (0)
 44 ("BN 52014" or BN52014).ti,ab. (0)
 45 ("CL 118532" or CL118532).ti,ab. (0)
 46 Debio.ti,ab. (1)
 47 diphereline.ti,ab. (0)
 48 moapar.ti,ab. (0)
 49 pamorelin.ti,ab. (0)
 50 trelstar.ti,ab. (0)
 51 triptodur.ti,ab. (0)
 52 ("WY 42422" or WY42422).ti,ab. (0)
 53 ("WY 42462" or WY42462).ti,ab. (0)
 54 gonapeptyl.ti,ab. (0)
 55 decapeptyl.ti,ab. (0)
 56 salvacyl.ti,ab. (0)
 57 Buserelin/ (0)
 58 buserelin.ti,ab. (0)
 59 bigonist.ti,ab. (0)
 60 ("hoe 766" or hoe-766 or hoe766).ti,ab. (0)
 61 profact.ti,ab. (0)
 62 receptal.ti,ab. (0)
 63 suprecur.ti,ab. (0)
 64 suprefact.ti,ab. (0)
 65 tiloryth.ti,ab. (0)
 66 histrelin.ti,ab. (0)
 67 "LHRH-hydrogel implant".ti,ab. (0)
 68 ("RL 0903" or RL0903).ti,ab. (0)
 69 ("SPD 424" or SPD424).ti,ab. (0)
 70 goserelin.ti,ab. (1)
 71 Goserelin/ (2)
 72 ("ici 118630" or ici118630).ti,ab. (0)
 73 ("ZD-9393" or ZD9393).ti,ab. (0)
 74 zoladex.ti,ab. (0)
 75 leuprorelin.ti,ab. (0)
 76 carcinil.ti,ab. (0)
 77 enanton*.ti,ab. (0)
 78 ginecrin.ti,ab. (0)
 79 leuplin.ti,ab. (0)
 80 Leuprolide/ (0)
 81 leuprolide.ti,ab. (0)

82 lucrin.ti,ab. (0)
 83 lupron.ti,ab. (0)
 84 provren.ti,ab. (0)
 85 procrin.ti,ab. (0)
 86 ("tap 144" or tap144).ti,ab. (0)
 87 (a-43818 or a43818).ti,ab. (0)
 88 Trenantone.ti,ab. (0)
 89 staladex.ti,ab. (0)
 90 prostap.ti,ab. (0)
 91 Nafarelin/ (0)
 92 nafarelin.ti,ab. (0)
 93 ("76932-56-4" or "76932564").ti,ab. (0)
 94 ("76932-60-0" or "76932600").ti,ab. (0)
 95 ("86220-42-0" or "86220420").ti,ab. (0)
 96 ("rs 94991 298" or rs94991298).ti,ab. (0)
 97 synarel.ti,ab. (0)
 98 deslorelin.ti,ab. (0)
 99 gonadorelin.ti,ab. (0)
 100 ("33515-09-2" or "33515092").ti,ab. (0)
 101 ("51952-41-1" or "51952411").ti,ab. (0)
 102 ("52699-48-6" or "52699486").ti,ab. (0)
 103 cetorelix.ti,ab. (0)
 104 cetrotide.ti,ab. (0)
 105 ("NS 75A" or NS75A).ti,ab. (0)
 106 ("NS 75B" or NS75B).ti,ab. (0)
 107 ("SB 075" or SB075).ti,ab. (0)
 108 ("SB 75" or SB75).ti,ab. (0)
 109 gonadoliberin.ti,ab. (0)
 110 kryptocur.ti,ab. (0)
 111 cetorelix.ti,ab. (0)
 112 cetrotide.ti,ab. (0)
 113 antagon.ti,ab. (0)
 114 ganirelix.ti,ab. (0)
 115 ("ORG 37462" or ORG37462).ti,ab. (0)
 116 orgalutran.ti,ab. (0)
 117 ("RS 26306" or RS26306).ti,ab. (0)
 118 ("AY 24031" or AY24031).ti,ab. (0)
 119 factrel.ti,ab. (0)
 120 fertagyl.ti,ab. (0)
 121 lutrelef.ti,ab. (0)
 122 lutrepulse.ti,ab. (0)
 123 relefact.ti,ab. (0)
 124 fertiral.ti,ab. (0)
 125 (hoe471 or "hoe 471").ti,ab. (0)
 126 relisorm.ti,ab. (0)
 127 cystorelin.ti,ab. (0)
 128 dirigestran.ti,ab. (0)
 129 or/33-128 (23)

130 32 and 129 (1)
 131 limit 130 to english language (1)
 132 limit 131 to yr="2000 -Current" (1)

Database: Embase

Platform: Ovid

Version: Embase <1974 to 2020 July 22>

Search date: 23/7/2020

Number of results retrieved: 367

Search strategy:

1 exp Gender Dysphoria/ (5399)
 2 Gender Identity/ (16820)
 3 "Sexual and Gender Disorders"/ (24689)
 4 Transsexualism/ (3869)
 5 exp Transgender/ (6597)
 6 Health Services for Transgender Persons/ (158848)
 7 exp Sex Reassignment Procedures/ or sex transformation/ (3058)
 8 (gender* adj3 (dysphori* or affirm* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (13005)
 9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (22509)
 10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (154446)
 11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (10327)
 12 (male-to-female or m2f or female-to-male or f2m).tw. (200166)
 13 or/1-12 (582812)
 14 exp juvenile/ or Child Behavior/ or Child Welfare/ or Child Health/ or infant welfare/ or "minor (person)"/ or elementary student/ (3437324)
 15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (1186161)
 16 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3586795)
 17 exp pediatrics/ (106214)
 18 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1491597)
 19 exp adolescence/ or exp adolescent behavior/ or adolescent health/ or high school student/ or middle school student/ (105108)
 20 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (641660)
 21 school/ or high school/ or kindergarten/ or middle school/ or primary school/ or nursery school/ or day care/ (103791)
 22 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (687437)
 23 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (138908)
 24 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (1562903)

25 or/14-24 (7130881)
 26 13 and 25 (182161)
 27 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw.
 (17)
 28 26 or 27 (182161)
 29 gonadorelin/ (37580)
 30 (pubert* adj3 block*).ti,ab. (142)
 31 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (21450)
 32 (GnRH adj2 analog*).ti,ab. (4013)
 33 GnRH*.ti,ab. (29862)
 34 "GnRH agonist".ti,ab. (6719)
 35 exp gonadorelin agonist/ or gonadorelin derivative/ or gonadorelin acetate/ (23304)
 36 Triptorelin/ (5427)
 37 triptorelin.ti,ab. (1182)
 38 arvekap.ti,ab. (3)
 39 ("AY 25650" or AY25650).ti,ab. (1)
 40 ("BIM 21003" or BIM21003).ti,ab. (0)
 41 ("BN 52014" or BN52014).ti,ab. (0)
 42 ("CL 118532" or CL118532).ti,ab. (0)
 43 Debio.ti,ab. (185)
 44 diphereline.ti,ab. (51)
 45 moapar.ti,ab. (0)
 46 pamorelin.ti,ab. (0)
 47 trelstar.ti,ab. (5)
 48 triptodur.ti,ab. (1)
 49 ("WY 42422" or WY42422).ti,ab. (0)
 50 ("WY 42462" or WY42462).ti,ab. (0)
 51 gonapeptyl.ti,ab. (10)
 52 decapeptyl.ti,ab. (307)
 53 salvacyl.ti,ab. (1)
 54 buserelin acetate/ or buserelin/ (5164)
 55 buserelin.ti,ab. (1604)
 56 bigonist.ti,ab. (1)
 57 ("hoe 766" or hoe-766 or hoe766).ti,ab. (89)
 58 profact.ti,ab. (4)
 59 receptal.ti,ab. (37)
 60 suprecur.ti,ab. (8)
 61 suprefact.ti,ab. (30)
 62 tiloryth.ti,ab. (0)
 63 histrelin/ (446)
 64 histrelin.ti,ab. (107)
 65 "LHRH-hydrogel implant".ti,ab. (1)
 66 ("RL 0903" or RL0903).ti,ab. (1)
 67 ("SPD 424" or SPD424).ti,ab. (1)
 68 goserelin.ti,ab. (1487)
 69 Goserelin/ (7128)
 70 ("ici 118630" or ici118630).ti,ab. (49)
 71 ("ZD-9393" or ZD9393).ti,ab. (0)

72 zoladex.ti,ab. (501)
 73 leuprorelin/ (11312)
 74 leuprorelin.ti,ab. (727)
 75 carcinil.ti,ab. (0)
 76 enanton*.ti,ab. (38)
 77 ginecrin.ti,ab. (1)
 78 leuplin.ti,ab. (26)
 79 leuprolide.ti,ab. (2788)
 80 lucrin.ti,ab. (47)
 81 lupron.ti,ab. (361)
 82 provren.ti,ab. (0)
 83 procrin.ti,ab. (11)
 84 ("tap 144" or tap144).ti,ab. (63)
 85 (a-43818 or a43818).ti,ab. (3)
 86 Trenantone.ti,ab. (7)
 87 staladex.ti,ab. (0)
 88 prostap.ti,ab. (11)
 89 nafarelin acetate/ or nafarelin/ (1441)
 90 nafarelin.ti,ab. (324)
 91 ("76932-56-4" or "76932564").ti,ab. (0)
 92 ("76932-60-0" or "76932600").ti,ab. (0)
 93 ("86220-42-0" or "86220420").ti,ab. (0)
 94 ("rs 94991 298" or rs94991298).ti,ab. (0)
 95 synarel.ti,ab. (28)
 96 deslorelin/ (452)
 97 deslorelin.ti,ab. (324)
 98 gonadorelin.ti,ab. (338)
 99 ("33515-09-2" or "33515092").ti,ab. (0)
 100 ("51952-41-1" or "51952411").ti,ab. (0)
 101 ("52699-48-6" or "52699486").ti,ab. (0)
 102 cetorelix/ (2278)
 103 cetorelix.ti,ab. (717)
 104 cetrotide.ti,ab. (113)
 105 ("NS 75A" or NS75A).ti,ab. (0)
 106 ("NS 75B" or NS75B).ti,ab. (0)
 107 ("SB 075" or SB075).ti,ab. (1)
 108 ("SB 75" or SB75).ti,ab. (76)
 109 gonadoliberin.ti,ab. (152)
 110 kryptocur.ti,ab. (6)
 111 cetorelix.ti,ab. (717)
 112 cetrotide.ti,ab. (113)
 113 antagon.ti,ab. (32)
 114 ganirelix/ (1284)
 115 ganirelix.ti,ab. (293)
 116 ("ORG 37462" or ORG37462).ti,ab. (4)
 117 orgalutran/ (1284)
 118 orgalutran.ti,ab. (68)
 119 ("RS 26306" or RS26306).ti,ab. (6)

120 ("AY 24031" or AY24031).ti,ab. (0)
 121 factrel.ti,ab. (14)
 122 fertagyl.ti,ab. (20)
 123 lutrelef.ti,ab. (7)
 124 lutrepulse.ti,ab. (6)
 125 relefact.ti,ab. (10)
 126 fertiral.ti,ab. (0)
 127 (hoe471 or "hoe 471").ti,ab. (4)
 128 relisorm.ti,ab. (6)
 129 cystorelin.ti,ab. (26)
 130 dirigestran.ti,ab. (5)
 131 or/29-130 (80790)
 132 28 and 131 (988)
 133 limit 132 to english language (940)
 134 133 not (letter or editorial).pt. (924)
 135 134 not (conference abstract or conference paper or conference proceeding or
 "conference review").pt. (683)
 136 nonhuman/ not (human/ and nonhuman/) (4649157)
 137 135 not 136 (506)
 138 limit 137 to yr="2000 -Current" (420)
 139 elsevier.cr. (25912990)
 140 138 and 139 (372)
 141 remove duplicates from 140 (367)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL

Platform: Wiley

Version:

CDSR – Issue 7 of 12, July 2020

CENTRAL – Issue 7 of 12, July 2020

Search date: 23/7/2020

Number of results retrieved: CDSR – 1; CENTRAL - 8.

#1 [mh ^"Gender Dysphoria"] 3
 #2 [mh ^"gender identity"] 227
 #3 [mh ^"sexual and gender disorders"] 2
 #4 [mh ^transsexualism] 27
 #5 [mh ^"transgender persons"] 36
 #6 [mh ^"health services for transgender persons"] 0
 #7 [mh "sex reassignment procedures"] 4
 #8 (gender* NEAR/3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus*
 or minorit* or queer*)):ti,ab 308
 #9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or
 transmen* or transperson* or transpeopl*):ti,ab 929
 #10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or
 genderqueer*):ti,ab 3915
 #11 ((sex or gender*) NEAR/3 (reassign* or chang* or transform* or transition*)):ti,ab 493
 #12 (male-to-female or m2f or female-to-male or f2m):ti,ab 489

#13 {or #1-#12} 6142
 #14 [mh infant] or [mh ^"infant health"] or [mh ^"infant welfare"] 27769
 #15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*):ti,ab 69476
 #16 [mh child] or [mh "child behavior"] or [mh ^"child health"] or [mh ^"child welfare"] 42703
 #17 [mh ^minors] 8
 #18 (child* or minor or minors or boy* or girl* or kid or kids or young*):ti,ab 175826
 #19 [mh pediatrics]661
 #20 (pediatric* or paediatric* or peadiatric*):ti,ab 30663
 #21 [mh ^adolescent] or [mh ^"adolescent behavior"] or [mh ^"adolescent health"] 102154
 #22 [mh ^puberty] 295
 #23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*):ti,ab 34139
 #24 [mh ^schools] 1914
 #25 [mh ^"Child Day Care Centers"] or [mh nurseries] or [mh ^"schools, nursery"] 277
 #26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*):ti,ab 54723
 #27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") NEAR/2 (year or years or age or ages or aged)):ti,ab 6710
 #28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") NEAR/2 (year or years or age or ages or aged)):ti,ab 196881
 #29 {or #14-#28} 469351
 #30 #13 and #29 2146
 #31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*):ti,ab 0
 #32 #30 or #31 2146
 #33 [mh ^"Gonadotropin-Releasing Hormone"] 1311
 #34 (pubert* NEAR/3 block*):ti,ab 1
 #35 ((gonadotrophin or gonadotropin) and releasing):ti,ab 2095
 #36 (GnRH NEAR/2 analog*):ti,ab 493
 #37 GnRH*:ti,ab 3764
 #38 "GnRH agonist*":ti,ab 1399
 #39 [mh ^"Triptorelin Pamoate"] 451
 #40 triptorelin:ti,ab 451
 #41 arvekap:ti,ab 4
 #42 ("AY 25650" or AY25650):ti,ab 0
 #43 ("BIM 21003" or BIM21003):ti,ab 0
 #44 ("BN 52014" or BN52014):ti,ab 0
 #45 ("CL 118532" or CL118532):ti,ab 0
 #46 Debio:ti,ab 301
 #47 diphereline:ti,ab 25
 #48 moapar:ti,ab 0
 #49 pamorelin:ti,ab 5
 #50 trelstar:ti,ab 3

#51	triptodur:ti,ab	0
#52	("WY 42422" or WY42422):ti,ab	0
#53	("WY 42462" or WY42462):ti,ab	0
#54	gonapeptyl:ti,ab	11
#55	decapeptyl:ti,ab	135
#56	salvacyl:ti,ab	0
#57	[mh ^Buserelin]	290
#58	Buserelin:ti,ab	339
#59	bigonist:ti,ab	0
#60	("hoe 766" or hoe-766 or hoe766):ti,ab	11
#61	profact:ti,ab	1
#62	receptal:ti,ab	4
#63	suprecur:ti,ab	0
#64	suprefact:ti,ab	28
#65	tiloryth:ti,ab	0
#66	histrelin:ti,ab	5
#67	"LHRH-hydrogel implant":ti,ab	0
#68	("RL 0903" or RL0903):ti,ab	0
#69	("SPD 424" or SPD424):ti,ab	0
#70	goserelin:ti,ab	761
#71	[mh ^goserelin]	568
#72	("ici 118630" or ici118630):ti,ab	7
#73	("ZD-9393" or ZD9393):ti,ab	1
#74	zoladex:ti,ab	318
#75	leuprorelin:ti,ab	248
#76	carcinil:ti,ab	0
#77	enanton*:ti,ab	21
#78	ginecrin:ti,ab	1
#79	leuplin:ti,ab	7
#80	[mh ^Leuprolide]	686
#81	leuprolide:ti,ab	696
#82	lucrin:ti,ab	21
#83	lupron:ti,ab	77
#84	provren:ti,ab	0
#85	procrin:ti,ab	2
#86	("tap 144" or tap144):ti,ab	24
#87	(a-43818 or a43818):ti,ab	0
#88	Trenantone:ti,ab	3
#89	staladex:ti,ab	0
#90	prostag:ti,ab	9
#91	[mh ^Nafarelin]	77
#92	nafarelin:ti,ab	114
#93	("76932-56-4" or "76932564"):ti,ab	0
#94	("76932-60-0" or "76932600"):ti,ab	2
#95	("86220-42-0" or "86220420"):ti,ab	0
#96	("rs 94991 298" or rs94991298):ti,ab	0
#97	synarel:ti,ab	10
#98	deslorelin:ti,ab	16

#99 gonadorelin:ti,ab 11
 #100 ("33515-09-2" or "33515092"):ti,ab 0
 #101 ("51952-41-1" or "51952411"):ti,ab 0
 #102 ("52699-48-6" or "52699486"):ti,ab 0
 #103 cetorelix:ti,ab 221
 #104 cetrotide:ti,ab 111
 #105 ("NS 75A" or NS75A):ti,ab 0
 #106 ("NS 75B" or NS75B):ti,ab 0
 #107 ("SB 075" or SB075):ti,ab 0
 #108 ("SB 75" or SB75):ti,ab 10
 #109 gonadoliberin:ti,ab 5
 #110 kryptocur:ti,ab 0
 #111 cetorelix:ti,ab 221
 #112 cetrotide:ti,ab 111
 #113 antagon:ti,ab 12
 #114 ganirelix:ti,ab 142
 #115 ("ORG 37462" or ORG37462):ti,ab 4
 #116 orgalutran:ti,ab 45
 #117 ("RS 26306" or RS26306):ti,ab 0
 #118 ("AY 24031" or AY24031):ti,ab 0
 #119 factrel:ti,ab 1
 #120 fertagyl:ti,ab 0
 #121 lutrelef:ti,ab 0
 #122 lutrepulse:ti,ab 1
 #123 relefact:ti,ab 1
 #124 fertiral:ti,ab 0
 #125 (hoe471 or "hoe 471"):ti,ab 3
 #126 relisorm:ti,ab 0
 #127 cystorelin:ti,ab 0
 #128 dirigestran:ti,ab 0
 #129 {or #33-#128} 6844
 #130 #32 and #129 27
 #131 #130 with Cochrane Library publication date Between Jan 2000 and Jul 2020, in Cochrane Reviews 1
 #132 #130 27
 #133 "conference":pt or (clinicaltrials or trialsearch):so 492465
 #134 #132 not #1339
 #135 #134 with Publication Year from 2000 to 2020, in Trials 8

Database: HTA

Platform: CRD

Version: HTA

Search date: 23/7/2020

Number of results retrieved: 26

Search strategy:

1 MeSH DESCRIPTOR Gender Dysphoria EXPLODE ALL TREES 0
 2 MeSH DESCRIPTOR Gender Identity EXPLODE ALL TREES 14

3 MeSH DESCRIPTOR Sexual and Gender Disorders EXPLODE ALL TREES 2

4 MeSH DESCRIPTOR Transsexualism EXPLODE ALL TREES 12

5 MeSH DESCRIPTOR Transgender Persons EXPLODE ALL TREES 3

6 MeSH DESCRIPTOR Health Services for Transgender Persons EXPLODE ALL TREES 0

7 MeSH DESCRIPTOR Sex Reassignment Procedures EXPLODE ALL TREES 1

8 ((gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*))) 28

9 ((transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*)) 76

10 ((trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*)) 83

11 (((sex or gender*) adj3 (reassign* or chang* or transform* or transition*))) 24

12 (male-to-female or m2f or female-to-male or f2m) 86

13 ((transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*)) 0

14 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 262

15 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13) IN HTA 30

*26 results are from 200 onwards. Downloaded as a set to sift for drug terms rather than continuing with search strategy.

Database: APA PsycInfo

Search date: July 2020 (Week 2)

Search Strategy:

1 Gender Dysphoria/ (936)

2 Gender Identity/ (8648)

3 Transsexualism/ (2825)

4 Transgender/ (5257)

5 exp Gender Reassignment/ (568)

6 (gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw. (15471)

7 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (13028)

8 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (7679)

9 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (5796)

10 (male-to-female or m2f or female-to-male or f2m).tw. (63688)

11 or/1-10 (99560)

12 exp Infant Development/ (21841)

13 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (150219)

14 Child Characteristics/ or exp Child Behavior/ or Child Psychology/ or exp Child Welfare/
or Child Psychiatry/ (23423)

15 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (984230)

16 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (78962)

17 Adolescent Psychiatry/ or Adolescent Behavior/ or Adolescent Development/ or
Adolescent Psychology/ or Adolescent Characteristics/ or Adolescent Health/ (62142)

18 Puberty/ (2753)

19 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert*
or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn.
(347604)

20 Schools/ or exp elementary school students/ or high school students/ or junior high
school students/ or middle school students/ (113053)

21 Child Day Care/ or Nursery Schools/ (2836)

22 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or
pupil* or student*).ti,ab,jn. (772814)

23 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or
"sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or
aged)).ti,ab. (21475)

24 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19")
adj2 (year or years or age or ages or aged)).ti,ab. (285697)

25 or/12-24 (1772959)

26 11 and 25 (49612)

27 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw.
(14)

28 26 or 27 (49613)

29 exp Gonadotropic Hormones/ (4226)

30 (pubert* adj3 block*).ti,ab. (29)

31 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (1060)

32 (GnRH adj2 analog*).ti,ab. (49)

33 GnRH*.ti,ab. (998)

34 "GnRH agonist*".ti,ab. (72)

35 triptorelin.ti,ab. (25)

36 arvekap.ti,ab. (0)

37 ("AY 25650" or AY25650).ti,ab. (0)

38 ("BIM 21003" or BIM21003).ti,ab. (0)

39 ("BN 52014" or BN52014).ti,ab. (0)

40 ("CL 118532" or CL118532).ti,ab. (0)

41 Debio.ti,ab. (7)

42 diphereline.ti,ab. (0)

43 moapar.ti,ab. (0)

44 pamorelin.ti,ab. (0)

45 trelstar.ti,ab. (0)

46 triptodur.ti,ab. (0)

47 ("WY 42422" or WY42422).ti,ab. (0)

48 ("WY 42462" or WY42462).ti,ab. (0)

49 gonapeptyl.ti,ab. (0)

50 decapeptyl.ti,ab. (3)

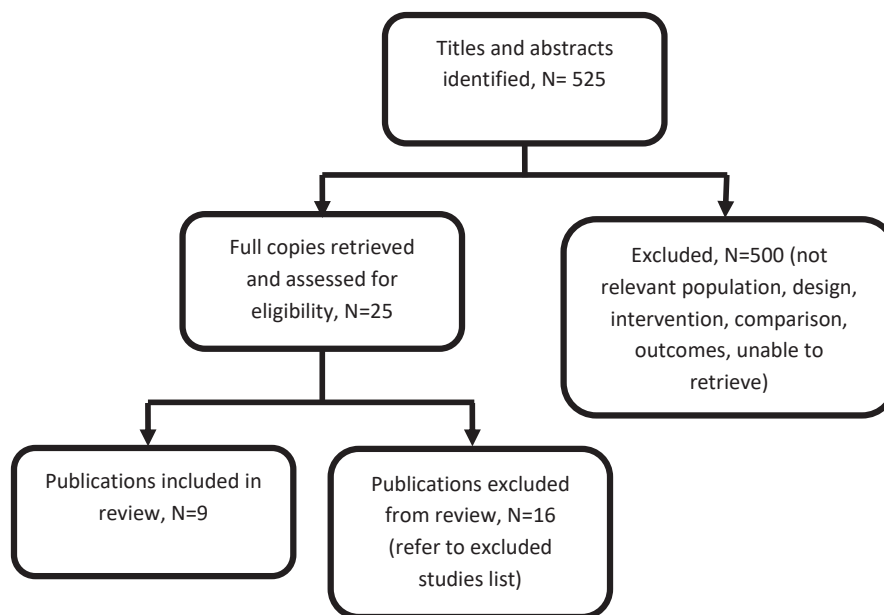
51 salvacyl.ti,ab. (1)

52 buserelin.ti,ab. (6)
 53 bigonist.ti,ab. (0)
 54 ("hoe 766" or hoe-766 or hoe766).ti,ab. (0)
 55 profact.ti,ab. (0)
 56 receptal.ti,ab. (0)
 57 suprecur.ti,ab. (0)
 58 suprefact.ti,ab. (0)
 59 tiloryth.ti,ab. (0)
 60 histrelin.ti,ab. (1)
 61 "LHRH-hydrogel implant".ti,ab. (0)
 62 ("RL 0903" or RL0903).ti,ab. (0)
 63 ("SPD 424" or SPD424).ti,ab. (0)
 64 goserelin.ti,ab. (30)
 65 ("ici 118630" or ici118630).ti,ab. (0)
 66 ("ZD-9393" or ZD9393).ti,ab. (0)
 67 zoladex.ti,ab. (3)
 68 leuprorelin.ti,ab. (12)
 69 carcinil.ti,ab. (0)
 70 enanton*.ti,ab. (1)
 71 ginecrin.ti,ab. (0)
 72 leuplin.ti,ab. (0)
 73 leuprolide.ti,ab. (79)
 74 lucrin.ti,ab. (1)
 75 lupron.ti,ab. (18)
 76 provren.ti,ab. (0)
 77 procrin.ti,ab. (0)
 78 ("tap 144" or tap144).ti,ab. (1)
 79 (a-43818 or a43818).ti,ab. (0)
 80 Trenantone.ti,ab. (0)
 81 staladex.ti,ab. (0)
 82 prostap.ti,ab. (0)
 83 nafarelin.ti,ab. (1)
 84 ("76932-56-4" or "76932564").ti,ab. (0)
 85 ("76932-60-0" or "76932600").ti,ab. (0)
 86 ("86220-42-0" or "86220420").ti,ab. (0)
 87 ("rs 94991 298" or rs94991298).ti,ab. (0)
 88 synarel.ti,ab. (0)
 89 deslorelin.ti,ab. (8)
 90 gonadorelin.ti,ab. (3)
 91 ("33515-09-2" or "33515092").ti,ab. (0)
 92 ("51952-41-1" or "51952411").ti,ab. (0)
 93 ("52699-48-6" or "52699486").ti,ab. (0)
 94 cetrotirelix.ti,ab. (9)
 95 cetrotide.ti,ab. (0)
 96 ("NS 75A" or NS75A).ti,ab. (0)
 97 ("NS 75B" or NS75B).ti,ab. (0)
 98 ("SB 075" or SB075).ti,ab. (0)
 99 ("SB 75" or SB75).ti,ab. (1)

100 gonadoliberin.ti,ab. (1)
 101 kryptocur.ti,ab. (0)
 102 cetorelix.ti,ab. (9)
 103 cetrotide.ti,ab. (0)
 104 antagonist.ti,ab. (0)
 105 ganirelix.ti,ab. (0)
 106 ("ORG 37462" or ORG37462).ti,ab. (0)
 107 orgalutran.ti,ab. (0)
 108 ("RS 26306" or RS26306).ti,ab. (0)
 109 ("AY 24031" or AY24031).ti,ab. (0)
 110 factrel.ti,ab. (0)
 111 fertagyl.ti,ab. (0)
 112 lutrelef.ti,ab. (0)
 113 lutrepulse.ti,ab. (0)
 114 relefact.ti,ab. (0)
 115 fertiral.ti,ab. (0)
 116 (hoe471 or "hoe 471").ti,ab. (0)
 117 relisorm.ti,ab. (0)
 118 cystorelin.ti,ab. (0)
 119 dirigestran.ti,ab. (0)
 120 or/29-119 (4869)
 121 28 and 120 (130)
 122 limit 121 to english language (120)
 123 limit 122 to yr="2000 -Current" (93)

Appendix C Evidence selection

The literature searches identified 525 references. These were screened using their titles and abstracts and 25 references were obtained and assessed for relevance. Of these, 9 references are included in the evidence review. The remaining 16 references were excluded and are listed in [appendix D](#).

Figure 1 – Study selection flow diagram

References submitted with Preliminary Policy Proposal

There is no preliminary policy proposal for this policy.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Achille, C., Taggart, T., Eaton, N.R. et al. (2020) Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: Preliminary results. <i>International Journal of Pediatric Endocrinology</i> 2020(1): 8	Intervention – data for GnRH analogues not reported separately from other interventions
Bechard, Melanie, Vanderlaan, Doug P, Wood, Hayley et al. (2017) Psychosocial and Psychological Vulnerability in Adolescents with Gender Dysphoria: A "Proof of Principle" Study. <i>Journal of sex & marital therapy</i> 43(7): 678-688	Population – no GnRH analogues at time of study
Chew, Denise, Anderson, Jemma, Williams, Katrina et al. (2018) Hormonal Treatment in Young People With Gender Dysphoria: A Systematic Review. <i>Pediatrics</i> 141(4)	All primary studies included apart from 1 conference abstract
de Vries, Annelou L C, McGuire, Jenifer K et al. (2014) Young adult psychological outcome after puberty suppression and gender reassignment. <i>Pediatrics</i> 134(4): 696-704	Population – relevant population included in de Vries et al. 2011
Ghelani, Rahul, Lim, Cheryl, Brain, Caroline et al. (2020) Sudden sex hormone withdrawal and the effects on body composition in late pubertal adolescents with gender dysphoria. <i>Journal of pediatric endocrinology & metabolism: JPEM</i> 33(1): 107-112	Outcomes – not in the PICO

Study reference	Reason for exclusion
Giovanardi, G, Morales, P, Mirabella, M et al. (2019) Transition memories: experiences of trans adult women with hormone therapy and their beliefs on the usage of hormone blockers to suppress puberty. Journal of endocrinological investigation 42(10): 1231-1240	Population – adults only
Hewitt, Jacqueline K, Paul, Campbell, Kasiannan, Porpavai et al. (2012) Hormone treatment of gender identity disorder in a cohort of children and adolescents. The Medical journal of Australia 196(9): 578-81	Outcomes – no data reported for relevant outcomes
Jensen, R.K., Jensen, J.K., Simons, L.K. et al. (2019) Effect of Concurrent Gonadotropin-Releasing Hormone Agonist Treatment on Dose and Side Effects of Gender-Affirming Hormone Therapy in Adolescent Transgender Patients. Transgender Health 4(1): 300-303	Outcomes – not in the PICO
Klaver, Maartje, de Mutsert, Renee, Wiepjes, Chantal M et al. (2018) Early Hormonal Treatment Affects Body Composition and Body Shape in Young Transgender Adolescents. The journal of sexual medicine 15(2): 251-260	Outcomes – not in the PICO
Klaver, Maartje, de Mutsert, Renee van der Loos, Maria A T C et al. (2020) Hormonal Treatment and Cardiovascular Risk Profile in Transgender Adolescents. Pediatrics 145(3)	Outcomes – not in the PICO
Lopez, Carla Marisa, Solomon, Daniel, Boulware, Susan D et al. (2018) Trends in the use of puberty blockers among transgender children in the United States. Journal of pediatric endocrinology & metabolism : JPEM 31(6): 665-670	Outcomes – not in the PICO
Schagen, Sebastian E E, Lustenhouwer, Paul, Cohen-Kettenis, Peggy T et al. (2018) Changes in Adrenal Androgens During Puberty Suppression and Gender-Affirming Hormone Treatment in Adolescents With Gender Dysphoria. The journal of sexual medicine 15(9): 1357-1363	Outcomes – not in the PICO
Swendiman, Robert A, Vogiatzi, Maria G, Alter, Craig A et al. (2019) Histrelin implantation in the pediatric population: A 10-year institutional experience. Journal of pediatric surgery 54(7): 1457-1461	Population – less than 10% of participants had gender dysphoria; data not reported separately
Turban, Jack L, King, Dana, Carswell, Jeremi M et al. (2020) Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation. Pediatrics 145(2)	Intervention – data for GnRH analogues not reported separately from other interventions
Vrouenraets, Lieke Josephina Jeanne Johanna, Fredriks, A Miranda, Hannema, Sabine E et al. (2016) Perceptions of Sex, Gender, and Puberty Suppression: A Qualitative Analysis of Transgender Youth. Archives of sexual behavior 45(7): 1697-703	Outcomes – not in the PICO
Zucker, Kenneth J, Bradley, Susan J, Owen-Anderson, Allison et al. (2010) Puberty-blocking hormonal therapy for adolescents with gender identity disorder: A descriptive clinical study. Journal of Gay & Lesbian Mental Health 15(1): 58-82	Intervention – data for GnRH analogues not reported separately from other interventions

Appendix E Evidence tables

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Brik T, Vrouenraets L, de Vries M, et al. (2020) Trajectories of adolescents treated with gonadotropin-releasing hormone analogues for gender dysphoria. Archives of Sexual Behaviour https://doi.org/10.1007/s10508-020-01660-8 Netherlands Retrospective observational single-centre study To document trajectories after the initiation of GnRH analogue and explore reasons for extended use and discontinuation of GnRH analogues. Includes participants seen between November 2010 and January 1, 2018.	Inclusion criteria were adolescents with gender dysphoria, according to the DSM-5 criteria, seen at the single centre and treated with GnRH analogues between November 2010 and January 1, 2018. The study excluded adolescents without a diagnosis of gender dysphoria, those who had coexisting problems that interfered with the diagnostic process and/or might interfere with successful treatment (not further defined), those adolescents not wanting hormones, those with ongoing diagnostic evaluation and those who did not attend appointments. The sample consisted of 143 adolescents meeting the inclusion/exclusion criteria, 38 transfemales, 105 transmales, with median ages of 15.0 years (range 11.1 to 18.6 years) and 16.1 years	The study only reports that GnRH analogues were given, no specific drug, dose, route, or frequency of administration are reported. No comparator cohort was used in the study. Follow-up was at (up to) 9 years (last follow-up July 2019).	Critical outcomes No critical outcomes assessed. Important outcomes <i>Psychosocial impact</i> Not assessed. Engagement with health care services Not formally assessed but the study reported that out of 214 age and developmentally appropriate adolescents for potential inclusion in the study, 9 were excluded as they stopped attending appointments (4.2%). Stopping treatment Of the 143 adolescents, 9 (6.2%, 1 transfemale and 8 transmales) stopped taking GnRH analogues after a median duration of 0.8 years (range 0.1 to 3.0). Four adolescents (2.8%) discontinued GnRH analogues although they wanted to continue endocrine treatments for gender dysphoria: 1 transmale stopped due to increase in mood problems, suicidal thoughts and confusion attributed to GnRH analogues (later had gender-affirming hormones at an adult gender clinic)¹ 1 transmale experienced hot flushes, increased migraines, had a fear of injections, stress at school and unrelated medical issues, and	This study was appraised using the Newcastle-Ottawa tool for cohort studies. Domain 1: Selection - somewhat representative - no-non exposed cohort - secure record - yes Domain 2: Comparability - no comparator Domain 3: Outcome - record linkage - yes - complete follow-up Overall quality is assessed as poor. Other comments: Physical and psychological comorbidity was poorly reported, concomitant use of other medicines was not reported. Source of funding: not reported.

	(range 10.1 to 17.9 years), respectively at commencement of GnRH analogues. Of the 143 adolescents in the study, 125 (87%, 36 transfemales and 89 transmales) subsequently started treatment with gender-affirming hormones after median 1.0 (range 0.5 to 3.8) years and 0.8 (0.3 to 3.7) years, respectively. Median age at the start of gender-affirming hormones was 16.2 years (range 14.5 to 18.6 years) in transfemales and 17.1 years (range 14.9 to 18.8 years) in transmales. Five adolescents who used GnRH analogues had not started gender-affirming hormones at the time of data collection as they were not yet eligible for this treatment due to age. At the time of data collection, they had used GnRH analogues for a median duration of 2.1 years (range 1.6 to 2.8). Tanner stage was not reported. Six adolescents had been referred to a gender clinic elsewhere for further		temporarily discontinued treatment (after 4 months)² • 1 transmale experienced mood swings 4 months after commencing GnRH analogues. After 2.2 years he developed unexplained severe nausea and rapid weight loss and due to his general condition discontinued GnRH analogues after 2.4 years³ • 1 transmale stopped GnRH analogues as his parents were unable to regularly collect medication from the pharmacy and take him to appointments for the injections⁴ Five adolescents (3.5%) stopped treatment as they no longer wished to continue with gender-affirming treatment. • 1 adolescent had been very distressed about breast development at the start of GnRH analogues and later thought that she might want to live as a woman without breasts. She did not want to live as a boy and discontinued GnRH analogues, although dreaded breast development and menstruation. • 1 adolescent experienced concurrent psychosocial problems interfering with the exploration of gender identity and did not currently want treatment.⁵ • 1 adolescent felt more in between male and female and therefore did not want to continue with GnRH analogues.⁶ • 1 adolescent made a social transition while using GnRH	

	treatment, including 1 who had prolonged use.		analogues and shortly after decided to discontinue treatment. ⁷ 1 adolescent discontinued after using GnRH analogues as the treatment allowed them to feel who they were.⁸	

¹ The adolescent later indicated "I was already fully matured when I started GnRH analogues, menstruations were already suppressed by contraceptives. For me, it had no added value" (transmale, age 19 years).

² The adolescent restarted endocrine treatment (testosterone) 5 months later.

³ The adolescent recovered over the next 2 years and subsequently started lynestrenol and testosterone treatment.

⁴ The adolescent subsequently started lynestrenol to suppress menses, he was not yet eligible for testosterone treatment.

⁵ The adolescent later reflected that "The decision to stop GnRH analogues to my mind was made by the gender team, because they did not think gender dysphoria was the right diagnosis. I do still feel like a man, but for me it is okay to be just me instead of a he or a she, so for now I do not want any further treatment" (adolescent assigned female sex at birth, age 16 years).

⁶ The adolescent stated "At the moment, I feel more like 'I am' instead of 'I am a woman' or 'I am a man'" (adolescent assigned female sex at birth, age 16 years).

⁷ The adolescent stated that "he had fallen in love with a girl and had never had such feelings, which made him question his gender identity. At subsequent visits, he indicated that he was happy living as a man.

⁸ The adolescent stated "After using GnRH analogues for the first time, I could feel who I was without the female hormones, this gave me peace of mind to think about my future. It was an inner feeling that said I am a woman" (adolescent assigned female sex at birth, age 18 years).

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Costa R, Dunsford M, Skagerberg E, et al. (2015) Psychological support, puberty suppression, and psychosocial functioning in adolescents with gender dysphoria . Journal of Sexual Medicine 12(11):2206-14. United Kingdom Prospective longitudinal observational single centre cohort study Includes participants referred to the service between 2010 and 2014.	Adolescents with gender dysphoria who completed a 6-month diagnostic process using DSM-IV-TR criteria for gender dysphoria (comprising the gender dysphoria assessment and psychological interventions) either immediately eligible for treatment with GnRH analogues or delayed eligible for treatment with GnRH analogues (received psychological support without any physical intervention). No exclusion criteria were reported. The sample consisted of 201 adolescents (sex assigned at birth male to female ratio 1:1.6)	Intervention 101 individuals were assessed as being immediately eligible for use of GnRH analogues (no specific treatment, dose or route, or frequency of administration reported but all received psychological support). Comparison The analyses were between the immediately eligible	Critical outcomes Impact on gender dysphoria The Utrecht gender dysphoria scale (UGDS) was used to assess adolescents' gender dysphoria related discomfort. The Cronbach's alpha (α) for the study was reported as 0.76 to 0.88, suggesting good internal consistency. UGDS was only reported once, for 160 adolescents (50 sex assigned at birth males and 110 sex assigned at birth females). The assessment time point is not reported (baseline or follow-up) and the comparison for gender related discomfort was between sex assigned at birth males and sex assigned at birth females. Sex assigned at birth males had a mean ($\pm$ SD) UGDS score of 51.6 [$\pm$ 9.7] versus sex assigned at birth	This study was appraised using the Newcastle-Ottawa tool for cohort studies. Domain 1: Selection 1. somewhat representative 2. drawn from the same community as the exposed cohort. 3. secure record 4. no Domain 2: Comparability 1. partial comparator Domain 3: Outcome 1. independent assessment (unclear if blinded) 2. yes 3. incomplete follow-up

	mean ($\pm$SD) age 15.52$\pm$1.41 years) from a sampling frame of 436 consecutive adolescents referred to the service between 2010 and 2014. The mean ($\pm$SD) age (n=201) at the start of GnRH analogues was 16.48 [$\pm$1.26], range 13 to 17 years. The interval from the start of the diagnostic procedure to the start of puberty suppression took approximately 1.5 years [$\pm$0.63] from baseline. None of the delayed eligible individuals received puberty suppression at the time of this study. Tanner stage was not reported.	and delayed eligible (n=100) adolescents, Baseline assessment (following diagnostic procedure) was followed by follow-up at 6 months from baseline (T1), 12 months from baseline (T2) and 18 months from baseline (T3).	females score of 56.1 [$\pm$4.3], <i>t</i>-test 4.07; <i>p</i><0.001. Impact on mental health Not assessed. Impact on quality of life Not assessed. Important outcomes Psychosocial impact The Children's Global Assessment Scale (CGAS) was used to assess adolescents' psychosocial functioning. The CGAS was administered by psychologists, psychotherapists, and psychiatrists (intra-class correlation assessment was 0.76 $\leq$ Cronbach's α $\leq$0.94). At baseline, CGAS scores were not associated with any demographic variable, in both sex assigned at birth males and sex assigned at birth females (all <i>p</i>>0.1). In comparison with sex assigned at birth females, sex assigned at birth males had statistically significantly lower mean ($\pm$SD) baseline CGAS scores (55.4 [$\pm$12.7] versus 59.2 [$\pm$11.8]; <i>t</i>-test 2.15; <i>p</i>=0.03). There was no statistically significant difference in mean ($\pm$SD) CGAS scores at baseline (T0) between immediately eligible adolescents and delayed eligible adolescents (n=201, 58.72 [$\pm$11.38] versus 56.63 [$\pm$13.14]; <i>t</i>-test 1.21; <i>p</i>=0.23). Immediately eligible compared with delayed eligible participants At follow-up, there was no statistically significant difference in mean ($\pm$SD)	Overall quality is assessed as poor. Other comments: Physical and psychological comorbidity was poorly reported, concomitant use of other medicines was not reported. Large unexplained loss to follow-up (64.7%) at T3. Source of funding: not reported.

			CGAS scores at any follow-up time point (T1, T2 or T3) between immediately eligible adolescents and delayed eligible adolescents: • T1, n=201, 60.89 [± 12.17] versus 60.29 [± 12.81]; <i>t</i>-test 0.34; <i>p</i>=0.73 • T2, n=121, 64.70 [± 13.34] versus 62.97 [± 14.10]; <i>t</i>-test 0.69; <i>p</i>=0.49 • T3, n=71, 67.40 [± 13.93] versus 62.53 [± 13.54]; <i>t</i>-test 1.49; <i>p</i>=0.14. All participants There was a statistically significant increase in mean ($\pm$SD) CGAS scores at any follow-up time point (T1, T2 or T3) compared with baseline (T0) for the all adolescents group: • T0 (n=201) versus T1 (n=201), 57.73 [± 12.27] versus 60.68 [± 12.47]; <i>t</i>-test 4.87; <i>p</i><0.001 • T0 (n=201) versus T2 (n=121), 57.73 [± 12.27] versus 63.31 [± 14.41]; <i>t</i>-test 3.70; <i>p</i><0.001 • T0 (n=201) versus T3 (n=71), 57.73 [± 12.27] versus 64.93 [± 13.85]; <i>t</i>-test 4.11; <i>p</i><0.001 There was a statistically significant increase in mean ($\pm$SD) CGAS scores when comparing the follow-up period T1 to T3 but not for the periods T1 to T2 and T2 to T3, for all adolescents: • T1 (n=201) versus T2 (n=121), 60.68 [± 12.47] versus 63.31 [± 14.41]; <i>t</i>-test 1.73; <i>p</i><0.08 • T1 (n=201) versus T3 (n=71), 60.68 [± 12.47] versus 64.93 [± 13.85], <i>t</i>-test 2.40; <i>p</i><0.02 • T2 (n=121) versus T3 (n=71), 63.31 [± 14.41] versus 64.93 [± 13.85], <i>t</i>-test 0.76; <i>p</i>=0.45	

			There were no statistically significant differences in CGAS scores between sex assigned at birth males and sex assigned at birth females with gender dysphoria in all the follow-up evaluations (all $p>0.1$). Delayed eligible and immediately eligible adolescents with gender dysphoria were not statistically significantly different for demographic variables (all $p>0.1$). Immediately eligible participants There was a statistically significant increase in mean ($\pm$SD) CGAS scores at follow-up times T2 and T3 compared with baseline (T0) but not for T0 versus T1, for the immediately eligible adolescents: • T0 (n=101) versus T1 (n=101), 58.72 [$\pm$11.38] versus 60.89 [$\pm$12.17]; t-test 1.31; $p=0.19$ • T0 (n=101) versus T2 (n=60), 58.72 [$\pm$11.38] versus 64.70 [$\pm$13.34]; t-test 3.02; $p=0.003$ • T0 (n=101) versus T3 (n=35), 58.72 [$\pm$11.38] versus 67.40 [$\pm$13.93]; t-test 3.66; $p<0.001$ There was a statistically significant increase in mean ($\pm$SD) CGAS scores when comparing the follow-up period T1 to T3 with each other but not for the periods T1 to T2 and T2 to T3, for the immediately eligible adolescents: • T1 (n=101) versus T2 (n=60), 60.89 [$\pm$12.17] versus 64.70 [$\pm$13.34]; t-test 1.85; $p=0.07$ • T1 (n=101) versus T3 (n=35), 60.89 [$\pm$12.17] versus 67.40 [$\pm$13.93], t-test 2.63; $p<0.001$	

			T2 (n=60) versus T3 (n=35), 64.70 [±13.34] versus 67.40 [±13.93], <i>t</i>-test 0.94; <i>p</i>=0.35 The immediately eligible adolescents had a CGAS score which was not statistically significantly different compared to the sample of children/adolescents without observed psychological /psychiatric symptoms after 12 months of puberty suppression (T3, <i>t</i>=0.01, <i>p</i>=0.99).	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
de Vries A, Steensma T, Doreleijers T, et al. (2011) Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. The Journal of Sexual Medicine 8 (8):2276-83. Netherlands Prospective longitudinal observational single centre before and after study.	The sample size was 70 adolescents receiving GnRH analogues (mean age [±SD] at assessment 13.6±1.8 years) from a sampling frame of 196 consecutive adolescents referred to the service between 2000 and 2008. Inclusion criteria were if they subsequently started gender-affirming hormones between 2003 and 2009 (mean [±SD] age at start of GnRH analogues was 14.75 [±1.92] years)¹. No specific exclusion criteria were described. No diagnostic criteria or concomitant treatments were reported. Tanner stage of the included adolescents was not reported.	Intervention 70 adolescents were assessed at baseline (T0) before the start of GnRH analogues (no specific treatment, dose or route of administration reported). Comparison The same 70 adolescents were assessed again at follow-up (T1), shortly before starting gender-affirming hormones. Not all adolescents completed all assessments for all items².	Critical outcomes Impact on gender dysphoria Impact on gender dysphoria was assessed using the Utrecht Gender Dysphoria Scale (UGDS). - There was no statistically significant difference in UGDS scores between T0 and T1 (n=41). There was a statistically significant difference between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting more gender dysphoria, <i>F</i> (<i>df</i>, <i>errdf</i>), <i>P</i>: 15.98 (1,39), <i>p</i><0.001. Impact on mental health Depressive symptoms were assessed using the Beck Depression Inventory (BDI-II). - There was a statistically significant reduction in BDI score between T0 and T1, n=41, 8.31 [±7.12] versus 4.95 [±6.72], <i>F</i> (<i>df</i>, <i>errdf</i>), <i>P</i>: 9.28 (1,39), <i>p</i>=0.004. - There was no statistically significant difference between sex assigned at	This study was appraised using the Newcastle-Ottawa tool for cohort studies. Domain 1: Selection - somewhat representative of children and adolescents who have gender dysphoria - no non-exposed cohort - no description - no Domain 2: Comparability - study controls for age, age at start of treatment, IQ, and parental factors Domain 3: Outcome - no description - no/unclear - complete Overall quality is assessed as poor. Other comments: Physical and psychological comorbidity was not reported, concomitant use of

			birth males and sex assigned at birth females, $F(df, errdf), P: 3.85(1,39)$, $p=0.057$. Anger and anxiety were assessed using Trait Anger and Anxiety (TPI and STAI, respectively) Scales of the State-Trait Personality Inventory. - There was no statistically significant difference in anger (TPI) scale scores between T0 and T1 ($n=41$). There was a statistically significant difference between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting increased anger compared with sex assigned at birth males, $F(df, errdf), P: 5.70(1,39)$, $p=0.022$. - Similarly, there was no statistically significant difference in anxiety (STAI) scale scores between T0 and T1 ($n=41$). There was a statistically significant difference between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting increased anxiety compared with sex assigned at birth males, $F(df, errdf), P: 16.07(1,39)$, $p<0.001$. Impact on quality of life Not assessed. Important outcomes Impact on body image Impact on body image was assessed using the Body Image Scale to measure body satisfaction (BIS).	other medicines was not reported. Source of funding: This study was supported by a personal grant awarded to the first author by the Netherlands Organization for Health Research and Development.

			There was no statistically significant difference between T0 and T1 for any of the 3 BIS scores (primary sex characteristics, secondary sex characteristics or neutral characteristics, n=57). There were statistically significant differences between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting more dissatisfaction, for: • primary sexual characteristics, $F(df, errdf)$, P: 4.11 (1,55), $p=0.047$. • secondary sexual characteristics, $F(df, errdf)$, P: 11.57 (1,55), $p=0.001$. But no statistically significant difference between sex assigned at birth males and sex assigned at birth females was found for neutral characteristics. However, there was a significant interaction effect between sex assigned at birth sex and the changes of gender dysphoria between T0 and T1; sex assigned at birth females became more dissatisfied with their secondary sex characteristics compared with sex assigned at birth males, $F(df, errdf)$, P: 14.59 (1,55), $p<0.001$ and neutral characteristics, $F(df, errdf)$, P: 15.26 (1,55), $p<0.001$). Psychosocial impact Psychosocial impact was assessed using both the Child Behaviour Checklist (CBCL) and the Youth Self-Report (YSR) to parents and adolescents, respectively. The Children's Global Assessment Scale was also reported. There was a statistically significant decrease in mean ($\pm$SD) total, internalising, and externalising³ parental	

			CBCL scores between T0 and T1⁴ for all adolescents (n=54): • Total score (T0 – T1) 60.70 [± 12.76] versus 54.46 [± 11.23], F (df, $errdf$), P: 26.17 (1,52), $p < 0.001$. • Internalising score (T0 – T1) 61.00 [± 12.21] versus 54.56 [± 10.22], F (df, $errdf$), P: 22.93 (1,52), $p < 0.001$. • Externalising score (T0 – T1) 58.04 [± 12.99] versus 53.81 [± 11.86], F (df, $errdf$), P: 12.04 (1,52), $p = 0.001$. There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for total and internalising CBCL score but there was a significant difference for the externalising score: • Externalising score, F (df, $errdf$), P: 6.29 (1,52), $p = 0.015$. There was a statistically significant decrease in mean ($\pm$SD) total, internalising, and externalising³ YSR scores between T0 and T1 for all adolescents (n=54): • Total score (T0 – T1) 55.46 [± 11.56] versus 50.00 [± 10.56], F (df, $errdf$), P: 16.24 (1,52), $p < 0.001$. • Internalising score (T0 – T1) 56.04 [± 12.49] versus 49.78 [± 11.63], F (df, $errdf$), P: 15.05 (1,52), $p < 0.001$. • Externalising score (T0 – T1) 53.30 [± 11.87] versus 49.98 [± 9.35], F (df, $errdf$), P: 7.26 (1,52), $p = 0.009$. There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for total and internalising YSR score but there was a significant difference for the externalising score:	

			Externalising score, $F(df, errdf), P: 9.14(1,52), p=0.004$. There was a statistically significant increase in CGAS mean ($\pm SD$) score between T0 and T1 ($n=41$), $70.24[\pm 10.12]$ versus $73.90[\pm 9.63]$, $F(df, errdf), P: 8.76(1,39), p=0.005$. There was a statistically significant difference between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting lower score for global functioning compared with sex assigned at birth males, $F(df, errdf), P: 5.77(1,52), p=0.021$. The proportion of adolescents scoring in the clinical range significantly decreased between T0 and T1, on the CBCL total problem scale (44.4% versus 22.2%, $X^2[1] = 6.00, p=0.001$), and the internalising scale (29.6% versus 11.1%, $X^2[1] = 5.71, p=0.017$) of the YSR.	

¹ There were statistically significant mean age [$\pm SD$] differences between sex assigned at birth males and sex assigned at birth females for age at assessment (13.14 [± 1.55] versus 14.10 [± 1.99] years, $p=0.028$), age at start of GnRH analogues (14.25 [± 1.79] versus 15.21 [± 1.95] years, $p=0.036$) and age at the start of gender-affirming hormones (16.24 [± 1.21] versus 16.99 [± 1.09] years, $p=0.008$). No statistically significant differences were seen for other baseline characteristics, time between GnRH analogue and gender-affirming hormones, full scale IQ, parental marital status, education, and sexual attraction to own, other or both sexes.

² Independent t-tests between mean scores on the CBCL, YSR, BDI, TPI, STAI, CGAS, UGS, and BIS of adolescents who completed both assessments and mean scores of adolescents who completed only one of the assessments revealed no significant differences on all used measures, at neither T0 or at T1.

³ The CBCL/YSR has 2 components: Internalising score which sums the anxious/depressed, withdrawn-depressed, and somatic complaints scores; externalising score which sums rule-breaking and aggressive behaviour. The total problems score is the sum of the scores of all the problem items. The YSR is a child self-report version of the CBCL.

⁴ A repeated measures ANOVA (analysis of variance) was used.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Joseph T, Ting J, Butler G. (2019) The effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria: findings from a large national cohort . Journal of pediatric endocrinology & metabolism 32(10): 1077-1081	Adolescents (12 to 14 years) with gender dysphoria (no diagnostic criteria described), $n=70$, including 31 transfemales and 39 transmales.	Treatment with a GnRH analogue for at least 1 year or ongoing until they reached 16 years. No specific treatment, dose or route of	Critical outcomes No critical outcomes assessed. Important outcomes Bone density: lumbar⁴ Lumbar spine bone mineral apparent density (BMAD)² 0 to 1 year Transfemales (mean [$\pm SD$]):	This study was appraised using the Newcastle-Ottawa quality assessment checklist for cohort studies. Domain 1: Selection

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
United Kingdom Retrospective longitudinal observational single centre study To investigate whether there is any significant loss of bone mineral density (BMD) and bone mineral apparent density (BMAD) for up to 3 years of GnRH analogues. To investigate whether there was a significant drop after 1 year of treatment following abrupt withdrawal. 2011 to 2016	All had been seen and assessed by a Gender Identity Development Service multi-disciplinary psychosocial health team for at least 4 assessments over a minimum of 6 months. All participants had entered puberty and all but 2 of the transmales were postmenarchal. 57% of the transfemales were in early puberty (G2–3 and testicular volume >4 mL) and 43% were in late puberty (G4–5). Details of the sampling frame were not reported. Further details of how the sample was drawn are not reported.	administration reported. No concomitant treatments were reported. No comparator.	0.235 (0.030) g/cm³ at baseline, 0.233 g/cm³ (0.029) at 1 year (p=0.459); z-score 0.859 (0.154) at baseline, -0.228 (1.027) at 1 year (p=0.000) Transmales (mean [±SD]): 0.196 (0.035) g/cm³ at baseline, 0.201 (0.033) g/cm³ at 1 year (p=0.074); z-score -0.186 (1.230) at baseline, -0.541 (1.396) at 1 year (p=0.006) Lumbar spine BMAD 0 to 2 years Transfemales (mean [±SD]): 0.240 (0.027) g/cm³ at baseline, 0.240 (0.030) g/cm³ at 2 years (p=0.865); z-score 0.486 (0.809) at baseline, -0.279 (0.930) at 2 years (p=0.000) Transmales (mean [±SD]): 0.195 (0.058) g/cm³ at baseline, 0.198 (0.055) at 2 years (p=0.433); z-score -0.361 (1.439) at baseline, -0.913 (1.318) at 2 years (p=0.001) Lumbar spine bone mineral density (BMD) 0 to 1 year Transfemales (mean [±SD]): 0.860 (0.154) kg/m² at baseline, 0.859 (0.129) kg/m² at 1 year (p=0.962); z-score -0.016 (1.106) at baseline, -0.461 (1.121) at 1 year (p=0.003) Transmales (mean [±SD]): 0.694 (0.149) kg/m² at baseline, 0.718 (0.124) kg/m² at 1 year (p=0.006); z-score -0.395 (1.428) at baseline, -1.276 (1.410) at 1 year (p=0.000) Lumbar spine BMD 0 to 2 years Transfemales (mean [±SD]): 0.867 (0.141) kg/m² at baseline, 0.878 (0.130) kg/m² at 2 years (p=0.395); z-score 0.130 (0.972) at baseline, -0.890 (1.075) at 2 years (p=0.000) Transmales (mean [±SD]):	1. Somewhat representative of children and adolescents who have gender dysphoria 2. Not applicable 3. Via routine clinical records 4. No Domain 2: Comparability 1. No control group Domain 3: Outcome 1. Via routine clinical records 2. Yes 3. No statement Overall quality is assessed as poor. Other comments: although the evidence is of poor quality, the results suggest a possible association between GnRH analogues and BMAD. However, the results are not reliable and could be due to bias or chance. Further details of how the sample was drawn are not reported. No concomitant treatments were reported. Source of funding: None disclosed

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			0.695 (0.220) kg/m² at baseline, 0.731 (0.209) kg/m² at 2 years (p=0.058); z-score -0.715 (1.406) at baseline, -2.000 (1.384) at 2 years (p=0.000) Bone density: femoral Femoral neck (hip) BMD 0 to 1 year Transfemales (mean [±SD]): 0.894 (0.118) kg/m² at baseline, 0.905 (0.104) kg/m² at 1 year (p=0.571); z-score 0.157 (0.905) at baseline, -0.340 (0.816) at 1 year (p=0.002) Transmales (mean [±SD]): 0.772 (0.137) kg/m² at baseline, 0.785 (0.120) kg/m² at 1 year (p=0.797); z-score -0.863 (1.215) at baseline, -1.440 (1.075) at 1 year (p=0.000) Femoral neck (hip) BMD 0 to 2 years Transfemales (mean [±SD]): 0.920 (0.116) kg/m² at baseline, 0.910 (0.125) kg/m² at 2 years (p=0.402); z-score 0.450 (0.781) at baseline, -0.600 (1.059) at 2 years (p=0.002) Transmales (mean [±SD]): 0.766 (0.215) kg/m² at baseline, 0.773 (0.197) at 2 years (p=0.604); z-score -1.075 (1.145) at baseline, -1.779 (0.816) at 2 years (p=0.001)	

¹ Lumbar spine (L1-L4) BMD was measured by yearly dual energy X-ray absorptiometry (DXA) scans at baseline (n=70), 1 year (n=70), and 2 years (n=31).

² BMAD is a size adjusted value of BMD incorporating body size measurements using UK norms in growing adolescents. Reported as g/cm³ and z-scores. Hip BMAD z-scores were not calculated as there were no available reference ranges.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Khatchadourian K, Shazhan A, Metzger D. (2014) Clinical management of youth with gender dysphoria in	27 young people with gender dysphoria who started GnRH analogues (at mean age [±SD] 14.7±1.9 years) out of 84 young	Intervention 84 young people with gender dysphoria were included. For GnRH analogues no	Critical Outcomes No critical outcomes assessed. Important outcomes Stopping treatment	This study was appraised using the Newcastle-Ottawa tool for cohort studies. Domain 1: Selection

Vancouver. The Journal of Pediatrics 164 (4): 906-11. Canada Retrospective observational chart review single centre study	people seen at the unit between 1998 and 2011. Note: the transmale and transfemale subgroups reported in the paper is discrepant, 15 transmales and 11 transfemales (n=26) reported in the outcomes section rather than the n=27 stated in the paper; complete outcome reporting is also incomplete for the transfemale group. Inclusion criteria were at least Tanner stage 2 pubertal development, previous assessment by a mental health professional and a confirmed diagnosis of gender dysphoria (diagnostic criteria not specified). No exclusion criteria are specified.	specific treatment, dose or route of administration reported. Comparison No comparator.	The authors report that of 15 transmales taking GnRH analogues: • 14 transitioned to testosterone treatment during the observation period • 7 continued taking GnRH analogues after starting testosterone • 7 discontinued GnRH analogues after a median of 3.0 years (range 0.2 to 9.2 years), of which: - o 5 discontinued after hysterectomy and salpingo-oophorectomy - o 1 discontinued after 2.2 years (transitioned to gender-affirming hormone) - o 1 discontinued after <2 months due to mood and emotional lability The authors report that of 11 transfemales taking GnRH analogues: • 5 received oestrogen treatment during the observation period • 4 continued taking GnRH analogues during oestrogen treatment • 1 discontinued GnRH analogues during oestrogen treatment (no reason reported) • 1 stopped GnRH analogues after a few months due to emotional lability • 1 stopped GnRH analogues before oestrogen treatment (the following year delayed due to heavy smoking) • 1 discontinued GnRH analogues after 13 months due to choosing not to pursue transition Safety Of the 27 patients treated with GnRH analogues:	1. not reported 2. no non-exposed cohort 3. secure record 4. no Domain 2: Comparability 1. not applicable Domain 3: Outcome 1. record linkage 2. yes 3. in complete missing data Overall quality is assessed as poor. Other comments: mental health comorbidity was reported for all participants but not for the GnRH analogue cohort separately. Concomitant use of other medicines was not reported. Source of funding: No source of funding identified.

			• 1 transmale participant developed sterile abscesses; they were switched from leuprolide acetate to triptorelin, and this was well tolerated. • 1 transmale participant developed leg pains and headaches on GnRH analogues, which eventually resolved without treatment. • 1 participant gained 19 kg within 9 months of initiating GnRH analogues, although their body mass index was >85 percentile before GnRH analogues.	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Klink D, Caris M, Heijboer A et al. (2015) Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. The Journal of clinical endocrinology and metabolism 100(2): e270-5 Netherlands Retrospective longitudinal observational single centre study To assess BMD development during GnRH analogues and at age 22 years in adolescents with gender dysphoria who started treatment for gender dysphoria during adolescence.	34 adolescents (mean age $\pm$SD 14.9$\pm$1.9 for transfemales and 15.0$\pm$2.0 for transmales at start of GnRH analogues). Participants were included if they met DSM-IV-TR criteria for gender identity disorder of adolescence and had been treated with GnRH analogues and gender-affirming hormones during their pubertal years. No concomitant treatments were reported.	The intervention was GnRH analogue monotherapy (triptorelin pamoate 3.75 mg subcutaneously every 4 weeks) followed by gender-affirming hormones from 16 years with discontinuation of GnRH analogue after gonadectomy. Median duration of GnRH analogue monotherapy in transfemales was 1.3 years (range, 0.5 to 3.8 years), and in transmales was 1.5 years	Critical outcomes No critical outcomes assessed. Important outcomes Bone density: lumbar Lumbar spine bone mineral apparent density (BMAD)¹ Change from starting GnRH analogue (mean age 14.9$\pm$1.9) to starting gender-affirming hormones (mean age 16.6$\pm$1.4) in transfemales (mean [$\pm$SD]): GnRH analogue: 0.22 (0.03) g/cm³, gender-affirming hormones: 0.22 (0.02) g/cm³ (NS); z-score GnRH analogue: -0.44 (1.10), gender-affirming hormones: -0.90 (0.80) (p=NS) Change from starting GnRH analogue (mean age 15.0$\pm$2.0) to starting gender-affirming hormones (mean age 16.4$\pm$2.3) in transmales (mean [$\pm$SD]): GnRH analogue: 0.25 (0.03) g/cm³, gender-affirming hormones: 0.24 (0.02) g/cm³ (NS);	This study was appraised using the Newcastle-Ottawa quality assessment checklist for cohort studies. Domain 1: Selection 1. somewhat representative of children and adolescents who have gender dysphoria 2. not applicable 3. via routine clinical records 4. no Domain 2: Comparability 1. no control group Domain 3: Outcome 1. via routine clinical records 2. yes 3. follow-up rate variable across timepoints and no description of those lost Overall quality is assessed as poor.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
1998 to 2012		(range, 0.25 to 5.2 years).	z-score GnRH analogue: 0.28 (0.90), gender-affirming hormones: -0.50 (0.81) (p=0.004) Lumbar spine bone mineral density (BMD)¹ Change from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales (mean [±SD]): GnRH analogue: 0.84 (0.13) g/m2, gender-affirming hormones: 0.84 (0.11) g/m2 (NS); z-score GnRH analogue: -0.77 (0.89), gender-affirming hormones: -1.01 (0.98) (NS) Change from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales (mean [±SD]): GnRH analogue: 0.95 (0.12) g/m2, gender-affirming hormones: 0.91 (0.10) g/m2 (p=0.006); z-score GnRH analogue: 0.17 (1.18), gender-affirming hormones: -0.72 (0.99) (p<0.001) Bone density; femoral Femoral area BMAD¹ Change from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales (mean [±SD]), GnRH analogue: 0.28 (0.04) g/cm3, gender-affirming hormones: 0.26 (0.04) g/cm3 (NS); z-score GnRH analogue: -0.93 (1.22), gender-affirming hormones: -1.57 (1.74) (p=NS) Change from starting GnRH analogue	Other comments: Within person comparison. Small numbers of participants in each subgroup. No concomitant treatments or comorbidities were reported. Source of funding: None disclosed

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			(mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales (mean [±SD]), GnRH analogue: 0.32 (0.04) g/cm³, gender-affirming hormones: 0.31 (0.04) (NS); z-score GnRH analogue: 0.01 (0.70), gender-affirming hormones: -0.28 (0.74) (NS) Femoral area BMD¹ Change from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales (mean [±SD]), GnRH analogue: 0.88 (0.12) g/m², gender-affirming hormones: 0.87 (0.08) (NS); z-score GnRH analogue: -0.66 (0.77), gender-affirming hormones: -0.95 (0.63) (NS) Change from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales (mean [±SD]), GnRH analogue: 0.92 (0.10) g/m², gender-affirming hormones: 0.88 (0.09) (p=0.005); z-score GnRH analogue: 0.36 (0.88), gender-affirming hormones: -0.35 (0.79) (p=0.001)	

¹ BMD and BMAD of the lumbar spine and femoral region (nondominant side) measured by DXA scans at start of GnRH analogues, (n=32), start of gender-affirming hormones (n=34), and at 22 years (n=34).

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Schagen SEE, Cohen-Kettenis PT, Delemarre-van de Waal HA et al. (2016)	Adolescents with gender dysphoria (n=116), median age (range) 13.6 years (11.6 to 17.9) in transfemales and 14.2 years (11.1 to	GnRH analogue monotherapy (triptorelin pamoate 3.75 mg at 0, 2 and 4	Critical outcomes No critical outcomes assessed. Important outcomes	This study was appraised using the Newcastle-Ottawa quality assessment checklist for cohort studies.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Efficacy and Safety of Gonadotropin-Releasing Hormone Agonist Treatment to Suppress Puberty in Gender Dysphoric Adolescents. The journal of sexual medicine 13(7): 1125-32 Netherlands Prospective longitudinal study To describe the changes in Tanner stage, testicular volume, gonadotropins, and sex steroids during GnRH analogues of adolescents with gender dysphoria to evaluate the efficacy. To report on liver enzymes, renal function and changes in body composition. 1998 to 2009	18.6) in transmales during first year of GnRH analogues. Participants were included if they met DSM-IV-TR criteria for gender dysphoria, had lifelong extreme gender dysphoria, were psychologically stable and were living in a supportive environment. No concomitant treatments were reported.	weeks followed by injections every 4 weeks, route of administration not described) for at least 3 months.	Other safety outcomes: liver function Glutamyl transferase was not elevated at baseline or during treatment in any subject. Mild elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) above the reference range were present at baseline but were not more prevalent during treatment than at baseline. Glutamyl transferase, AST, and ALT levels did not significantly change from baseline to 12 months of treatment. No values or statistical analyses were reported. Other safety outcomes: kidney function Change in serum creatinine between 0 and 1 year Transfemales (mean [±SD]): 70 (12) micromol/l at baseline, 66 (13) micromol/l at 1 year (p=0.20) Transmales (mean [±SD]): 73 (8) micromol/l at baseline, 68 (13) micromol/l at 1 year (p=0.01)	Domain 1: Selection 1. somewhat representative of children and adolescents who have gender dysphoria 2. not applicable 3. via routine clinical records 4. no Domain 2: Comparability 1. no control group Domain 3: Outcome 1. via routine clinical records 2. yes 3. no statement Overall quality is assessed as poor. Other comments: Within person comparison. No concomitant treatments or comorbidities were reported. Source of funding: Ferring pharmaceuticals (triptorelin manufacturer)

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Staphorsius A, Baudewijntje P, Kreukels P, et al. (2015) Puberty suppression and executive functioning: an fMRI-study	The inclusion criteria were diagnosed with Gender Identity Disorder according to the DSM-IV-TR and at least 12 years old and Tanner stage of at least B2 or G2 to G3 with	Intervention GnRH analogues (triptorelin pamoate 3.75 mg every 4 weeks	Critical Outcomes No critical outcomes assessed. Important outcomes Psychosocial impact	This study was appraised using the Newcastle-Ottawa tool for cohort studies. Domain 1: Selection domain

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
in adolescents with gender dysphoria. Psychoneuroendocrinology 565:190-9. Netherlands Cross-sectional (single time point) assessment single centre study	measurable oestradiol and testosterone levels in girls and boys, respectively. For all group's exclusion criteria were an insufficient command of the Dutch language (how assessed not reported), unadjusted endocrine disorders, neurological or psychiatric disorders that could lead to deviant test results (details not reported) use of psychotropic medication, and contraindications for an MRI scan. Additionally, adolescents receiving puberty delaying medication or any form of hormones besides oral contraceptives were excluded as controls. The sample size was 85 of whom 41 were adolescents (the numbers are discrepant with the number for whom outcomes are reported n=40) with gender dysphoria (20 of whom were being treated with GnRH analogues); 24 girls and 21 boys without gender dysphoria acted as controls (not further reported here). Details of the sampling frame are not reported. The ages at which GnRH analogues were started was not reported. The mean duration of treatment was 1.6 years (SD 1.0) Mean ($\pm$SD) Tanner stage for each group was reported: - Transfemales 3.9 [$\pm$1.1] - Transfemales on GnRH analogues 4.1 [$\pm$1.0]	subcutaneously or intramuscularly). Comparison The comparison was between adolescents with gender dysphoria receiving GnRH analogues and those without GnRH analogues.	The Child Behaviour Checklist (CBCL) was used to assess psychosocial impact. The CBCL was administered once during the study. The reported outcomes for each group were (n, mean [$\pm$SD]): - Transfemales (all, n=18) 57.8 [$\pm$9.2] - Transfemales on GnRH analogues (n=8) 57.4 [$\pm$9.8] - Transfemales without GnRH analogues (n=10) 58.2 [$\pm$9.3] - Transmales (all, n=22) 60.4 [$\pm$10.2] - Transmales on GnRH analogues (n=12) 57.5 [$\pm$9.4] - Transmales without GnRH analogues (n=10) 63.9 [$\pm$10.5] The analysis of the CBCL data is not discussed, and statistical analysis is unclear. Cognitive development or functioning IQ¹ - Transfemales (mean [$\pm$SD]) on GnRH analogues: 94.0 (10.3) - Transfemales (mean [$\pm$SD]) without GnRH analogues: 109.4 (21.2) - Transmales (mean [$\pm$SD]) on GnRH analogues: 95.8 (15.6) - Transmales (mean [$\pm$SD]) without GnRH analogues: 98.5 (15.9) Reaction time² - Transfemales (mean [$\pm$SD]) on GnRH analogues: 10.9 (4.1) - Transfemales (mean [$\pm$SD]) without GnRH analogues: 9.9 (3.1)	- somewhat representative of children and adolescents who have gender dysphoria drawn from the same community as the exposed cohort - via routine clinical records - no Domain 2: Comparability - study controls for age and diagnosis Domain 3: Outcome - via clinical assessment - yes - unclear Overall quality is assessed as poor. Other comments: Physical and psychological comorbidity was not reported, concomitant use of other medicines was not reported. Source of funding: This work was supported by an educational grant from the pharmaceutical firm Ferring BV, and by a VICI grant (453-08-003) from the Dutch Science Foundation. The authors state that funding sources did not play a role in any component of this study.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
	- Transfemales without GnRH analogues 3.8 [± 1.1] - Transmales 4.5 [± 0.9] - Transmales on GnRH analogues 4.1 [± 1.1] Transmales without GnRH analogues 4.9 [± 0.3]		- Transmales (mean [$\pm$SD]) on GnRH analogues: 9.9 (3.1) - Transmales (mean [$\pm$SD]) without GnRH analogues: 10.0 (2.0) Accuracy³ - Transfemales (mean [$\pm$SD]) on GnRH analogues: 73.9 (9.1) - Transfemales (mean [$\pm$SD]) without GnRH analogues: 83.4 (9.5) - Transmales (mean [$\pm$SD]) on GnRH analogues: 85.7 (10.5) - Transmales (mean [$\pm$SD]) without GnRH analogues: 88.8 (9.7)	

¹ Estimated with 4 subscales (arithmetic, vocabulary, picture arrangement, and block design) of the Wechsler Intelligence Scale for Children, third edition (WISC-III®, Wechsler 1991) or the Wechsler Adult Intelligence Scale, third edition (WAIS-III®, Wechsler 1997), depending on the participant's age.

² Reaction time in seconds in the Tower of London task

³ Percentage of correct trials in the Tower of London task

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Vlot, Mariska C, Klink, Daniel T, den Heijer, Martin et al. (2017) Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents . Bone 95: 11-19 Netherlands Retrospective observational data analysis study	Adolescents with gender dysphoria, n=70. Median age (range) 15.1 years (11.7 to 18.6) for transmales and 13.5 years (11.5 to 18.3) for transfemales at start of GnRH analogues. Participants were included if they had a diagnosis of gender dysphoria according to DSM-IV-TR criteria who were treated with GnRH analogues and then gender-affirming hormones. No concomitant treatments were reported. The study categorised	GnRH analogues (triptorelin pamoate 3.75 mg every 4 weeks subcutaneously).	Critical outcomes No critical outcomes reported Important outcomes Bone density: lumbar Lumbar spine bone mineral apparent density (BMAD) Change from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of <15 years; median [range]), GnRH analogue: 0.21 (0.17 to 0.25) g/cm ³ , gender-affirming hormones: 0.20 (0.18 to 0.24) g/cm ³ (NS); z-score GnRH analogue: -0.20 (-1.82 to 1.18), gender-affirming hormones: -1.52 (-2.36 to 0.42) (p=0.001)	This study was appraised using the Newcastle-Ottawa quality assessment checklist for cohort studies. Domain 1: Selection 1. Somewhat representative of children and adolescents who have gender dysphoria 2. Not applicable 3. Via routine clinical records 4. No Domain 2: Comparability 1. No control group Domain 3: Outcome 1. Via routine clinical records 2. Yes

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
To investigate the course of 3 bone turnover markers in relation to bonemineral density, in adolescents with gender dysphoria during GnRH analogue and gender-affirming hormones. 2001 to 2011	participants into a young and old pubertal group, based on their bone age. The young transmales had a bone age of <14 years and the old transmales had a bone age of ≥14 years. The young transfemales group had a bone age of <15 years and the old transfemales group ≥15 years.		Change from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of ≥15; median [range]), GnRH analogue: 0.22 (0.18 to 0.25) g/cm³, gender-affirming hormones: 0.22 (0.19 to 0.24) g/cm³ (NS); z-score GnRH analogue: -1.18 (-1.78 to 1.09), gender-affirming hormones: -1.15 (-2.21 to 0.08) (p≤0.1) Change from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of <15 years; median [range]), GnRH analogue: 0.23 (0.20 to 0.29) g/cm³, gender-affirming hormones: 0.23 (0.19 to 0.28) g/cm³ (NS); z-score GnRH analogue: -0.05 (-0.78 to 2.94), gender-affirming hormones: -0.84 (-2.20 to 0.87) (p=0.003) Change from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of ≥15; median [range]), GnRH analogue: 0.26 (0.21 to 0.29) g/cm³, gender-affirming hormones: 0.24 (0.20 to 0.28) g/cm³ (p≤0.01); z-score GnRH analogue: 0.27 (-1.60 to 1.80), gender-affirming hormones: -0.29 (-2.28 to 0.90) (p≤0.0001) Bone density; femoral Femoral neck BMAD Change from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of <15 years; median [range]), GnRH analogue: 0.29 (0.20 to 0.33) g/cm³, gender-affirming hormones: 0.27 (0.20 to 0.33) g/cm³ (p≤0.1); z-score GnRH analogue: -0.71 (-3.35 to	3. Follow-up rate variable across outcomes and no description of those lost Overall quality is assessed as poor. Other comments: Within person comparison. No concomitant treatments were reported. Source of funding: grant from Abbott diagnostics

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			0.37), gender-affirming hormones: -1.32 (-3.39 to 0.21) (p≤0.1) Change from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of ≥15; median [range]), GnRH analogue: 0.30 (0.26 to 0.36) g/cm³, gender-affirming hormones: 0.30 (0.26 to 0.34) g/cm³ (NS); z-score GnRH analogue: -0.44 (-1.37 to 0.93), gender-affirming hormones: -0.36 (-1.50 to 0.46) (NS) Change from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of <15 years; median [range]), GnRH analogue: 0.31 (0.26 to 0.36) g/cm³, gender-affirming hormones: 0.30 (0.22 to 0.35) g/cm³ (NS); z-score GnRH analogue: -0.01 (-1.30 to 0.91), gender-affirming hormones: -0.37 (-2.28 to 0.47) (NS) Change from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of ≥15; median [range]), GnRH analogue: 0.33 (0.25 to 0.39) g/cm³, gender-affirming hormones: 0.30 (0.23 to 0.41) g/cm³ (p≤0.01); z-score GnRH analogue: 0.27 (-1.39 to 1.32), gender-affirming hormones: -0.27 (-1.91 to 1.29) (p=0.002)	

Appendix F Quality appraisal checklists

Newcastle-Ottawa tool for cohort studies

Question	
Domain: Selection	
1. Representativeness of the exposed cohort	Truly representative of the average [describe] in the community Somewhat representative of the average [describe] in the community Selected group of users e.g. nurses, volunteers No description of the derivation of the cohort
2. Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort Drawn from a different source No description of the derivation of the non-exposed cohort
3. Ascertainment of exposure	Secure record (e.g. surgical records) Structured interview Written self-report No description
4. Demonstration that outcome of interest was not present at start of study	Yes / No
Domain: Comparability	
1. Comparability of cohorts on the basis of the design or analysis	Study controls for [select most important factor] Study controls for any additional factor [this criteria could be modified to indicate specific control for a second important factor]
Domain: Outcome	
1. Assessment of outcome	Independent blind assessment Record linkage Self-report No description
2. Was follow-up long enough for outcomes to occur	Yes [select and adequate follow up period for outcome of interest] No
3. Adequacy of follow up of cohorts	Complete follow up (all subjects accounted for) Subjects lost to follow up unlikely to introduce bias (small number lost to follow up [select an adequate %] follow up or description provided of those lost) Follow up rate [select an adequate %] and no description of those lost No statement

Appendix G Grade profiles

Table 2: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – gender dysphoria

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on gender dysphoria									
Mean±SD Utrecht Gender Dysphoria Scale ¹ (version(s) not reported), time point at baseline (before GnRH analogues) versus follow-up (before gender-affirming hormones, higher scores indicate more gender dysphoria)									
1 cohort study de Vries et al 2011	Serious limitations ²	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 53.20±7.91 GnRH analogue: 53.9±17.42 P=0.333	Critical	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; P, P-value; SD, Standard deviation.

¹ The UGDS is a validated screening tool for both adolescents and adults to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. The higher the UGDS score the greater the gender dysphoria.

² Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

Table 3: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – mental health

QUALITY					Summary of findings		IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)	Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result	
Impact on mental health								

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Mean±SD Beck Depression Inventory-II, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones). (Lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 8.31±7.12 GnRH analogue: 4.95±6.72 P=0.004	Critical	VERY LOW
Mean±SD Trait Anger (TPI), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 18.29±5.54 GnRH analogue: 17.88±5.24 P=0.503	Critical	VERY LOW
Mean±SD Trait Anxiety (STAI), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 39.43±10.07 GnRH analogue: 37.95±9.38 P=0.276	Critical	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; P, P-value; SD, Standard deviation.

¹ Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

Table 4: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – body image

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on body image									
Mean±SD Body Image Scale (primary sexual characteristics), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=57	None	Baseline: 4.10±0.56 GnRH analogue: 3.98±0.71 P=0.145	Important	VERY LOW
Mean±SD Body Image Scale (secondary sexual characteristics), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=57	None	Baseline: 2.74±0.65 GnRH analogue: 2.82±0.68 P=0.569	Important	VERY LOW
Mean±SD Body Image Scale (neutral characteristics), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=57	None	Baseline: 2.41±0.63 GnRH analogue: 2.47±0.56 P=0.620	Important	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; P, P-value; SD, Standard deviation.

¹ Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

Table 5: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – psychosocial impact

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Psychosocial impact									
Mean [±SD] Children's Global Assessment Scale score, at baseline, higher scores indicate benefit)									
1 cohort study Costa et al 2015	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	n=101 58.72 [±11.38]	n=100 56.63 [±13.14]	P=0.23	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, at 6 months² (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	n=101 60.89 [±12.17]	n=100 60.29 [±12.81]	P=0.73	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, at 12 months³ (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	n=60 64.70 [±13.34]	n=61 62.97 [±14.10]	P=0.49	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, at 18 months⁴ (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	n=35 67.40 [±13.93]	n=36 62.53 [±13.54]	P=0.14	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 6 months compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=101	None	Baseline: 58.72±11.38 6 months: 60.89±12.17 P=0.19	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 12 months compared to baseline (higher scores indicate benefit).									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 cohort study Costa et al 2015	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=60	None	Baseline: 58.72±11.38 12 months: 64.70±13.34 P=0.003	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 18 months compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=35	None	Baseline: 58.72±11.38 18 months: 67.40±13.93 P<0.001	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 12 months compared to 6 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=60	None	6 months: 60.89±12.17 12 months: 64.70±13.34 P=0.07	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 18 months compared to 6 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=35	None	6 months: 60.89±12.17 18 months: 67.40±13.93 P<0.001	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 18 months compared to 12 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=60 N=35	None	12 months: 64.70±13.34 18 months: 67.40±13.93 P=0.35	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 6 months² compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=201	None	Baseline: 57.73±12.27 6 months: 60.68±12.47 P<0.001	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 12 months³ compared to baseline (higher scores indicate benefit).									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 cohort study Costa et al 2015	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=201 N=121	None	Baseline: 57.73±12.27 12 months: 63.31±14.41 <i>P</i> <0.001	Important	VERY LOW
Mean±SD Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 18 months⁴ compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=201 N=71	None	Baseline: 57.73±12.27 18 months: 64.93±13.85 <i>P</i> <0.001	Important	VERY LOW
Mean±SD Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 12 months compared to 6 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=201 N=121	None	6 months: 60.68±12.47 12 months: 63.31±14.41 <i>P</i> <0.08	Important	VERY LOW
Mean±SD Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 18 months compared to 6 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=201 N=71	None	6 months: 60.68±12.47 18 months: 64.93±13.85 <i>P</i> <0.02	Important	VERY LOW
Mean±SD Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 18 months compared to 12 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations ¹	No serious indirectness	No serious inconsistency	Not calculable	N=121 N=71	None	12 months: 63.31±14.41 18 months: 64.93±13.85 <i>P</i> <0.45	Important	VERY LOW
Mean±SD Children's Global Assessment Scale score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, higher scores indicate benefit).									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 cohort study de Vries et al 2011	Serious limitations ⁵	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 70.24±10.12 GnRH analogue: 73.90±9.63 P=0.005	Important	VERY LOW
Mean±SD Child Behaviour Checklist (total T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations ⁵	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 60.70±12.76 GnRH analogue: 54.46±11.23 P<0.001	Important	VERY LOW
Mean±SD Child Behaviour Checklist (internalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations ⁵	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 61.00±12.21 GnRH analogue: 52.1±9.81 P<0.001	Important	VERY LOW
Mean±SD Child Behaviour Checklist (externalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations ⁵	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 58.04±12.99 GnRH analogue: 53.81±11.86 P=0.001	Important	VERY LOW
Proportion of adolescents scoring in the clinical range Child Behaviour Checklist total problem scale, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations ⁵	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 44.4% GnRH analogue: 22.2% P=0.001	Important	VERY LOW
Mean±SD Youth Self-Report (total T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormone, lower scores indicate benefit).									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 cohort study de Vries et al 2011	Serious limitations ⁵	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 55.46±11.56 GnRH analogue: 50.00±10.56 P<0.001	Important	VERY LOW
Mean±SD Youth Self-Report (internalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations ⁵	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 56.04±12.49 GnRH analogue: 49.78±11.63 P<0.001	Important	VERY LOW
Mean±SD Youth Self-Report (externalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations ⁵	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 53.30±11.87 GnRH analogue: 49.98±9.35 P=0.009	Important	VERY LOW
Proportion of adolescents scoring in the clinical range Youth Self-Report (internalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations ⁵	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 29.6% GnRH analogue: 11.1% P=0.017	Important	VERY LOW
Mean±SD Child Behaviour Checklist score, transfemales (lower scores indicate benefit)									
1 cross-sectional study Staphorsius et al 2015	Serious limitations ⁶	No serious indirectness	Not applicable	Not calculable	N=8	N=10	GnRH analogue: 57.4 [±9.8] No GnRH analogue: 58.2 [±9.3]	Important	VERY LOW
Mean±SD Child Behaviour Checklist score, transmales (lower scores indicate benefit)									
1 cross-sectional study	Serious limitations ⁶	No serious indirectness	Not applicable	Not calculable	N=12	N=10	GnRH analogues: 57.5 [±9.4] No GnRH analogue: 63.9 [±10.5]	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Staphorsius et al 2015									

Abbreviations: GnRH, gonadotrophin releasing hormone; P, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by Costa et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

2 6 months from baseline (after 6 months of psychological support – both groups).

3 12 months from baseline (delayed eligible gender dysphoria [GD] adolescents, after 12 months of psychological support; immediately eligible GD adolescents, after 12 months of psychological support + 6 months of puberty suppression).

4 18 months from baseline (delayed eligible gender dysphoria [GD] adolescents, after 12 months of psychological support; immediately eligible GD adolescents, after 12 months of psychological support + 6 months of puberty suppression).

5 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

6 Downgraded 1 level - the cohort study by Staphorsius et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding and no randomisation).

Table 6: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – engagement with healthcare services

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Engagement with healthcare services									
Number (proportion) failing to engage with health care services (did not attend clinic), at (up to) 9 years follow-up									
1 cohort study Brik et al 2018	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	9/214 (4.2%)	None	9 adolescents out of 214 failed to attend clinic and were excluded from the study (4.2%)	Important	VERY LOW
Loss to follow-up									
1 cohort study	Serious limitations ²	No serious indirectness	Not applicable		201	None	The sample size at baseline and 6 months was 201, which dropped by 39.8% to 121 after	Important	VERY LOW

QUALITY					Summary of findings		IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)	Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result	
Costa et al 2015				Not calculable			12 months and by 64.7% to 71 at 18 months follow-up. No explanation of the reasons for loss to follow-up are reported.	

Abbreviations: GnRH, gonadotrophin releasing hormone.

1 Downgraded 1 level - the cohort study by Brik et al. (2018) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

2 Downgraded 1 level - the cohort study by Costa et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

Table 7: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – stopping treatment

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Stopping treatment									
Number (proportion) stopping GnRH analogues, at (up to) 9 years follow-up									
1 cohort study Brik et al 2018	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	9/143 (6.2%)	None	9/143 adolescents stopped GnRH analogues (6.2%) ²	Important	VERY LOW
Number (proportion) stopping from GnRH analogues, at (up to) 13 years follow-up									
1 cohort study Khatchadourian et al 2014	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	11/27 (42%)	None	11/26 stopped GnRH analogues (42%) ⁴	Important	VERY LOW
Number (proportion) stopping GnRH analogues but who wished to continue endocrine treatment, at (up to) 9 years follow-up									

QUALITY					Summary of findings		IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)	Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result	
1 cohort study Brik et al 2018	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	4/143 (2.8%)	None	4/143 adolescents stopped GnRH analogues but wished to continue treatment (2.8%)	Important
Number (proportion) stopping GnRH analogues who no longer wished gender-affirming treatment, at (up to) 9 years follow-up								
1 cohort study Brik et al 2018	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	5/143 (3.5%)	None	5/143 adolescents stopped GnRH analogues and no longer wished to continue gender-affirming treatment (3.5%)	Important

Abbreviations: GnRH, gonadotrophin releasing hormone.

1 Downgraded 1 level - the cohort study by Brik et al. (2018) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

2 Median duration of 0.8 years (range 0.1 to 3.0). Five adolescents stopped treatment because they no longer wished to receive gender-affirming treatment for various reasons. In 4 adolescents (all transmales), although they wanted to continue treatments for gender dysphoria, GnRH analogues were stopped mainly because of adverse effects (such as mood and emotional lability).

3 Downgraded 1 level - the cohort study by Khatchadourian et al. (2014) was assessed as at high risk of bias (poor quality overall; lack of blinding, no control group and high number of participants lost to follow-up).

4 Because of transitioning to gender-affirming hormones or gender-affirming surgery, adverse effects (such as mood and emotional lability) or no longer wishing to pursue transition.

Table 8. Question 2. For children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – bone density

QUALITY					Summary of findings		IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)	Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result	
Bone density: change in lumbar BMAD								
Change in lumbar spine BMAD from baseline to 1 year in transfemales								

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 observational study Joseph et al. (2019)	Serious limitations [†]	No serious indirectness	Not applicable	Not calculable	N=31	None	Mean (SD), g/cm ³ Baseline: 0.235 (0.030) 1 year: 0.233 (0.029) p=0.459 z-score Baseline: 0.859 (0.154) 1 year: -0.228 (1.027) p=0.000	IMPORTANT	VERY LOW
Change in lumbar spine BMAD from baseline to 1 year in transmales									
1 observational study Joseph et al. (2019)	Serious limitations [†]	No serious indirectness	Not applicable	Not calculable	N=39	None	Mean (SD), g/cm ³ Baseline: 0.196 (0.035) 1 year: 0.201 (0.033) p=0.074 z-score Baseline: -0.186 (1.230) 1 year: -0.541 (1.396) p=0.006	IMPORTANT	VERY LOW
Change in lumbar spine BMAD from baseline to 2 years in transfemales									
1 observational study Joseph et al. (2019)	Serious limitations [†]	No serious indirectness	Not applicable	Not calculable	N=10	None	Mean (SD), g/cm ³ Baseline: 0.240 (0.027) 2 years: 0.240 (0.030) p=0.865 z-score Baseline: 0.486 (0.809) 2 years: -0.279 (0.930) p=0.000	IMPORTANT	VERY LOW
Change in lumbar spine BMAD from baseline to 2 years in transmales									
1 observational study	Serious limitations [†]	No serious indirectness	Not applicable	Not calculable	N=21	None	Mean (SD), g/cm ³ Baseline: 0.195 (0.058) 2 years: 0.198 (0.055) p=0.433	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Joseph et al. (2019)							z-score Baseline: −0.361 (1.439) 2 years: −0.913 (1.318) p=0.001		
Change in lumbar BMAD from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales									
1 observational study Klink et al. 2015	Serious limitations ²	No serious indirectness	Not applicable	Not calculable	N=11 N=12	None	Mean (SD), g/cm ³ GnRH analogue: 0.22 (0.03) Gender-affirming hormones: 0.22 (0.02) NS z-score GnRH analogue: −0.44 (1.10) Gender-affirming hormones: −0.90 (0.80) p-value: NS	IMPORTANT	VERY LOW
Change in lumbar BMAD from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales									
1 observational study Klink et al. 2015	Serious limitations ²	No serious indirectness	Not applicable	Not calculable	N=18	None	Mean (SD), g/cm ³ GnRH analogue: 0.25 (0.03) Gender-affirming hormones: 0.24 (0.02) NS z-score GnRH analogue: 0.28 (0.90) Gender-affirming hormones: −0.50 (0.81) p-value: 0.004	IMPORTANT	VERY LOW
Change in lumbar BMAD from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of <15 years)									
1 observational study Vlot et al. 2017	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=15	None	Median (range), g/cm ³ GnRH analogue: 0.21 (0.17 to 0.25) Gender-affirming hormones: 0.20 (0.18 to 0.24)	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							NS z-score GnRH analogue: −0.20 (−1.82 to 1.18) Gender-affirming hormones: −1.52 (−2.36 to 0.42) p-value: <0.01		
Change in lumbar BMAD from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of ≥15)									
1 observational study Vlot et al. 2017	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=5	None	Median (range), g/cm ³ GnRH analogue: 0.22 (0.18 to 0.25) Gender-affirming hormones: 0.22 (0.19 to 0.24) NS z-score GnRH analogue: −1.18 (−1.78 to 1.09) Gender-affirming hormones: −1.15 (−2.21 to 0.08) p-value: p≤0.1	IMPORTANT	VERY LOW
Change in lumbar BMAD from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of <14 years)									
1 observational study Vlot et al. 2017	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=11	None	Median (range), g/cm ³ GnRH analogue: 0.23 (0.20 to 0.29) Gender-affirming hormones: 0.23 (0.19 to 0.28) NS z-score GnRH analogue: −0.05 (−0.78 to 2.94) Gender-affirming hormones: −0.84 (−2.20 to 0.87) p-value: ≤0.01	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Change in lumbar BMAD from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of ≥ 14)									
1 observational study Vlot et al. 2017	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=23	None	Median (range), g/cm ³ GnRH analogue: 0.26 (0.21 to 0.29) Gender-affirming hormones: 0.24 (0.20 to 0.28) p $\leq$ 0.01 z-score GnRH analogue: 0.27 (-1.60 to 1.80) Gender-affirming hormones: -0.29 (-2.28 to 0.90) p-value: p $\leq$ 0.01)	IMPORTANT	VERY LOW
Bone density: change in lumbar BMD									
Change in lumbar spine BMD from baseline to 1 year in transfemales									
1 observational study Joseph et al. (2019)	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=31	None	Mean (SD), kg/m ² Baseline: 0.860 (0.154) 1 year: 0.859 (0.129) p=0.962 z-score Baseline: -0.016 (1.106) 1 year: -0.461 (1.121) p=0.003	IMPORTANT	VERY LOW
Change in lumbar spine BMD from baseline to 1 year in transmales									
1 observational study Joseph et al. (2019)	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=39	None	Mean (SD), kg/m ² Baseline: 0.694 (0.149) 1 year: 0.718 (0.124) p=0.006 z-score Baseline: -0.395 (1.428) 1 year: -1.276 (1.410) p=0.000	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Change in lumbar spine BMD from baseline to 2 years in transfemales									
1 observational study Joseph et al. (2019)	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=10	None	Mean (SD), kg/m2 Baseline: 0.867 (0.141) 2 years: 0.878 (0.130) p=0.395 z-score Baseline: 0.130 (0.972) 2 years: -0.890 (1.075) p=0.000	IMPORTANT	VERY LOW
Change in lumbar spine BMD from baseline to 2 years in transmales									
1 observational study Joseph et al. (2019)	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=21	None	Mean (SD), kg/m2 Baseline: 0.695 (0.220) 2 years: 0.731 (0.209) p=0.058 z-score Baseline: -0.715 (1.406) 2 years: -2.000 (1.384) p=0.000	IMPORTANT	VERY LOW
Change in lumbar BMD from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales									
1 observational study Klink et al. 2015	Serious limitations ²	No serious indirectness	Not applicable	Not calculable	N=12 N=11	None	Mean (SD), g/m2 GnRH analogue: 0.84 (0.13) Gender-affirming hormones: 0.84 (0.11) NS z-score GnRH analogue: -0.77 (0.89) Gender-affirming hormones: -1.01 (0.98) NS	IMPORTANT	VERY LOW
Change in lumbar BMD from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 observational study Klink et al. 2015	Serious limitations ²	No serious indirectness	Not applicable	Not calculable	N=18	None	Mean (SD), g/m2 GnRH analogue: 0.95 (0.12) Gender-affirming hormones: 0.91 (0.10) p-value: 0.006 z-score GnRH analogue: 0.17 (1.18) Gender-affirming hormones: -0.72 (0.99) p-value: <0.001	IMPORTANT	VERY LOW
Bone density: change in femoral neck (hip) BMD									
Change in femoral neck BMD from baseline to 1 year in transfemales									
1 observational study Joseph et al. (2019)	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=31	None	Mean (SD), kg/m2 Baseline: 0.894 (0.118) 1 year: 0.905 (0.104) p=0.571 z-score Baseline: 0.157 (0.905) 1 year: -0.340 (0.816) p=0.002	IMPORTANT	VERY LOW
Change from baseline to 1 year in femoral neck BMD in transmales									
1 observational study Joseph et al. (2019)	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=39	None	Mean (SD), kg/m2 Baseline: 0.772 (0.137) 1 year: 0.785 (0.120) p=0.797 z-score Baseline: -0.863 (1.215) 1 year: -1.440 (1.075) p=0.000	IMPORTANT	VERY LOW
Change from baseline to 2 years in femoral neck BMD in transfemales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 observational study Joseph et al. (2019)	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=10	None	Mean (SD), kg/m2 Baseline: 0.920 (0.116) 2 years: 0.910 (0.125) p=0.402 z-score Baseline: 0.450 (0.781) 2 years: -0.600 (1.059) p=0.002	IMPORTANT	VERY LOW
Change from baseline to 2 years in femoral neck BMD in transmales									
1 observational study Joseph et al. (2019)	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=21	None	Mean (SD), kg/m2 Baseline: 0.766 (0.215) 2 years: 0.773 (0.197) p=0.604 z-score Baseline: -1.075 (1.145) 2 years: -1.779 (0.816) p=0.001	IMPORTANT	VERY LOW
Bone density: change in femoral neck (hip) BMAD									
Change from starting GnRH analogue to starting gender-affirming hormones in femoral neck BMAD in transfemales (bone age of <15 years)									
1 observational study Vlot et al. 2017	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=16	None	Median (range), g/cm3 GnRH analogue: 0.29 (0.20 to 0.33) Gender-affirming hormones: 0.27 (0.20 to 0.33) p≤0.1 z-score GnRH analogue: -0.71 (-3.35 to 0.37) Gender-affirming hormones: -1.32 (-3.39 to 0.21) p≤0.1	IMPORTANT	VERY LOW
Change in femoral neck BMAD from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of ≥15)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 observational study Vlot et al. 2017	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=6	None	Median (range), g/cm ³ GnRH analogue: 0.30 (0.26 to 0.36) Gender-affirming hormones: 0.30 (0.26 to 0.34) NS z-score GnRH analogue: -0.44 (-1.37 to 0.93) Gender-affirming hormones: -0.36 (-1.50 to 0.46) NS	IMPORTANT	VERY LOW
Change in femoral neck BMAD from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of <14 years)									
1 observational study Vlot et al. 2017	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=10	None	Median (range), g/cm ³ GnRH analogue: 0.31 (0.26 to 0.36) Gender-affirming hormones: 0.30 (0.22 to 0.35) NS z-score GnRH analogue: -0.01 (-1.30 to 0.91) Gender-affirming hormones: -0.37 (-2.28 to 0.47) NS	IMPORTANT	VERY LOW
Change in femoral neck BMAD from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of ≥14)									
1 observational study Vlot et al. 2017	Serious limitations ³	No serious indirectness	Not applicable	Not calculable	N=23	None	Median (range), g/cm ³ GnRH analogue: 0.33 (0.25 to 0.39) Gender-affirming hormones: 0.30 (0.23 to 0.41) p-value: ≤0.01 z-score	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							GnRH analogue: 0.27 (−1.39 to 1.32) Gender-affirming hormones: −0.27 (−1.91 to 1.29) p-value: ≤0.01		
Bone density: change in femoral area BMD									
Change in femoral BMD from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales									
1 observational study Klink et al. 2015	Serious limitations ²	No serious indirectness	Not applicable	Not calculable	N=14 N=6	None	Mean (SD), g/m2 GnRH analogue: 0.88 (0.12) Gender-affirming hormones: 0.87 (0.08) NS z-score GnRH analogue: −0.66 (0.77) Gender-affirming hormones: −0.95 (0.63) NS	IMPORTANT	VERY LOW
Change in femoral BMD from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales									
1 observational study Klink et al. 2015	Serious limitations ²	No serious indirectness	Not applicable	Not calculable	N=18 N=13	None	Mean (SD), g/m2 GnRH analogue: 0.92 (0.10) Gender-affirming hormones: 0.88 (0.09) p-value: 0.005 z-score GnRH analogue: 0.36 (0.88) Gender-affirming hormones: −0.35 (0.79) p-value: 0.001	IMPORTANT	VERY LOW
Bone density: change in femoral area BMAD									
Change in femoral BMAD from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 observational study Klink et al. 2015	Serious limitations ²	No serious indirectness	Not applicable	Not calculable	N=12 N=10	None	Mean (SD), g/cm3 GnRH analogue: 0.28 (0.04) Gender-affirming hormones: 0.26 (0.04) NS z-score GnRH analogue: -0.93 (1.22) Gender-affirming hormones: -1.57 (1.74) p-value: NS	IMPORTANT	VERY LOW
Change in femoral BMAD from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales									
1 observational study Klink et al. 2015	Serious limitations ²	No serious indirectness	Not applicable	Not calculable	N=18 N=18	None	Mean (SD), g/cm3 GnRH analogue: 0.32 (0.04) Gender-affirming hormones: 0.31 (0.04) NS z-score GnRH analogue: 0.01 (0.70) Gender-affirming hormones: -0.28 (0.74) NS	IMPORTANT	VERY LOW

Abbreviations: BMAD, bone mineral apparent density; BMD, bone mineral density; GnRH, gonadotrophin releasing hormone; NS, not significant; SD, standard deviation.

1 Downgraded 1 level - the cohort study by Joseph et al. (2019) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

2 Downgraded 1 level - the cohort study by Klink et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding, no randomisation, no control group and high number of participants lost to follow-up).

3 Downgraded 1 level - the cohort study by Vlot et al. (2017) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control).

Table 9 Question 2: For children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – cognitive development or functioning

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Cognitive development or functioning (1 cross-sectional study)									
IQ (4 subscales: arithmetic, vocabulary, picture arrangement, and block design) at a single time point between GnRH analogue treated and untreated transfemales									
1 Cross-sectional study Staphorsius et al. 2015	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=8 Mean (SD) 94.0 (10.3)	N=10 Mean (SD) 109.4 (21.2)	NR	IMPORTANT	VERY LOW
IQ (4 subscales: arithmetic, vocabulary, picture arrangement, and block design) at a single time point between GnRH analogue treated and untreated transmales									
1 Cross-sectional study Staphorsius et al. 2015	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=12 Mean (SD) 95.8 (15.6)	N=10 Mean (SD) 98.5 (15.9)	NR	IMPORTANT	VERY LOW
Reaction time at a single time point between GnRH analogue treated and untreated transfemales									
1 Cross-sectional study Staphorsius et al. 2015	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=8 Mean (SD) 10.9 (4.1)	N=10 Mean (SD) 9.9 (3.1)	NR	IMPORTANT	VERY LOW
Reaction time at a single time point between GnRH analogue treated and untreated transmales									
1 Cross-sectional study	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=12 Mean (SD) 9.9 (3.1)	N=10 Mean (SD) 10.0 (2.0)	NR	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Staphorsius et al. 2015									
Accuracy at a single time point between GnRH analogue treated and untreated transfemales									
1 cohort study Staphorsius et al. 2015	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=8 Mean (SD) 73.9 (9.1)	N=10 Mean (SD) 83.4 (9.5)	NR	IMPORTANT	VERY LOW
Accuracy at a single time point between GnRH analogue treated and untreated transmales									
1 cohort study Staphorsius et al. 2015	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=12 Mean (SD) 85.7 (10.5)	N=10 Mean (SD) 88.8 (9.7)	NR	IMPORTANT	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; NR, not reported; P, P-value; SD, Standard deviation.

¹ Downgraded 1 level - the cohort study by Staphorsius et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding and no randomisation).

Table 10: Question 2: In children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – other safety outcomes

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Other safety outcomes: change in serum creatinine									
Change in serum creatinine (micromol/l) between baseline and 1 year in transfemales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 observational study Schagen et al. 2016	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=28	None	Mean (SD) Baseline: 70 (12) 1 year: 66 (13) p-value: 0.20	IMPORTANT	VERY LOW
Change in serum creatinine (μmol/l) between baseline and 1 year in transmales									
1 observational study Schagen et al. 2016	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	N=29	None	Mean (SD) Baseline: 73 (8) 1 year: 68 (13) p-value: 0.01	IMPORTANT	VERY LOW
Other safety outcomes: liver enzymes									
Presence of elevated liver enzymes (AST, ALT, and glutamyl transferase) between baseline and during treatment									
1 observational study Schagen et al. 2016	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	39	None	Glutamyl transferase was not elevated at baseline or during treatment in any subject. Mild elevations of AST and ALT above the reference range were present at baseline but were not more prevalent during treatment than at baseline. Glutamyl transferase, AST, and ALT levels did not significantly change from baseline to 12 months of treatment.	IMPORTANT	VERY LOW
Other safety outcomes: adverse effects									
Proportion of patients reporting adverse effects									
1 cohort study Khatchadourian et al 2014	Serious limitations ²	No serious indirectness	Not applicable	Not calculable ²	27	None	3/27 adolescents ³	Important	VERY LOW

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GnRH, gonadotrophin releasing hormone; P, P-value; SD, standard deviation.

1 Downgraded 1 level - the cohort study by Schagen et al. (2016) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control).

2 Downgraded 1 level - the cohort study by Khatchadourian et al. (2014) was assessed as at high risk of bias (poor quality overall; lack of blinding, no control group and high number of participants lost to follow-up).

3 1 transmale developed sterile abscesses; they were switched from leuprolide acetate to triptorelin, and this was well tolerated. 1 transmale developed leg pains and headaches, which eventually resolved without treatment. 1 participant gained 19 kg within 9 months of initiating GnRH analogues.

Table 11: Question 4. From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may derive more (or less) advantage from treatment with GnRH analogues than the wider population of children and adolescents with gender dysphoria? – critical outcomes

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		
Subgroups: sex assigned at birth males compared with sex assigned at birth females									
Impact on gender dysphoria									
Mean [±SD] Utrecht Gender Dysphoria Scale (version(s) not reported), time point at baseline (before GnRH _a) versus follow-up (just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	n-NR ² score at T0 47.95 [±9.70] score at T1 49.67 [±9.47]	n-NR ² score at T0 56.57 [±3.89] score at T1 56.62 [±4.0]	F-ratio 15.98 (df, errdf: 1,39), P<0.001	Critical	VERY LOW
Impact on mental health									
Mean [±SD] Beck Depression Inventory-II, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		
1 cohort study de Vries et al 2011	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	n-NR ² score at T0 5.71 [±4.31] score at T1 3.50 [±4.58]	n-NR ² score at T0 10.34 [±8.24] score at T1 6.09 [±7.93]	F-ratio 3.85 (df, errdf: 1,39), P=0.057	Critical	VERY LOW
Mean [±SD] Trait Anger (TPI), time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	n-NR ² score at T0 5.22 [±2.76] score at T1 5.00 [±3.07]	n-NR ² score at T0 6.43 [±2.78] score at T1 6.39 [±2.59]	F-ratio 5.70 (df, errdf: 1,39), P=0.022	Critical	VERY LOW
Mean [±SD] Trait Anxiety (STAI), time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	n-NR ² score at T0 4.33 [±2.68] score at T1 4.39 [±2.64]	n-NR ² score at T0 7.00 [±2.36] score at T1 6.17 [±2.69]	F-ratio 16.07 (df, errdf: 1,39), P<0.001	Critical	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; NR, not reported; P, P-value; SD, Standard deviation.

¹ Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

² The overall sample size completing the outcome at both time points was 41.

Table 11: Question: 4. From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may derive more (or less) advantage from treatment with GnRH analogues than the wider population of children and adolescents with gender dysphoria? – important outcomes

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		
Subgroups: sex assigned at birth males compared with sex assigned at birth females									
Impact on body image									
Mean [±SD] Body Image Scale (primary sexual characteristics), time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	n-NR ² score at T0 4.02 [±0.16] score at T1 3.74 [±0.78]	n-NR ² score at T0 4.16 [±0.52] score at T1 4.17 [±0.58]	F-ratio 4.11 (df, errdf: 1,55), P=0.047	Important	VERY LOW
Mean [±SD] Body Image Scale (secondary sexual characteristics), time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	n-NR ² score at T0 2.66 [±0.50] score at T1 2.39 [±0.69]	n-NR ² score at T0 2.81 [±0.76] score at T1 3.18 [±0.42]	F-ratio 11.57 (df, errdf: 1,55), P=0.001 ³	Important	VERY LOW
Mean [±SD] Body Image Scale (neutral characteristics), time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		
1 cohort study de Vries et al 2011	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	n-NR ² score at T0 2.60 [±0.58] score at T1 2.32 [±0.59]	n-NR ² score at T0 2.24 [±0.62] score at T1 2.61 [±0.50]	F-ratio 0.081 (df, errdf: 1,55), P=0.777 ³	Important	VERY LOW
Psychosocial impact									
Mean [±SD] Children's Global Assessment Scale score, at baseline.									
1 cohort study Costa et al 2015	Serious limitations ⁴	No serious indirectness	No serious inconsistency	Not calculable	n=not reported 55.4 [±12.7]	n=not reported 59.2 [±11.8]	t-test 2.15; P=0.03 ⁵	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	n-NR ⁶ score at T0 73.10 [±8.84] score at T1 77.33 [±8.69]	n-NR ⁶ score at T0 67.25 [±11.06] score at T1 70.30 [±9.44]	F-ratio 5.77 (df, errdf: 1,39), P=0.021	Important	VERY LOW
Mean [±SD] Child Behaviour Checklist (total T) score, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	n-NR ⁷ score at T0 59.42 [±11.78] score at T1 50.38 [±11.78]	n-NR ⁷ score at T0 61.73 [±13.60]	F-ratio 2.64 (df, errdf: 1,52), P=0.110	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		
					[±10.57]	score at T1 57.73 [±10.82]			
Mean [±SD] Child Behaviour Checklist (internalising T) score, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	n-NR ⁷ score at T0 60.00 [±9.51] score at T1 52.17 [±9.81]	n-NR ⁷ score at T0 61.80 [±14.12] score at T1 56.30 [±10.33]	F-ratio 1.16 (df, errdf: 1,52), P=0.286	Important	VERY LOW
Mean [±SD] Child Behaviour Checklist (externalising T) score, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	n-NR ⁷ score at T0 54.71 [±12.91] score at T1 48.75 [±10.22]	n-NR ⁷ score at T0 60.70 [±12.64] score at T1 57.87 [±11.66]	F-ratio 6.29 (df, errdf: 1,52), P=0.015	Important	VERY LOW
Mean [±SD] Youth Self-Report (total T) score, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	n-NR ⁷ score at T0 53.56 [±12.26] score at T1 47.84 [±10.86]	n-NR ⁷ score at T0 57.10 [±10.87] score at T1 51.86 [±10.11]	F-ratio 1.99 (df, errdf: 1,52), P=0.164	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		
Mean [±SD] Youth Self-Report (internalising T) score, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	n-NR ⁷ score at T0 55.88 [±11.81] score at T1 49.24 [±12.24]	n-NR ⁷ score at T0 56.17 [±13.25] score at T1 50.24 [±11.28]	F-ratio 0.049 (df, errdf: 1,52), P=0.825	Important	VERY LOW
Mean [±SD] Youth Self-Report (externalising T) score, time point at baseline (T0 before GnRH) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations ¹	No serious indirectness	Not applicable	Not calculable	n-NR ⁷ score at T0 48.72 [±11.83] score at T1 46.52 [±9.23]	n-NR ⁷ score at T0 57.24 [±10.59] score at T1 52.97 [±8.51]	F-ratio 9.14 (df, errdf: 1,52), P=0.004	Important	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; NR, not reported; P, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

2 The overall sample size completing the outcome at both time points was 57.

3 There was a significant interaction effect between sex assigned at birth and BDI between T0 and T1; sex assigned at birth females became more dissatisfied with their secondary F (df, errdf), P: 14.59 (1,55), P<0.001 and neutral F (df, errdf), P: 15.26 (1,55), P<0.001 sex characteristics compared with sex assigned at birth males.

4 Serious limitations – the cohort study by Costa et al. 2015 was assessed as at high risk of bias (poor quality).

5 At baseline, CGAS scores were not associated with any demographic variable, in both sex assigned at birth males and females. There were no statistically significant differences in CGAS scores between gender dysphoric sex assigned at birth males and females in all follow-up evaluations (P>0.1; full data not reported).

6 The overall sample size completing the outcome at both time points was 41

7 The overall sample size completing the outcome at both time points was 54.

Glossary

Beck Depression Inventory-II (BDI-II)	The BDI-II is a tool for assessing depressive symptoms. There are no specific scores to categorise depression severity, but it is suggested that 0 to 13 is minimal symptoms, 14 to 19 is mild depression, 20 to 28 is moderate depression, and severe depression is 29 to 63.
Body Image Scale (BIS)	The BIS is used to measure body satisfaction. The scale consists of 30 body features, which the person rates on a 5-point scale. Each of the 30 items falls into one of 3 basic groups based on its relative importance as a gender-defining body feature: primary sex characteristics, secondary sex characteristics, and neutral body characteristics. A higher score indicates more dissatisfaction.
Bone mineral apparent density (BMAD)	BMAD is a size adjusted value of bone mineral density (BMD) incorporating body size measurements using UK norms in growing adolescents.
Child Behaviour Checklist (CBCL)	CBCL is a checklist parents complete to detect emotional and behavioural problems in children and adolescents.
Children's Global Assessment Scale (CGAS)	The CGAS tool is a validated measure of global functioning on a single rating scale from 1 to 100. Lower scores indicate poorer functioning.
Gender	The roles, behaviours, activities, attributes, and opportunities that any society considers appropriate for girls and boys, and women and men.
Gender dysphoria	Discomfort or distress that is caused by a discrepancy between a person's gender identity (how they see themselves regarding their gender) and that person's sex assigned at birth (and the associated gender role, and/or primary and secondary sex characteristics).
Gonadotrophin releasing hormone (GnRH) analogues	GnRH analogues competitively block GnRH receptors to prevent the spontaneous release of 2 gonadotropin hormones, Follicular Stimulating Hormone (FSH) and Luteinising Hormone (LH) from the pituitary gland. The reduction in FSH and LH secretion reduces oestradiol secretion from the ovaries in those whose sex assigned at birth was female and testosterone secretion from the testes in those whose sex assigned at birth was male.
Sex assigned at birth	Sex assigned at birth (male or female) is a biological term and is based on genes and how external and internal sex and reproductive organs work and respond to hormones. Sex is the label that is recorded when a baby's birth is registered.
Tanner stage	Tanner staging is a scale of physical development.
Trait Anger Spielberger scales of the State-Trait Personality Inventory (TPI)	The TPI is a validated 20-item inventory tool which measures the intensity of anger as the disposition to experience angry feelings as a personality trait. Higher scores indicate greater anger.
Transgender (including transmale and transfemale)	Transgender is a term for someone whose gender identity is not congruent with their birth-registered sex. A transmale is a person who identifies as male and a transfemale is a person who identifies as female.

Utrecht Gender Dysphoria Scale (UGDS)	The UGDS is a validated screening tool for both adolescents and adults to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. The higher the UGDS score the greater the impact on gender dysphoria.
Youth Self-Report (YSR)	The self-administered YSR is a checklist to detect emotional and behavioural problems in children and adolescents. It is self-completed by the child or adolescent. The scales consist of a Total problems score, which is the sum of the scores of all the problem items. An internalising problem scale sums the anxious/depressed, withdrawn-depressed, and somatic complaints scores while the externalising problem scale combines rule-breaking and aggressive behaviour.

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Guidance for Transgender Inclusion in Domestic Sport



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Foreword from our CEOs

We want sport to be a place where everyone can be themselves, where everyone can take part and where everyone is treated with kindness, dignity and respect.

Over the past 18 months we, the five Sports Councils responsible for supporting and investing in sport across England, Wales, Scotland and Northern Ireland, have been working together to develop new guidance to support the inclusion of transgender people in sport, recognising that the existing guidance from 2013 was out of date and no longer fit for purpose.

We also recognised that sport at every level required more practical advice and support in this area to be able to maximise opportunities for inclusion and accessibility.

The ultimate aim of this work is to better support our partners in understanding current needs and challenges in this area and to ensure that sports can make informed decisions in seeking to become as inclusive as possible. The guidance has been developed following a review which was divided into two parts.

One involved an extensive independent consultation which considered the views and experiences of hundreds of people within sport, from grassroots through to elite competition. Specialist groups and individuals were also consulted by interviews and surveys and the respondents were a diverse group spread across more than 54 sports and representing 175 organisations. We want to thank everyone who gave up their time and took part, particularly because we know that for many, doing so was challenging and emotive. We are hugely grateful for your input.

The second part of the review explored the background to current policies domestically and internationally and considered the latest scientific findings relating to the inclusion of transgender people in sport, such as testosterone suppression in transgender women, and the use of case-by-case assessments. It explored and considered up-to-date peer reviewed and published studies, up to early 2021.

While our consultation found that there was widespread support for ensuring that sport was a welcoming place for everyone in society, including for transgender people, it also highlighted that there were concerns relating to safety and fairness in relation to transgender inclusion, particularly in female sport, and that there was no consensus on a single solution as to how this should be addressed.

It was clear too that a wider range of solutions than those that are currently on offer needed to be identified so that everyone taking part could do so in a fair, safe and inclusive way.

Our work exploring the latest research, evidence and studies made clear that there are retained differences in strength, stamina and physique between the average woman compared with the average transgender woman or non-binary person registered male at birth, with or without testosterone suppression.

Based on our conclusions, we are publishing suggested recommendations for the National Governing Bodies (NGBs and Scottish Governing Bodies (SGBs we work with and a framework for them to consider when they are developing their own policies in this area, as well as a summary of the research we considered.

This will support NGBs and SGBs and other partners to define the best options for their activity, depending on their own assessment as to their priorities, and consider a range of options as to how they might achieve those. We believe that this provides a significantly stronger, more specific, and authoritative framework than has ever existed before in relation to transgender inclusion in sport.

Our recommendations encourage our NGBs and SGBs to think in innovative and creative ways to ensure nobody is left out.

We want this guidance to open up, rather than close down opportunities for everyone, recognising that many other people already feel excluded from sport and physical activity.

We now want to see meaningful and respectful consultation in developing these approaches, which we hope will facilitate increased transgender participation and help sport to become more open, inclusive and diverse. We all recognise that in order to survive and thrive in the future, sport must adapt to reflect modern society, and that often, it is too slow to do so.

Society is changing, and sport must face the challenge of accommodating participation from every group – even if this means recognising that their traditional structures are not always set up to do so. We believe that this guidance therefore offers a chance for a reimagining of what sport can look like – and we will work closely to support those sports who want to embrace this fresh thinking.

We will be alert and responsive to emerging research and evidence and will commit to reviewing the guidance on a more regular basis to ensure it is fit for purpose. We also commit to continuing to work closely with our partners to support them to navigate the use of the guidance to help them make informed decisions for their sport.

This has been a challenging and emotive piece of work – but we believe we are putting forward pragmatic solutions for sports to work with, so sport can be a place where everyone can take part.

Introduction

As set out in the foreword from our CEOs, The Sports Councils' Equality Group (SCEG) commissioned a review of its existing Guidance (2013/15) for the inclusion of transgender people in sport last year, recognising that sport at every level required more practical advice and support.

This review investigated the views, knowledge, and experience of hundreds of people with a lived experience in sport, including transgender people, and also explored the background to current policies domestically and internationally and considered the latest scientific findings affecting the inclusion of transgender people in domestic sport.

It was clear throughout that this is a complex area, and that there is an ongoing requirement for education and engagement with the aim of creating an environment in which the inclusion of all people in sport and physical activity is expected, accepted and celebrated.

There are a number of supporting documents to this Guidance, which gives further background and understanding of the recommendations. You can find these documents at <https://equalityinsport.org/resources>.

Summary of what the review found

The review found that while there was widespread support for ensuring that sport was a welcoming place for everyone in society, there were some concerns relating to safety and sporting fairness in the inclusion of transgender people, particularly transwomen, and no consensus on how this should be addressed.

Two divergent groups emerged amongst respondents. One group believed wholly in the value of inclusion over and above anything else and believe that transgender people should be able to take part in sport at every level with limited to no restrictions.

The second group believed in what they would describe as fair sporting competition and adherence to rules which give sport validity – and therefore, they believe that transgender participation should be subject to regulation.

The review concluded that the views of these two groups couldn't be reconciled within the existing structure of sport and that the system requires a reset and fresh thinking.

The overarching recommendation is that NGBs and SGBs are encouraged to enter a decision-making process, set out below, in which they can best accommodate transgender inclusion, fairness, and safety in their sport.

What the review is recommending

As a result of what the review found, the Guidance concludes that the inclusion of transgender people into female sport cannot be balanced regarding transgender inclusion, fairness and safety in gender-affected sport where there is meaningful competition. This is due to retained differences in strength, stamina and physique between the average woman compared with the average transgender woman or non-binary person assigned male at birth, with or without testosterone suppression.

Sports, however, are incredibly diverse and there can be no 'one-size fits all' approach. This review has concluded therefore that, for many sports, there may not be a common single competition model which will meet the needs of full transgender inclusion while retaining competitive fairness, particularly in female sport.

We are therefore encouraging and advising NGBs and SGBs to define the best options for their sport and determine whether it may be possible to offer more than one version of their sport to achieve the different aims.

NGBs and SGBs are encouraged, and will be supported, to use the decision-making framework set out below, in which they can consider how gender affected their sport is, and if appropriate, consider how this might be modified and adapted to offer multiple competitive or participation models.

The Sports Councils are committed to facilitating and promoting the education and decision-making process to enable NGBs and SGBs to make the best decisions for their sport and for their communities.

This Guidance also sets out the underlying principles which NGBs should consider when developing policies in this area, which are designed to create opportunities for sport to increase inclusion and the breadth of sport for everyone in society.

Guiding Principles

These 10 Guiding Principles are for sports to use when developing policies in this area:

1. All of the Sports Councils are committed to the inclusion of transgender people in sport and physical activity.

In keeping with the findings of this review, the goals of acceptance, social inclusion and physical activity may be best achieved outside of the sex binary in grassroots and domestic sport. The introduction of new and different models within sport offers an alternative option to meet the needs of people across all the strands of the Equality Act.

2. Categorisation within the sex binary is and remains the most useful and functional division relative to sporting performance.

This categorisation acknowledges the broad ranging and significant performance differences between the sexes. Hence, sports should retain sex categorisation, along with age and disability (and weight as appropriate) categories.

3. Evidence indicates it is fair and safe for transgender people to be included within the male category in most sports.

This is on the assumption that the transgender person will generally be using testosterone supplementation, for which a Therapeutic Use Exemption (TUE) will be required in many sports. The NGBs and SGBs of contact, collision or combat sports in which size may impact safety considerations may consider further parameters to ensure safety of transgender people, including transgender men, non-binary and gender fluid people recorded female at birth.

4. Competitive fairness cannot be reconciled with self-identification into the female category in gender-affected sport.

This principle is in keeping with the provisions of the Equality Act, and acknowledges the average differences in strength, stamina, and physique between the sexes.

Self-identification through the 'acceptance of people as they present' may be appropriate in those sports which are not gender-affected. In this instance, for clarity and inclusion, these sports may appropriately be considered 'mixed' or 'universal' sports, in which everyone may participate and compete together.

5. Based upon current evidence, testosterone suppression is unlikely to guarantee fairness between transgender women and natal females in gender-affected sports:

- a) Transgender women are on average likely to retain physical advantage in terms of physique, stamina, and strength. Such physical differences will also impact safety parameters in sports which are combat, collision or contact in nature.
- b) Recent international policy on testosterone limits are set at a level below 5nmol/L in sports which choose to provide entry into female sports for transgender women. This is more appropriate than the 10nmol/L which is stipulated by the International Olympic Committee and which remains within the normal range for males. The current preliminary 12-month period is unlikely to result in the achievable minimisation of physical capacity.

6. 'Case-by-case' assessment is unlikely to be practical nor verifiable for entry into gender-affected sports.

NGBs may wish to consider the following when determining the appropriateness of this:

- It has not been scientifically validated as to whether any parameters of physical capacity or ability can be defined with a certain cut-off point at which someone is considered appropriately 'female' or appropriately 'male'.
- Many tests related to sports performance are volitional. This means a person must try their very best to get an appropriate measurement. It is difficult to foresee how someone could be expected to provide maximal effort when a positive outcome for them relies on achieving a lesser result.
- Panel members are unlikely to be able to manage a situation in which their decisions can determine the suitability of some individuals, and not others. In the absence of a scientific rationale this places the panel members in a difficult situation.
- Case-by-case analysis may fall outside of the provisions of the Equality Act (whereby provision is for average advantage not individual advantage) and may be based on criteria which cannot be lawfully justified. Some transgender people will be included, some will be excluded through criteria outside of their own control.

7. Categorisation by sex is lawful, and hence the requirement to request information relating to birth sex is appropriate.

No individual is compelled to provide any information to a sports organisation. However, failure to provide such information would mean that person may not be able to compete in the category of their choice. Sports should provide options for those people who prefer not to advise of their sex or gender.

All data acquired by a sporting agency should be afforded appropriate protection under the Data Protection Act 2018.

8. There are likely to be times in which some transgender people cannot or choose not to be registered, either in the short or long-term, within sex binary categories.

It is imperative that gender-affected sports provide other opportunities for participation in these cases.

9. The ability of NGBs and SGBs to provide the best mix of sporting options for the broader community may be determined by whether a model is intended as physical activity and participation, or whether it represents 'meaningful competition'.

An assessment of the merits of fairness and/or inclusion can be determined by the sports' stakeholders to inform policy development, and whether this should be different at different levels of sport.

10. Achieving inclusion across all the strands of the Equality Act is complex and nuanced.

It is recognised that many NGBs and SGBs may find the task of developing appropriate policy and protocols both difficult and time-consuming. It is important that views of a wide range of stakeholders are canvassed and that everyone is given an appropriate platform in which to contribute, and that different views and experiences are heard and respected. The Sports Councils are committed to facilitating education and decision making within sports in the UK.

The way forward

For many NGBs, the development of policy and practice will depend on a closer understanding of the gender-affected nature of their sport, and the priorities which they place on transgender inclusion, fairness and safety. The following table and considerations are offered as a starting point for sports to analyse their current competition format.

In accordance with the Equality Act 2010: A gender-affected activity is a sport, game, or other activity of a competitive nature in circumstances in which the physical strength, stamina, or physique of average persons of one sex would put them at a disadvantage compared with average persons of the other sex as competitors in events involving the activity.

Some useful questions for NGBs and SGBs to consider in order to help them to make informed decisions in seeking to become as inclusive as possible, are:

Question	Considerations
Is your sport 'gender affected', and how is that manifest?	Most, but not all sports are impacted by the physical differences between males and females. Sports which are mainly skillful may not be gender-affected.
Does your sport reward greater strength, stamina or physique?	If there is a material advantage for being bigger, stronger, fitter and faster in your sport then it is likely that it is gender-affected.
If your sport is not gender affected, or some forms of your sport are not gender affected, what are the reasons to retain sex categories for that competition in the future?	This might include considerations of socio-cultural factors, or aspects such as faith or ethnic groups.
What is the purpose of the sex categories in your sport?	This refers to whether your sport considers that the categories exist to provide inclusion or whether it is to provide fairness in competition.
Do you consider inclusion to be the first priority?	If so, then your decisions are based around this priority.
Is fairness paramount to your sport? Is safety paramount to your sport?	Again, if these are the priorities then that informs your decision-making.
Could your sport offer alternative competitive models which may be specific to inclusion or fairness but not necessarily both?	If novel or modified versions of your sport could be developed, then this could increase options for inclusion.
Does your sport currently accommodate consideration of female characteristics such as smaller playing surface, lighter weighted implements, lower net or hurdle height, shorter length of event or distance covered?	If so, it may mean that fairness cannot be achieved alongside inclusion in this format of your sport.

Question	Considerations
Does your sport have modified rules for females, males or other categories such as juniors?	This is the case for some sports and would potentially require modification to promote inclusion.
Does, or could your sport offer modified versions of your playing rules?	This would assist inclusion if at all possible.
Are there some versions which are more specific to categorisation for competitive fairness, and others which would be more appropriate for inclusive sport?	If so, this might create opportunities for inclusion through different models within your sport.
Do you think the emphasis on inclusion and fairness should be different between grassroots community participation compared with sport which offers 'meaningful competition'?	It is important to consider how competitors assess their involvement in sport. Some grassroots sports may be fiercely competitive, and other high-level sport may be considered non-competitive by the participants.
Do you believe your sport's categorisation gives fairness within and access to competition to all participants?	Consultation is needed within your sport to ensure opinions are sought from a range of stakeholders.
Does your sport offer secondary or consequential reward to those who are successful? Does your sport consider this to be an outcome of fair competition or inclusion?	This might relate to things like prizes or winning scholarships, or gaining entry to courses in higher education, or a professional career in sport.
Is your sport able to offer non-competitive outcomes irrespective of the level of competition?	This is relevant if there is an opportunity for 'social' or 'recreational' sport for your participants or club members.

Hierarchy of 'contact'

This relates to perceptions of both fairness and, more importantly, to safety as a criterion for gender-affected sport. The nature of a given sport allows for different rules/laws and different degrees of physical contact with opposing competitors. Sports can be viewed on a continuum ranging from zero contact to full-force striking and grappling of opponents.

An understanding of levels of physical contact provide an extra dimension of safety, whereby the factors of strength, stamina and physique puts one sex (female) at a disadvantage and prevent greater risk of injury.

A hierarchy can be presented as:

- 1 Sports which compete in parallel: for example, gymnastics, dressage, skateboarding, downhill skiing, track sprints, rowing, darts, pool swimming.
- 2 Contact sport (within the same space): for example, netball, basketball, football, hockey, some track and road cycling, athletics track races over 400m.
- 3 Collision sports: for example, both rugby codes.
- 4 Combat sports: for example, boxing, taekwondo, judo, karate.

Other considerations and examples of assessment of gender-affected sport

Some sports are more attributed to skill, or may have an 'implement', which may limit the gender-affected nature of competition, for example:

- Darts, curling, bowls, shooting, snooker, equestrian.

Sports which rely significantly on physical capacity – physique (including height), strength, stamina – despite not being contact or collision sports, will be considered 'gender-affected', for example:

- Rowing, volleyball, climbing, athletics.

Some sports which use implements may or may not have consideration for physical capacity, for example:

- Archery, motorsports.

Some 'judged sports' are more dependent on skill rather than strength, such as rhythmic gymnastics. However, some have significant physical factors of strength, stamina, and physique due to the nature of the activity, such as artistic swimming. Those sports which use lower nets, shorter boundaries, or lighter implements in female competition implicitly recognise themselves as 'gender-affected', and this acknowledges direct competition between the sexes is considered unfair (and perhaps unsafe). Many sports have an age after which mixed competition is prohibited, and it is evident from such rules that mixed competition after this age is considered unfair and/or unsafe.

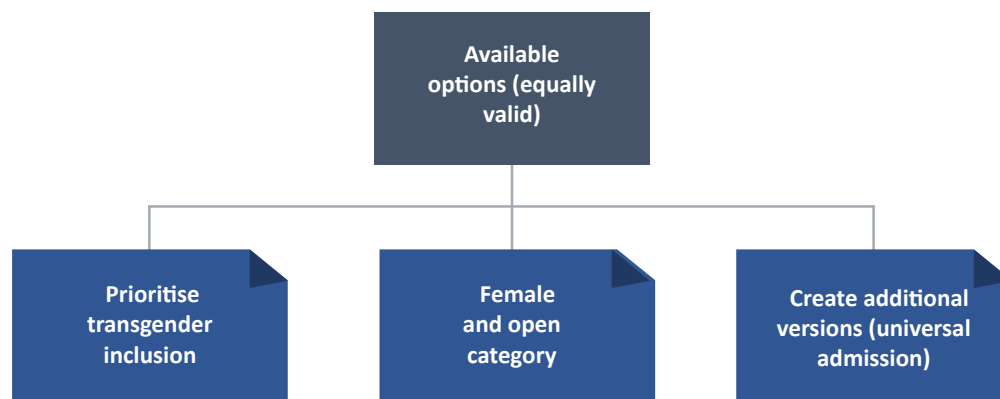
Objectively measured, individual sports may be able to use competition records to make comparisons of physical performance between the sexes, while other sports (such as most team sports) will need to rely on contributing information. It is also relevant to consider the effects of gender-affected sport within a team, and not just compared with the opposing team. In this way, aspects of fairness and safety will also impact decisions around selection within a team and across a club or association.

An assessment should be made as to whether a sport considers all levels of grassroots and domestic competition and participation should retain similar policy and rules, or whether there are different imperatives at varying levels of competition. Estimation of safety is relevant at all levels of sport, and in some cases may be more important at community-level competition where lower skill level may increase risk.

Three options to be considered

This Guidance suggests the following three options be considered by each governing body.

These options are stated in no particular order and for the avoidance of doubt, are not stated in the order of importance. Each of transgender inclusion, fairness and safety are important, but the role each may play in different individual sports will differ, due to the nature of the sport.



The choice of competitive format is not intended to be mutually exclusive, and NGBs and SGBs can opt to provide competition in more than one model. The Sports Councils encourage all NGBs and SGBs to be creative and accommodating in order to be maximally inclusive for all participants including, if possible, disabled participants and people across the age groups. Different formats of competition will also allow participation for those people who may self-exclude from a holistically inclusive environment. SCEG can offer advice and education to assist NGBs and SGBs in making plans and policy for sport programmes.

Given the assessment of the nature of the sport, along with the priorities of transgender inclusion, fairness, and safety, the following choices are suggested: if a sport is deemed to be gender-affected it should offer either the option relating to transgender inclusion, or the option relating to fairness.

Where possible, NGBs and SGBs should also offer an appropriate version of the option relating to safety as well, within the confines of the sport.

Where appropriate, NGBs and SGBs will need to consider pathways for elite performers into national competition, and compliance with regulations from international federations.

Prioritise transgender inclusion

Based on the current system, which prioritises inclusion of transgender people into existing sex categories of gender-affected sport.

This is 'management' of the inherent differences between the sexes for transgender people wishing to compete in their affirmed gender (and for non-binary or gender fluid people who wish to compete in the sex category not aligned to sex registered at birth). As outlined earlier in Principles 4, 5 and 6, no current method of inclusion of transgender people can guarantee sporting fairness for the female category. Hence, this option is considered appropriate for a sport which has determined that inclusion rather than fairness is the objective of the category. In most sports, transgender men will be able to compete without restriction in the male (or open) category. However, those sports which include collision or combat may wish to institute safety guidance for the sake of the transgender competitor.

Those gender-affected sports which wish to include transgender women, or non-binary or gender fluid people recorded male at birth, within the female category should institute testosterone limits defined by blood tests. More recent policy indicates a level less than 5 nmol/L is more appropriate than the level of 10nmol/L (and per protocols defined in international sport) for a preliminary period before entry into the first competition, and then maintained for as long as the transgender person remains competitive. Current evidence indicates 12 months is likely to be too short a time to minimise performance differences. As testosterone blood levels can vary over a short time period under most treatment regimes, tests should be conducted at least quarterly, and can include further markers of testosterone suppression. Considerations include the need to have a dedicated officer who is able to administer athletes' test results throughout the competitive and off-seasons. Should any athlete be away from testing for any time, they should complete another preliminary period before they can compete again.

Transgender men should not compete in female categories once treatment with testosterone commences, as this would constitute a doping violation as per UK Anti-Doping (and World Anti-Doping Agency) regulations. All competitors, at any level of competition, must adhere to anti-doping regulations and this includes use of TUEs for prohibited medications.

Female and open category

NGBs and SGBs may choose to offer sport in which the female category is protected for reasons of competitive fairness and/or safety if they are gender affected. These sports would offer both a female category and an open category. Female entries would be required to declare themselves as recorded female at birth.

An open category would be available for any competitor to enter. Some sports may choose to acknowledge safety parameters as part of team selection in contact sports.

All competitors will need to be compliant with anti-doping regulations, including in relation to prior or current use of anabolic agents, including testosterone.

It is lawful to offer sex categories in sport through the provisions in the Equality Act in respect of gender-affected sport.

Create additional versions (universal admission)

A third option for many sports would focus on universal community inclusion which may not require estimation of ability.

NGBs and SGBs are encouraged to develop a model of their sport in which participation is not dependent on a competitor's sex or gender, and the classification based on the sex binary is withdrawn for this competition. Registration for these competitions will not require declaration of any determinant beyond entry above a nominal age (this may be above the age of 12, depending on the rules of sport competition and physical contact level). All people, including transgender people who are transitioning, those who do not seek to transition, and those who may de-transition or be gender fluid, should be able to compete within a universal admission policy.

Sports which are not gender-affected may choose to offer universal admission as the primary form of competition. However, it must be recognised that a universal admission policy may not equate to full participation for many reasons, one of which may be self-exclusion.

How best to develop a model of this will be based on decisions relating to how a sport manifests being 'gender-affected' and whether this relates to level of contact, and hence safety, or whether it is because of the physical nature of competition which is relevant to fairness (or both). Further, an understanding of the role of the competition is important; whether it is purely for recreational participation or whether it offers meaningful competition. For many sports it will be a combination of factors. In keeping with Principle 6 (case-by-case assessment), it is likely to be impractical and invalid for methodology around body type to be instituted for categorisation.

Sport with a universal admission policy will have modified rules such that it can be played by all people, and for which fairness and safety can be optimised. These models may already exist in some sports. As much as is possible all adults, including disabled people, should be factored into these offerings. Adaptations of rules include non-contact versions of team sports, handicap competitions, modified playing areas or implements/balls, walking versions of team sports, multi-events and non-traditional formats, distances or length of play. Some sports (such as golf) already have an acknowledgement of 'handicap', and others have options for such modifications (some running, swimming and cycling events). Modern sports allow opportunities to adapt scoring systems to accommodate a wide range of participants, as practiced in some para sports.

It is acknowledged that for some NGBs there will not be an option for universal admission, and this includes those sports which are inherently gender-affected due primarily to safety concerns: modifications to remove physical contact may be impractical, and this includes most of the combat sports. However, elements of such sport, such as competitive 'kata' in karate, may be appropriate.

Conclusion

This Guidance concludes that for many sports, the inclusion of transgender people, fairness and safety cannot co-exist in a single competitive model.

Each NGB and SGB should use the framework provided to define the priorities for their sport, and whether the current format of their sport will provide a focus on either inclusion or fairness (and safety where relevant). This is a choice.

Where a governing body considers that transgender inclusion, fairness, and safety are all priorities, then a model for decision making around the best options and opportunities should be developed.

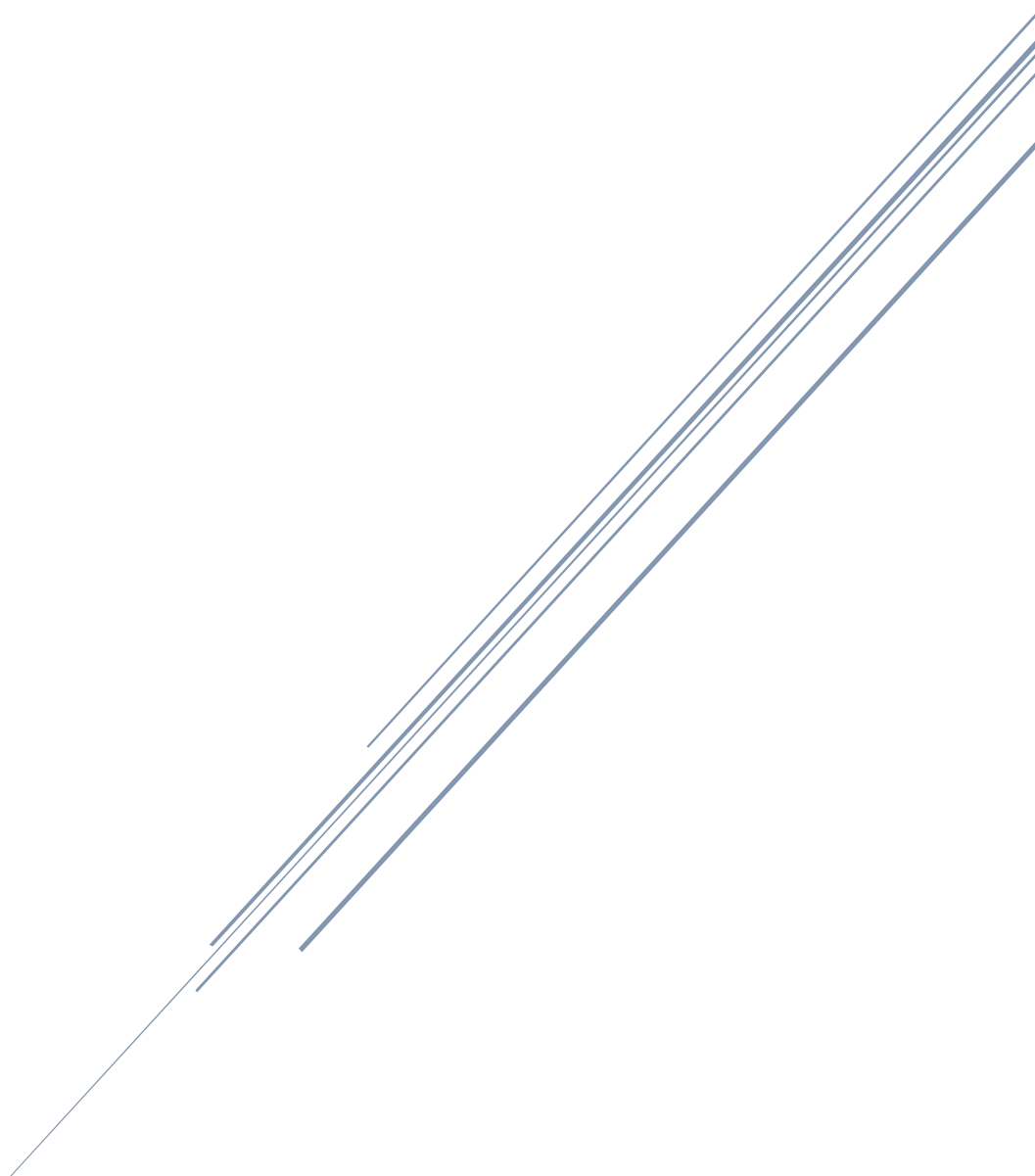
Some governing bodies will need to create a mechanism whereby domestic competition can lead to an international competition pathway.

The Sports Councils will work with NGBs and SGBs in order to find the optimal outcome for their sport. Education and training in policy development will be offered to facilitate best practice and the greatest opportunities for inclusion in sport.

For further background, you can read the supporting documents to this Guidance at <https://equalityinsport.org/resources>.

INTERNATIONAL RESEARCH LITERATURE REVIEW

SCEG Project for Review and Redraft of Guidance for
Transgender Inclusion in Domestic Sport 2020



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Confidential – Sports Council

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This document is produced specifically as part of the Review and Redraft of the Guidance for Transgender Inclusion in Sport for the Sports Councils' Equality Group of UK.

The literature review includes published scientific research relating to transgender inclusion in sport, and is based largely on peer-reviewed data, but also some pertinent opinion pieces (outlined in the text). It is written in a general chronological order, with reference to important milestones in international sport to provide context and relevance to historical events and policy decisions. In keeping with the remit from UKSport, the document focusses on scientific and medical literature related to performance, rather than sociological or ethical considerations. For simplicity and clarity, the terminology used here is male/female and transgender man/transgender woman/transgender people.

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Executive summary

The research base for the inclusion of transgender people in sport remains limited but is rapidly evolving.

The evidence outlining the sex dimorphism, or physical variance, between the sexes is robust: There are significant differences between the sexes which render direct competition between males and females unfair in most 'gender-affected sports' due to the physical advantages of males, and often unsafe in sports which allow physical contact and collisions.

Recent international guidelines, and subsequent policies, on the inclusion of transgender people (particularly transgender women) have attempted to negate male physical advantage, thereby allowing fair (and safe) competition. However, there is currently no direct evidence that this can be achieved by suppression of hormone levels. On the contrary, there are apparent life-long physiological advantages in the adult male, only some of which can be reversed, and it is not known whether physical benefit(s) may be retained in someone who does not achieve full maturity.

Transgender people face health concerns related to their transition and are prone to chronic side effects which are likely to be ameliorated by physical activity. On the other hand, female athletes are subject to specific health and injury concerns in direct relation to their reproductive physiology and

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cyclic metabolism. It is not known if these differences create a meaningful disparity in performance sport.

Everyone benefits from physical activity for both physical and mental health, and there are reported advantages in relation to the social aspects of team sports in particular. These benefits should be available to everyone in our community, and it is known that transgender people face barriers in access to sport.

This short review presents a chronological precis of current evidence which impacts decision making on how best to include transgender people in sport.

Introduction

Transgender inclusion transects the established categorisation in sport and, by including those who have transitioned from the alternate sex category, has created challenges. The binary of sex categories in sport has existed for more than a century and arguably since the beginning of sport in ancient times when females were largely excluded. Sports have historically been developed for able-bodied males by able-bodied males, and the opportunity for females, children, masters' athletes, and disabled people has been an evolution of increased opportunity and inclusion through categorisation over many decades. It is important to note that all subsequent categories within competitive sport, including weight categories, have always been underpinned by the sex binary, and inclusion of other groups has been largely by the addition of new and separate competition within that binary.

Research literature for the evidential basis of inclusion for transgender people in sport remains limited. The definitive longitudinal studies tracking prospective gender transition in athletes, with appropriate objective measurements, competition results and with a relevant control population, have not yet been reported. Further, the scientific literature on performance differences between males and females across the sports is also limited because, until now, the relevance of this difference was questionable as the sexes have not routinely competed against each other. Hence much of the known information is laboratory based, rather than specific to sporting competition.

Population-based differences between the sexes – the rationale for gender-affected competition

In adulthood, there are clear differences in muscle mass, strength, and physiological capacity even after controlling for differences in height and weight between the sexes. On average, males have 40-50% greater upper limb strength, 20-40% greater lower limb strength, and an average of 12kg more skeletal muscle mass than age-matched females at any given body weight (Janssen et al 2000, Handelsman et al 2018).

Following full growth, males are measured at an average 13-15cm (5-6 inches) taller than females. The National Health Service in 2018 quotes the average young adult male in England at a height of 178.0cm (5ft 10in) with an estimated standard deviation (SD) of 9.19cm. The average young adult female in England is 164.1cm (5ft 4 1/2in), SD 7.51cm. In the USA the statistics are very similar: Males average 175.9cm, SD 7.42cm, and females average 162.1cm, SD 7.11cm.

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When plotted across the population it is evident that 50% of males are taller than some 97% of females. So, in any random grouping of males and females, half of the males will be taller than nearly all females.

Handgrip dynamometry is probably the most commonly used method to characterize overall human muscle strength (Bohannon et al 2019). European data of over 2000 young adult males and females demonstrates “mean maximal hand-grip strength showed clear difference between men (541 Newtons) and women (329 Newtons); 90% of females produced less force than 95% of males”. And further.... “highly trained female athletes corresponded to only the 25th percentile of the (untrained) male subjects” (Leyk et al, 2007).

Therefore, this would mean that in a random group of ten males and ten females, only the strongest female is likely to be stronger than the weakest male.

Males have a larger, stronger and denser skeleton, with longer levers (arms and legs), and bigger hands and feet. Males also have larger hearts and greater blood volume with higher haemoglobin concentration, and hence greater oxygen carrying capacity, with bigger lungs and airway capacity compared with females. The differences in physical/physiological capacity are synergistic such that males are larger, stronger and faster, with greater aerobic capacity and for which the summation is likely to be greater than the individual differences.

The muscle strength, physiological and size differences between the sexes correlate with significant sporting achievement from around 10-12% for most linear swimming and running events, 20% difference in jumping events, and a 35% difference in weightlifting ability in weight matched males and females. If an average sized male is compared with an average size female (based on the NHS data, 2018) the weightlifting ability increases to 50% greater for males (World Record Snatch; 85kg Male - 187kg lift; 69kg Female - 123kg lift).

It is often assumed that children have similar physical capacity regardless of their sex, and hence mixed competition is allowed in many sports up until the age of around 11 years (to coincide with puberty). However large-scale data reports on children from the age of six show that young males have significant advantage in cardiovascular endurance, muscular strength, muscular endurance, speed/agility and power tests, but score lower on flexibility tests (Tambalis et al, 2016; Catley & Tomkinson, 2013).

In adults the average advantage of 10-12% in running events can be interpreted for both the ‘average’ competitor, as well as for elite performers where the percentage difference remains the same for similarly trained people. When measured in absolute time, i.e. the difference to reach the finish line, this will vary based on the ability of the athletes; but the distance between the competitors remains the same. In this way a 10-12% better performance by a competitor would see Adam Peaty being beaten by half a length in the short-course 100m breaststroke and Dina Asher Smith by 22m in the 200m track sprint. And Sir Mo Farah would be lapped twice in the 10,000m track race.

While there may be many differences between competitors of the same sex (such as height, skill, and training methods), what is relevant about the advantage between the sexes and the reason for the category division, is the scale of advantage across virtually all sports. World Rugby (2020) has referred to “...the almost perfect sensitivity of biological sex.... since in a ranking list of the top thousand performances in most sport, every year, every single one will be biologically male”. The winning margin (the difference in performance by which a competitor misses a gold medal, any medal, or making the final) in elite athletics or swimming events during the last three Olympics is

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less than just 1% for both male and female events, compared with up to a 50% difference between sex-based performances.

Derivation of performance difference between the sexes in sport

The known dichotomy in athletic performance between the sexes has long been acknowledged to largely be in relation to the difference in gonadal androgens, namely testes derived testosterone and its more potent metabolite dihydrotestosterone in males, and ovarian estrogen in females.

Males are prenatally (before birth) and perinatally (soon after birth) exposed to high level androgens, and then experience a further surge in testosterone levels during puberty, which is maintained throughout adult life. On the other hand, females normally never experience testosterone exposure beyond a basal level at any time during life ($<2\text{nmol/L}$). From the onset of male puberty, the testes secrete 20 times more testosterone, resulting in circulating testosterone levels that are 15 times greater in healthy young males than in age-similar healthy females (Handelsman et al 2018).

However, females enter maturational puberty at least a year before males, and this may create a brief equivalence in the height of children around the age of 10, before males enter puberty from around the age of 11.

Anabolic steroids, of which testosterone is the significant 'natural' form, were one of the original groups of banned drugs when anti-doping practices developed in the 1970s. Both endogenous (made within the body) and exogenous testosterone (delivered into the body from an external source) are identical chemical substances and have equivalent effects in the body. Testosterone concentration positively correlates with leg press strength, thigh muscle volume and haemoglobin levels, and the anabolic response to testosterone can largely be predicted by the dose administered (Bhasin et al 2001). Testosterone is largely responsible for the increased muscle mass through increases in muscle fibre numbers and size, muscle satellite cell numbers, numbers of myonuclei (muscle cells nucleus), and size of motor neurones (nerve cells) as well as advantageous biochemical changes in muscle function in males. Importantly stimulation of myonuclei is life-long (Handelsman et al 2018). This is so-called 'muscle memory' and is one of the reasons why doping sanctions were increased to four years to try to account for this long-term effect on performance.

For ethical and doping control reasons it has not been possible to evaluate the effect of testosterone in healthy young athletes beyond cross sectional studies, but observational reports have lent credence to this understanding. During the era of the former German Democratic Republic, systematic doping of athletes was developed and later confirmed on release of the so-called 'Stasi Files'. Regime scientists stated after the 1972 Munich Olympics: "the effects of the treatment with androgenic hormones were so spectacular, particularly in female athletes in strength dependent events, that few competitors not using the drugs had a chance of winning". Further, the long-term effect of androgenic/anabolic steroids was attested by the acknowledgement that "after a critical period of increase in muscle strength, a higher performance level is reached that does not return to pre-treatment values after the drug is withdrawn" (Franke & Berendonk 1997).

History of sex categories and inclusion of transgender athletes

Previous practices of 'gender (sex) verification' for female athletes were developed "in order to exclude those in which a genetic alteration gives the competitor registered as a female anatomical advantages of masculinization" (Hay 1985). There was no perception that females would pose a

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competitive threat to male athletes. Genetic testing, which received “great support” from athletes, was contentious within the scientific community and was subsequently abandoned in 2000 for the Sydney Olympics (Ljungqvist 2000). This was largely due to some infamous cases in which inadequate processes resulted in inappropriate disqualification of athletes.

The Stockholm Consensus of the IOC in 2003 established the first international policy for transgender inclusion in international sport. This was not a referenced document; “at the time, there was no published scientific literature that would justify the inclusion of transgender women” (Harper 2015). Transgender people were at this time required to have full surgical transition in order to compete in their acquired gender.

Dr Arne Ljungqvist, the then IOC Medical Commission Chair, is reported (Harper 2015) to have relied heavily on the opinion of Dr Louis Gooren who went on to publish in 2004 the first comparative study of the physical/physiological attributes of transsexual men and women. In this study the metabolic and morphological changes of 17 transgender men and 19 transgender women were studied before and after their gender-affirming medication. The pre-treatment data serves as control groups for the respective treatment groups for statistical analysis. Muscle mass (measured by MRI) and serum haemoglobin were compared across one and then three years of treatment.

Following one year of androgen(testosterone) deprivation, muscle mass decreased significantly in the transgender women, but remained significantly higher than the pre-treatment transgender men (female) group. On the other hand, the transgender men on testosterone supplementation increased muscle mass such that there was no statistical difference between these subjects and the pre-treatment transgender women (male) group. There was no difference between the treatment groups (transgender men and transgender women) after one year of treatment. There was a further non-significant loss of muscle mass following a further two years of treatment of transgender women. Haemoglobin levels converted into the respective ranges of the acquired gender in each group within the first year. This would have a corresponding effect on blood oxygen carrying capacity, and hence aerobic ability. It was noted that height was a strong independent predictor of muscle mass in both males and females, and both pre- and post- gender transition (Gooren and Bunck 2004).

Following cessation of gender/sex (chromosomal) testing in 2000, athletes with Disorders (Differences) of Sexual Development (DSD) were successful in major athletic competitions; notably at the Athletics World Championships in 2009. There followed a decade during which several athletes with the genetic disorder ‘46XY 5ARD’ (46 XY chromosome women in which an enzyme abnormality causes testosterone to rise to high levels) were in dispute with the IAAF/World Athletics through lengthy court proceedings in relation to their hyperandrogenic status. While these cases do not have direct relevance to transgender inclusion in sport what is important is that as a result of the requirement for evidence and information for court documentation, there was a significant increase in both the research and academic literature on the effect of testosterone in sports performance over this period.

During the Daegu World Athletics Championships in 2011, research on behalf of the IAAF and WADA on the normative values of serum androgen levels of elite track and field athletes was conducted in order to inform the blood steroidal module of the Athlete Biological Passport for doping control (Bermón et al 2014). This research was able to define the median value of serum testosterone in elite female athletes at 0.69 nmol/L with a 25-75% range of 0.50 to 0.91nmol/L, and a 99th percentile calculated at 3.08nmol/L. The testosterone levels in the DSD group were as high as 29.30nmol/L, while the standard male range of testosterone is 7.7 to 29.4nmol/L (Handelsman 2018). It was

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calculated that, within the elite athlete population, hyperandrogenism in relation to XY DSD was 140 times more common than in the general population.

Researcher Joanna Harper published comparative data in 2015, around the time that the second IOC Consensus Statement on Sex Reassignment was published. In this study, the race times of eight transgender/transsexual women were recorded both pre- and post- transition. All subjects were recreational distance runners who self-reported race times (which were verified where possible) in equivalent events over a period stretching from one year up to twenty-seven years apart. No testosterone levels were reported for the athletes, either before or after the transition. Calculations were made to compare their race times with those of age-graded performances in the respective gender. The findings indicated that the comparative race times were equivalent pre- and post-transition, and this implies that transition did not give these transgender women a competitive advantage (Harper 2015). This was the first study to attempt to measure physical performance following transition, compared with pre-transition ability and, while there were several acknowledged limitations to the study, this information appears to have been crucial in the subsequent deliberations of the second IOC Consensus Meeting.

The second Consensus Paper of the IOC was published in November 2015. Surgery is no longer required to be eligible to compete, and transgender women are required to suppress testosterone levels to below 10nmol/L for 12 months before competition. This testosterone level is 5-10 times the testosterone level of females of any age and remains within the accepted range for males, and it has not been defined as to how this level was determined by the IOC. Transgender men can enter male competition without requirement.

Over the past two decades there have been a dozen published research papers (five of which were published in 2018-20) for a total of some 800 participants which investigated the effect of testosterone suppression on muscle mass, and in some instances muscle strength, in transgender women.

Post-suppression testosterone levels measured in these studies were all less than 10nmol/L, most being below 5nmol/L, and seven studies where testosterone level was less than 1nmol/L (ie at the level of females). Most studies included estrogen therapy for participants. On review by Hilton and Lundberg, the findings from the composite of existing research was that loss of muscle mass and/or strength following 12 months of testosterone suppression is relatively modest compared with the initial advantage. The average loss of muscle mass across all studies was around 5%, which is less than the 9% loss measured in the seminal work of Gooren and Bunck. In those studies which recorded the retained muscle mass/strength, there was an average of 25% residual advantage for transgender women at 12 months treatment compared with reference a group of females (Hilton and Lundberg 2020).

In the most recent study, by Wiik and colleagues from the Karolinska Institute in Sweden, there was minimal loss of muscle mass or strength in transgender women following 12 months of testosterone suppression, and some subjects gained strength. After treatment transgender women remained 48% stronger, with 35% larger quadriceps mass compared with the control population of females (Wiik et al 2020).

Harper and colleagues also reviewed the available scientific literature and published in the British Journal of Sports Medicine in March 2021. They concluded that "haemoglobin levels rapidly reduce in transwomen" while "strength may be well preserved during the first 3 years of hormone therapy" (Harper et al 2021).

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Recent research citing retrospective data from military personnel in the US has shown that transgender women retain an advantage in running speed after more than two years of follow-up on testosterone suppression, at a residual of some 12% faster than the known normative values for females. In the same study, values for numbers of 'push-ups' and 'sit-ups' had reverted to female levels, but data on training levels and performance targets was lacking. Results for the transgender men studied exceeded those of the average performance for age-matched males after one year of testosterone supplementation (Roberts et al, 2020).

From the synthesis of current research, the understanding is that testosterone suppression for the mandated one year before competition will result in little or no change to the anatomical differences between the sexes, and a more complete reversal of some acute phase metabolic pathways such as haemoglobin levels although the impact on running performance appears limited, and a modest change in muscle mass and strength: The average of around 5% loss of muscle mass and strength will not reverse the average 40-50% difference in strength that typically exists between the two sexes. These findings are at odds with the accepted intention of current policy in sport, in which twelve months of testosterone suppression is expected to create equivalence between transgender women and females.

It is recognised that research to date has not been carried out in an elite athletic population (although military data includes well-trained individuals), and it is not known if the relative muscle loss will be more or less in those who are undergoing training, relative to the published results in non-athletic populations. It is known however, that males who undergo androgen suppression as part of treatment for prostate cancer can improve muscle strength and mass when also undertaking a training program, whereas the absence of training results in 4% reductions in muscle mass, similar to those observed in trans women whose testosterone is suppressed without training (Galvao et al 2006). The implication is that training during a period of testosterone suppression may attenuate the reductions observed in the longitudinal studies, which would increase the retained advantage when comparisons are made with a reference group of females.

The notion of safety in sport is related to size and maturity of competitors and is one of the reasons that junior athletes are not routinely eligible to play against adults in contact and collision sports. Because the two sexes have not historically competed against each other as adults in these sports, there is not yet experience of the injury risk to which females may be exposed in such competition, nor with the inclusion of transgender people beyond anecdotal reports. Injury risk can be appreciated through analysis of the combination of mass and speed of competitors and hence the force that can be generated, in which the larger and faster opponent will pose a risk to those that are smaller and slower when tackled. At a conference convened by World Rugby in London in February 2020, information was presented (and subsequently published as part of World Rugby Transgender Guideline) of a theoretical framework for injury risk based on validated mechanical modelling, relevant to the size differential of male players compared with female players. While not including the speed of a bigger opponent, nor the neck strength of the smaller, the increased mass alone accounted for an estimated increase in the risk factors for head and neck injury of 20-30%. Given the modest reduction of body mass by testosterone reduction in transgender women this was estimated to pose an unacceptable risk to female players and, in part, resulted in the decision to render transgender women ineligible to compete in international contact rugby union (World Rugby 2020).

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Debate about the role of testosterone

Writing an 'Observation' in the Scientific American journal in June 2019, Rebecca Jordan-Young and Katrina Karkazis, authors of "Testosterone; an Unauthorised Biography", question the validity of ascribing the differences between male and female athletes solely to endogenous levels of testosterone. They draw attention to the inconsistency between measured testosterone levels and performance. The research published on behalf of the IAAF (Bermón & Garnier 2017) received criticism from the scientific community and required formal correction. Jordan-Young and Karkazis stress that in three of the eleven running events cited, it was the group with the lowest testosterone levels who performed best, and there was a strong negative association between testosterone levels and 100m race time.

The authors quote published work from Pielke, Tucker and Boye (2019), which questions the validity of IAAF(WA) research which was requisite by the Court of Arbitration in Sport (CAS) to demonstrate that "high androgen levels confer a significant performance advantage over other female competitors, comparable to the performance advantage that male athletes enjoy over female athletes".

In the event, the full evidence base presented by IAAF/World Athletics was ultimately successful at CAS, and this was defended again on appeal. However, the contention remains in the scientific community that the case has not been made that circulating testosterone can fully explain all the observed difference in male/female performance variables (Jordan-Young & Karkazis 2019).

Importantly, the corollary of circulating testosterone levels not being fully accountable for this difference is that there must be another, as yet undefined factor(s), which must account for the remaining differences following testosterone suppression. The retained advantage may mean that previous testosterone exposure is responsible for long-term effects, or there is another explanation, perhaps referable to genetic differences, which has not yet been identified.

Following the legal cases, World Athletics also created policy for the inclusion of transgender women based on suppression of testosterone levels to 5nmol/L. Between 2018 to 2019, several major sporting international governing bodies developed policies at the 5nmol/L level for transgender women, in comparison with the 10nmol/L defined by the IOC.

Medical and Psychosocial Aspects

A review published in 2017 by Bethany Jones and colleagues from Nottingham/Loughborough Universities looked at research that explored the experience of transgender people in sport, as well as the policies which were in place at the time which influenced such experience. While only eight research papers met the criteria for the study, in those which looked at the experience of transgender inclusion, it was acknowledged that the experience of transgender people in sport was largely negative. The authors' assessment of the available literature on physical parameters was to highlight the lack of direct comparative data in athletes on which to base exclusionary policies. They indicate that "There are several areas of future research required to significantly improve our knowledge of transgender people's experience in sport, inform the development of more inclusive sport policies, and most importantly, enhance the lives of transgender people, both physically and psychosocially" (Jones et al, 2017).

Differences in physiology and health parameters between males and females have long been acknowledged and recent research has shed light on how this affects performance, as well as health,

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illness and injury. The menstrual cycle creates challenges for many female athletes and the variable nature of ovarian hormones can limit training and performance, and also alter perceptions of wellbeing. Furthermore, amenorrhoea (loss of menstrual cycling) is common in sport due to high training loads and inadequate energy intake. This has secondary consequence of not just altered fertility but increased rates of injury and illness. The naturally lower bone density of females is further reduced with the hormonal deprivation of amenorrhoea and this group is particularly prone to stress fractures, a significant problem in running sports. Female athletes are not immune to gynaecological illnesses, and endometriosis which has an incidence of up to 20% in the general population, has plagued the career of several high-profile athletes who have chosen to go public with their inability to compete as a result of pain and illness.

Recent research has highlighted the relationship of the menstrual cycle and the observed increased injury incidence and slower recovery in women compared with men, in particular for concussion (McGroarty et al 2020), and major ligament injury such as anterior cruciate ligament tears (Wojtys et al 2002). The physical problems related to the menstrual cycle are now so well appreciated that ongoing research in health and hormonal monitoring is taking place in the UK (Football Association) and abroad. This research is designed to define parameters whereby limitations to training and performance can be minimised.

By way of comparison, it is known that transgender people suffer increased risk of ill-health as a result of medication and cross-sex hormone therapy. Transgender women face heightened risk of thrombo-embolic disease, arterial disease, liver dysfunction and breast cancer (although at levels lower than females). Transgender men risk high red cell levels (polycythaemia), hypertension and arterial disease, as well as reproductive cancer. These are chronic conditions for which exercise is both preventive and therapeutic and are unlikely to present any direct negative effects in relation to sporting performance. Certainly, evidence indicates that bone health and density is maintained in transgender women despite testosterone suppression (Van Caenegem et al 2015).

Over time it may become apparent that medically transitioning will lead to health and injury issues specific to transgender athletes, but this will not have the cyclical nature of gynaecological function and any sport specific concerns are likely to be different to those experienced by females and males. It will be important to track and define the health consequence of the required medical treatments required by sports agencies to compete in one's affirmed gender.

We are not aware of research which will allow any conclusions to be drawn on the current medical practice of transition in younger people, and what effect this may have on physical and sporting capacity. In the UK, so-called 'puberty blockers' are generally not used until Tanner maturation stage 2-3 (i.e. after puberty has progressed into early sexual maturation), and medical practice is currently under review. As described above it is evident that current knowledge cannot explain the exact derivation of all the performance differences between the sexes, and correspondingly what, if anything, can be done to reverse these differences in adults.

While exercise and activity are known to positively impact mental health, elite level training and competition are known to increase stress. Both competitive athletes and transgender people have separately reported high levels of mental ill-health, notably anxiety states, depression, and poor coping mechanisms with stress: These include self-harm and eating disorders. It is not known how the stresses of competition may affect transgender athletes.

Reports of suicidality in transgender people are contentious. A recent large-scale meta-analysis of five peer-reviewed papers of over 1000 study subjects found a prevalence of suicide attempts of 14.8% (Surace et al, 2020). This is at odds with other commissioned reports of smaller sample sizes which give much higher estimates.

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There is no contention however as to the value of physical activity and community membership on mental health outcomes. These benefits should be available to all.

Ethical Considerations

The notion of ethics within sport is largely based on established theories of fairness and fair play, advantage, inclusion, safety and values. The competing 'rights' of individuals can be explored through both legal and philosophical discourse. These writings are beyond the scope of this document; however, it is relevant to consider the implication of sporting rules (such as testosterone suppression or use of puberty blockers) which may or may not have a desired outcome, and which have can have unintended poor health outcomes for the individual. Further, the development of protocols within sport which create an environment whereby 'case-by-case' analysis judgements of an individual may restrict their rights, as well as those of others, can be fraught.

Conclusion

Sexual dimorphism in relation to sport is significant and the most important determinant of sporting capacity. The challenge to sporting bodies is most evident in the inclusion of transgender people in female sport.

Current international rules require testosterone suppression to achieve equity in female sporting competition. In the light of existing evidence, the following is likely to be true:

Testosterone supplementation in transgender men results in strength and stamina (haemoglobin) parity with males within twelve months. Skeletal differences (smaller physique) will remain in keeping with female dimensions.

Testosterone suppression has differing effects for different body systems, and this can be correlated with the factors of 'gender-affected sport'; Strength, Stamina and Physique;

- Strength; Modest change within 12 months: Muscle mass (and perhaps cardiac size) and hence strength - appears retained at significantly higher levels than females.
- Stamina; Restoration of haemoglobin levels to female typical levels within 12 months: with relevant effect on oxygen carrying capacity as yet undefined.
- Physique; Minimal change: Structural features including the skeleton, bone density, height, lung and airway size, and tendon/ligament strength will remain, with modest loss of muscle mass.

This evidence suggests that parity in physical performance in relation to gender-affected sport cannot be achieved for transgender people in female sport through testosterone suppression. Theoretical estimation in contact and collision sport indicate injury risk is likely to be increased for female competitors.

There are significant ethical and legal considerations associated with the requirement for treatment which may not result in the desired outcome. Ongoing research may allow better understanding of comparative data to inform decision making.

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The health and social imperative to include transgender people in physical activity and sport is paramount. The task for the National Governing Bodies of sport is to achieve safe, fair and inclusive sport, and/or inclusive, fair and safe sport. How this can be achieved will be explored within this review process.

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FAIRNESS AND ENJOYMENT IN SCHOOL SPONSORED YOUTH SPORTS

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Abstract The purpose of this study was to expand upon research in organizational justice by introducing the construct into a school sponsored sports setting from a sociological perspective. Three dimensions of organizational justice – distributive justice, procedural justice, and interpersonal justice – were assessed to determine if the fairness of coaches, as perceived by their student athletes ($N = 259$), was associated with the sports the students' enjoyed participating in the most or the least. Two research questions answered by this study were: 1) do fairness perceptions differ between the sport the students enjoy the most and the sport they enjoy the least, and 2) did those perceptions influence the students' desire to continue participating in those referent sports. The findings indicated that perceptions of each of the three dimensions differed between the referent sports selected by the student athletes, and those differences were significant ($p < .001$). The findings also suggested that a linear relationship existed between each dimension and their intent to continue playing the referent sports.

Key words • organizational justice • sports

Research directed at the relationship between student athletes and their coaches is important in that the behavior of coaches may impact the players' desire to continue playing sports. An important component of that relationship is the level of fairness used by coaches when making decisions which impact athletes. While most organizational justice research has been drawn from management and psychology literature, this study attempts to sever, what Sage (1997) referred to as 'intellectual boundaries' which may have in the past cast doubt on the relevance of framing organizational justice studies in the realm of sociological research. With the primary focus of Sociology being on the interaction between social relationships and the attitudes and behaviors derived from those relationships (Schaefer, 2004), coach/player interactions fall well within the domain of sociology research.

Few changes have occurred in the structure and purpose of school sponsored sports over the past century (Sage, 1998). Sports have been promoted as an integral part of the educational experience when the physical wellness attributes of sport participation are combined with the intellectual acquisition which occurs in the classroom (Kanaby, 2003). Sport exposes students to the dynamics of organizational culture which in turn influence the sociological outcomes of sport participation. Supporters of sports in the schools have summarized the numerous

benefits derived from participation (NFHS, 2003) as supporting the overall academic mission of the schools (higher grades, better attendance, lower dropout rates, fewer discipline problems), providing practical life skills learning (self-discipline, teamwork, and self-confidence), and promoting success in life after graduation. Participation in interscholastic sports has also been found to increase the likelihood of lifelong participation in sports as an adult as well as positively correlated with income earnings as an adult (Curtis et al., 1999, 2003).

While the adults who control school sponsored sports see athletic participation as a critical component of the educational process, Sage (1997) notes Coleman's perspective, 'that high school athletics is more important as a value among high school students than intellectual achievements' (p. 325). Students take a more pragmatic view of sport participation. Research has consistently demonstrated that participation is driven by one or more of three dominant factors: the student athletes' craving to hone and exploit their physical skills; the need for social interaction and support from significant individuals in their lives; and the desire to have fun (Butcher et al., 2002; Weiss, 2000; Weiss et al., 2001). Lumpkin et al. (2003) propose that students often drop out of sports when they no longer have fun participating, due to issues associated with their perceptions of fairness fostered within the schools' athletic programs. As such, a better understanding of the factors which influence the climate of fairness in athletics, framed within the context of organizational justice, can assist in moderating fairness perceptions, thus potentially reducing dropout rates.

Organizational Justice

The concept of justice has received much attention in the social sciences over the last 40 years (Colquitt, 2001). This area of research has attempted to determine the criteria used by individuals when developing perceptions of justice (fairness) and the influence these perceptions have on various attitudes and behaviors. Recent work by Colquitt and colleagues (Colquitt, 2001; Colquitt et al., 2001) established that organizational justice is most likely composed of separate constructs, three of which are distributive justice, procedural justice, and interpersonal justice. Distributive justice is defined as the perceived fairness of outcomes received by an individual (Adams, 1965), similar to other allocation theories which suggest outcomes should be distributed equally to all members (Deutsch, 1975; Lerner, 1975). Procedural justice is centered on the processes used to determine the outcomes (Leventhal, 1980; Thibaut and Walker, 1975). Interpersonal justice was initially introduced by Bies and Moag (1986), who suggested that interpersonal justice was based on the treatment and quality of information received by an individual in a work setting. Greenberg (1990), Colquitt (2001), and Colquitt et al. (2001) demonstrated that interpersonal justice is based on the extent to which an individual is treated with respect, dignity and in a polite manner by personnel representing the organization or who occupy decision-making positions.

Organizational justice research in the social sciences has demonstrated that the aforementioned constructs collectively and individually influence an individual's perceptions of fairness. Research has also shown a relationship between percep-

tions of fairness and numerous employee attitudes and behaviors such as job satisfaction (Martin and Bennett, 1996), organizational commitment (Sweeney and McFarlin, 1993), citizenship behaviors (Moorman, 1991), as well as turnover and absenteeism (Masterson et al., 2000). There has been discussion that these relationships might also be evident within a sport context (Chelladurai, 1999; Greenberg et al., 1985; Jordan et al., 2004). However, there have been only a limited number of attempts to study the influence of organizational justice in sport.

Organizational Justice and Sport

The first application of organizational justice theory in a sport setting was by Greenberg et al. (1985) who theorized distributive and procedural justice principles could influence the perceived fairness of outcomes and processes used in sport and games. The authors suggested that the structures, processes, and dynamics of sport would provide a context to study the influence of organizational justice on the attitudes and behaviors of sport participants. Additionally, they suggested that this line of inquiry would expand the overall understanding of organizational justice not only within the domain of sport, but for other types of organizations as well.

Currently, organizational justice research in sport has begun to examine the influence of multiple justice constructs on individual perceptions of fairness. Jordan et al. (2004) proposed that relationships between justice constructs and employee attitudes and behaviors evident in non-sport organizations might be applicable in a team sport setting. These authors suggested that improving player perceptions of fairness might lead to increased satisfaction, commitment and desire to continue participating in the sport. An initial attempt to study the influence of justice constructs on the attitudes of players found a relationship between organizational justice (distributive, procedural, and interpersonal justice) and high school student-athletes' level of commitment to a particular sport (Whisenant, 2005). Players who had positive perceptions of the three justice constructs demonstrated higher levels of commitment and were more likely to continue their participation in their referent sport. Whisenant and Jordan (2006) found that a positive relationship also existed between organizational justice perceptions and team performance. The present study is an extension of this line of research which has studied the influence of organizational justice among players in school sponsored sports. The first objective was to determine if the justice dimensions differed between the sport the students enjoyed the most and the sport the students enjoyed the least. The second objective was to determine the extent to which each of the justice dimensions influenced the students' desire to continue participating in those same referent sports.

Methodology

The subjects for the study were student athletes from six high schools in Texas. Parental consent forms were sent home with approximately 1400 student athletes.

The following day, those students who were granted permission to participate in the study by their parents gathered during their regularly scheduled time period allocated for sports to complete the questionnaire. To minimize the likelihood that the responses of the students might be influenced by their coaches, coaches were denied entry into the testing area.

The instrument used to collect the fairness data was based upon the Justice Measure developed by Colquitt (2001). To ensure the students considered all of their sports when making their referent selections to answer the fairness questions, the athletes were first asked to identify all the sports they had played that year in high school. The students were then asked to identify the sport they enjoyed playing the most. They were then instructed to use that sport as the referent sport when responding to the fairness statements. The students were then instructed to turn the questionnaire over and similarly complete the survey using the sport they enjoyed playing the least that year as their referent sport. The average of the multiple responses within each of the sections was then used to determine the level of perceived fairness within each dimension with higher scores indicating more positive perceptions of fairness. The students were also asked if they intended to continue their participation in the referent sport during the next season. A Likert-type scaled response of 1 to 10, with 10 being strongly agree and 1 being strongly disagree was used to assess intent to continue participation.

Paired Samples Statistics were used to compare the mean responses of each of the three dimensions for the analyses addressing the first research question. Pearson's correlation coefficient was used to answer the second research question. An alpha level of .05 was used for all analyses. The measure instrument developed by Colquitt was found to have a reliability ranging from .90 to .93 (Colquitt and Shaw, 2005), the reliability coefficients for this study produced an alpha of .77.

Results

Parental approval for participation was given to 630 students. Of those students, 41 percent ($n = 259$) provided data on both sports. Student demographics are provided in Table 1. The sex of the participants – boys 59 percent and girls 41 percent – closely aligned with national participation rates. The ethnic composition of the sample was as follows: 33 percent Black/African American; 36 percent Hispanic; 29 percent White; and 2 percent indicated an ethnicity other than the three previously mentioned. This demographic was representative of the state's student population. The majority of the students were freshmen (39%), while 25 percent were second year students, 24 percent were juniors, and the fewest participants being seniors (12%). Frequency counts of the students by the referent sports they used to respond to the questions regarding fairness perceptions are listed in Table 1.

The first objective was to determine if the justice dimensions differed between the sport the students enjoyed the most and the sport the students enjoyed the least. Table 2 contains the descriptive statistics for each of the justice

Table 1 Referent Sports

Sport	Enjoyed the most		Enjoyed the least	
	Boys	Girls	Boys	Girls
Baseball	18	n/a	9	n/a
Basketball	26	15	34	18
Football	73	n/a	23	n/a
Other	6	2	15	9
Soccer	10	11	12	1
Softball	n/a	17	n/a	12
Tennis	1	3	5	1
Track & cross-country	20	21	56	33
Volleyball	n/a	30	n/a	29
Powerlifting	0	6	0	2

Note: Other includes golf, swimming, wrestling, cheerleading, and dance.

Table 2 Correlations of Fairness Perceptions and Intent to Continue Participation

Enjoyed most		(PJ)	(DJ)	(IJ)
Continue participation	(<i>M</i> = 6.32; <i>SD</i> = 1.46)	.170*	.243*	.238*
<i>R</i> ²		.029	.059	.057
Procedural justice (PJ)	(<i>M</i> = 5.0; <i>SD</i> = 1.2)			
Distributive justice (DJ)	(<i>M</i> = 5.6; <i>SD</i> = 1.3)			
Interpersonal justice (IJ)	(<i>M</i> = 5.7; <i>SD</i> = 1.2)			
Enjoyed least		(PJ)	(DJ)	(IJ)
Continue participation	(<i>M</i> = 4.86; <i>SD</i> = 2.51)	.271*	.295*	.349*
<i>R</i> ²		.076	.084	.112
Procedural justice (PJ)	(<i>M</i> = 4.7; <i>SD</i> = 1.5)			
Distributive justice (DJ)	(<i>M</i> = 5.0; <i>SD</i> = 1.6)			
Interpersonal justice (IJ)	(<i>M</i> = 5.3; <i>SD</i> = 1.5)			

Note: $p < .05^*$; continue participation data excludes seniors ($n = 228$).

dimensions. For each dimension the differences between the sport the students liked most and liked least were significant: procedural justice $t(258) = 3.694$, $p < .001$; distributive justice $t(258) = 4.869$, $p < .001$; and interpersonal justice $t(258) = 3.775$, $p < .001$.

The second objective was to determine the extent to which each of the justice dimensions influenced the students' desire to continue participating in the referent sports. The findings indicated a linear relationship did exist between each of the justice dimensions and the students' intent to continue participating in the referent sport they liked most and liked least. These findings are also noted in Table 2.

Discussion

While the numerous studies previously cited have indicated that having fun is the leading factor influencing the level of enjoyment the athlete experiences through participation, coaches play a critical role in influencing the level of enjoyment athletes experience. The findings of this study provide greater insight into the influence coaches have over the organizational climate within their teams. The findings also support previously held, yet untested, presumptions that the perceptions of fairness held by athletes influence their attitudes toward the sports they play. While there may be some sociological skepticism about standardized tests such as the justice measure developed by Colquitt (2001), no other suitable alternative instrument was available which met the needs of this study. In this study, for each of the three dimensions of organizational justice, the perceptions of fairness held by the athletes regarding their coaches' behavior differed significantly between a referent sport the athletes enjoyed playing the most and a referent sport the athletes enjoyed the least. While perceptions of fairness were positive for both groups of sports – those sports they enjoyed most and those they enjoyed least – the level of fairness was greater for the sports the students enjoyed most. Within each of the three dimensions, the fairness perceptions were consistent regarding how each dimension ranked in fairness. For both the referent sports the students enjoyed most or least, interpersonal justice perceptions were the most positive ($M = 5.7$ and $M = 5.3$). Distributive justice followed for both groups with positive levels of fairness ($M = 5.6$ and $M = 5.0$). The lowest perception levels were for procedural justice ($M = 5.0$ and $M = 4.7$).

The degree to which students intended to continue playing a sport was significantly influenced by the athletes' perceptions of fairness within the context of each of the three justice dimensions explored in this study. As indicated in Table 2, the correlations among the justice dimensions and the athletes' intentions to continue playing were significant for both groups of the referent sports. The justice dimensions were most influential on the sports the students enjoyed least. Integrating the findings of the two research objectives provides a greater understanding of how organizational justice impacts sports participation among high school students.

Overall, student athletes who participated in the study indicated that they felt they were treated with dignity and respect by their coaches, as indicated by the responses associated with interpersonal justice. When assessing this dimension in conjunction with the student's intent to continue playing the referent sport, interpersonal justice had the greatest influence over the likelihood of continued participation in the sport the athlete enjoyed least. This would suggest that the treatment of the athletes by their coaches plays an integral part in establishing the student's level of enjoyment. When enjoyment from participation diminishes, the likelihood that the student will continue participating in the sport is reduced. With that relationship at the forefront, athletic directors who see a large dropout rate within one sport might expect to find coaches who fail to show their athletes the proper level of respect or treatment. Improvements in retention and reductions in self-elimination may be accomplished by focusing on the coach's interpersonal interactions with the athletes.

There are a limited number of outcomes in sport (i.e. playing time, position, etc.) and the allocation of these outcomes is often not based on the principle of equity. It is not uncommon for players who put forth the most effort to not receive the outcomes they would prefer, such as playing time or earning a starting position. While research has extensively shown that winning is not the driving force behind participation, student athletes may have reconciled that for their coaches, winning is the most important outcome of sports competition or participation. As a result, the students understand that the coaches play to win, so decisions regarding athlete participation in competition are left to the coaches. The decisions made by the coaches are given the benefit of the doubt by the students, trusting that decisions are focused on the goal of winning. The outcomes based upon those decisions do, however, have a greater impact on the sports the students like the least. One factor may be that students might question the decisions made by the coach when the students are rationalizing a decision to discontinue participating in a sport.

Fairness perceptions associated with procedural justice were also positive for both groups of the sports. Coaches generally do not afford athletes much decision control or decision influence, particularly during the time of competition. If players feel they have limited 'voice' in the processes of the team and the distribution of outcomes, they are likely to experience lowered perceptions of fairness for decision processes used by coaches. Their experience may have demonstrated to them that one level of consistency among all coaches and sports tends to be that the better players get more playing time than the less talented players. As a result, the processes used to determine outcomes associated with playing time are consistent and somewhat free from bias among sport organizations. The students may also recognize that mechanisms for dealing with incorrect decisions made by the coaches are evident. These changes come in the form of roster changes and changes in game plans based upon the level of success the team may be having at the time of competition.

An organizational climate embracing fairness is a critical factor influencing student athletes' attitude towards the sports they participate in and their desire to continue participation. As found to be the case in the work of Butcher et al. (2002), coaches have a significant influence on self-elimination in sport. If the coaches reduce the level of fun the athlete experiences or the social interactions are diminished or the student no longer has the opportunity to hone his or her athletic skills, the probability of sport self-elimination increases. Coaches have the opportunity to reduce the likelihood of self-elimination by building strong interpersonal relationships with their athletes by treating them with dignity and respect during multiple and complex decision processes. The athletes appear to be less concerned with decision outcomes and the processes used by the coaches to arrive at their decisions. For sport administrators, when making staffing decisions regarding coaches, they should place a great deal of emphasis on the communication and interpersonal skills possessed by the coaching candidates to help the athletic program maximize student participation.

For the overwhelming majority of the students participating in interscholastic athletics, their competitive sport careers end at high school graduation. For many, their experiences shape their self-esteem, personal self-worth, and may

influence their social standing in their communities. The behaviors they experience while in high school can shape how they will behave in organizational environments long after they leave high school. With athletics being so entrenched in the educational process, further studies associated with organizational justice in sport are needed. Areas of further study should include perceptions of justice over the participation lifespan of student athletes or over the course of a season in a longitudinal study. Work could also involve the inclusion of group value and attribution theories of organizational justice in sports.

As Greenberg et al. (1985) suggested two decades ago, sport organizations are mini-social systems that impact society in many ways and as such will provide a greater understanding of how organizations outside of sport function. Understanding how student athletes perceive decision outcomes within the context of organizational justice while involved in sport, may provide the foundation as to how they will behave in organizations as adults. With sport participation playing such an integral role in the educational and socialization process of young adults, every effort to minimize the likelihood of sport elimination should be undertaken.

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Transgender Stigma and Health: A Critical Review of Stigma Determinants, Mechanisms, and Interventions

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Abstract

Rationale—Transgender people in the United States experience widespread prejudice, discrimination, violence, and other forms of stigma.

Objective—This critical review aims to integrate the literature on stigma towards transgender people in the US.

Results—This review demonstrates that transgender stigma limits opportunities and access to resources in a number of critical domains (e.g., employment, healthcare), persistently affecting the physical and mental health of transgender people. The applied social ecological model employed here elucidates that transgender stigma operates at multiple levels (i.e., individual, interpersonal, structural) to impact health. Stigma prevention and coping interventions hold promise for reducing stigma and its adverse health-related effects in transgender populations.

Conclusion—Additional research is needed to document the causal relationship between stigma and adverse health as well as the mediators and moderators of stigma in US transgender populations. Multi-level interventions to prevent stigma towards transgender people are warranted.

Keywords

Transgender; Stigma; Health; Inequities; Interventions

Transgender is as an umbrella term used to define individuals whose gender identity or expression differs from the culturally-bound gender associated with one's assigned birth sex (i.e., male or female) (Davidson, 2007; Valentine, 2007). While there is considerable variability in who falls under the transgender umbrella, it is estimated that 0.03–0.05% of the population are transgender (Conron et al., 2012; Gates, 2011; Reisner et al., 2014a).

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Transgender individuals define their gender identity (e.g., man, woman, transgender man, transgender woman, genderqueer, bigender, butch queen, femme queen) and express their gender in a variety of ways, which may vary according to racial/ethnic background, socio-economic status, and place of residence (Valentine, 2007). Some transgender individuals choose to socially transition (e.g., change their name, pronoun, gender expression) and/or medically transition (e.g., cross-sex hormones, surgery) to align their gender expression with their gender identity, while others choose to have a gender expression or identity outside of the traditional gender binary (e.g. gender nonconforming people) (Davidson, 2007). In the US, transgender individuals are considered deviant for having a gender identity or expression that is discordant with the gender typically associated with their assigned birth sex and experience widespread stigma as a result (Bockting et al., 2013; Grant, 2011; Lombardi et al., 2002).

Stigma is the social process of labeling, stereotyping, and rejecting human difference as a form of social control (Link & Phelan, 2001; Phelan et al., 2008). Given that stigma is a complex and dynamic process, the measurement of stigma is inherently thwarted by challenges including concerns regarding the level (e.g., interpersonal, structural) and perspective (e.g., objective versus subjective experiences) at which to operationalize stigma and measure its severity and frequency (e.g., hate crimes versus everyday discrimination) (Meyer, 2003a). Here we draw on sociological and public health theory (socio-ecological model; Baral et al., 2013; Link & Phelan, 2006), operationalizing stigma according to the levels and means through which it is experienced—*structural*, *interpersonal*, and *individual* (Figure 1). *Structural* stigma refers to the societal norms and institutional policies that constrain access to resources, while *interpersonal* stigma refers to direct or enacted forms of stigma such verbal harassment, physical violence, and sexual assault due to one's gender identity or expression. At the *individual* level, stigma includes the feelings people hold about themselves or the beliefs they perceive others to hold about them that may shape future behavior such as the anticipation and avoidance of discrimination. Structural, interpersonal, and individual forms of stigma are highly prevalent among transgender people and have been linked to adverse health outcomes including depression, anxiety, suicidality, substance abuse, and HIV (Clements-Nolle et al., 2006; Grant, 2011; Nemoto et al., 2011; Reisner et al., 2014b; Sevelius, 2013).

Stigma is a fundamental cause of adverse health in transgender populations as it works directly to induce stress (a key driver of morbidity and mortality) and indirectly by restricting access to health protective resources (e.g. knowledge, money, power) (Hatzenbuehler et al., 2013; Link & Phelan, 1995). Transgender stigma works through multiple risk factors to impact multiple health outcomes. Indeed, interpersonal and structural stigma are associated with inequities in employment, healthcare, and housing for transgender people compared to cisgender (non-transgender) people—fundamental resources that when restricted are associated with poor health in transgender communities (e.g., depression, suicidality, conditions requiring emergency care) (Clements-Nolle et al., 2006; Nemoto et al., 2011; Reisner et al., 2015b). Consistent with fundamental cause theory, transgender stigma occurs across place and time, such that even when one form of stigma is eliminated (e.g., healthcare providers become knowledgeable about transgender care), other

forms of stigma (e.g., insurance policies impede access to gender affirming care) will continue to ensure adverse health outcomes for transgender individuals.

While emerging evidence suggests that stigma makes transgender persons vulnerable to stress and subsequent mental and physical health problems (Bockting et al., 2013; Gamarel et al., 2014; Operario et al., 2014; Reisner et al., 2015b; Xavier et al., 2013), to our knowledge, synthesized findings on the health consequences of transgender stigma and interventions to reduce stigma towards transgender people remain absent from the literature. This article aims to fill the gap in the literature by reviewing transgender stigma at the multiple levels it operates to influence the health of transgender people. This review then summarizes interventions targeting transgender stigma at multiple levels and concludes by outlining a research agenda to understand and reduce stigma toward this marginalized segment of the US population.

Stigma at Multiple Levels

Stigma has the ability to affect transgender health at multiple levels. Using an applied ecological model, this section reviews transgender stigma at the structural, interpersonal, and individual levels.

Level 1: Stigma at the Structural-Level

Structural stigma refers to the societal norms, environmental conditions, and institutional laws and practices that limit the resources, opportunities, and wellbeing of stigmatized people (Hatzenbuehler et al., 2010). Central to structural stigma is power, which is used by the stigmatizing majority to exclude and marginalize those who are different. Across modern Euro-American history, cultural schemas have created and reinforced a binary gender system (i.e., male and female) derived from biological sex characteristics (e.g., chromosomes and genitalia) (West & Zimmerman, 1987). Under this binary system, having a gender identity or expression that aligns with one's sex characteristics is seen as normative, while transgender people are seen as the "other" (Link & Phelan, 2014; Schilt & Westbrook, 2009). It is the very process of labeling transgender people as non-normative (e.g., through community beliefs, medical/psychiatric diagnoses) that legitimatizes social norms and bestows the cisgender majority ("gender normals") with power and privilege (Link & Phelan, 2014; Schilt & Westbrook, 2009). Structural stigma in this context may therefore operate as a form symbolic violence in which structures, such as communities, institutions, or governments perpetrate violence through the laws, policies, and community mores that restrict and forcibly reshape transgender individuals in ways that ultimately serve to maintain the power and privilege of the cisgender minority (Valentine, 2007).

The medicalization of gender nonconformity represents one form of structural stigma that both shapes and reinforces societal perceptions of transgender people as deviant. The movement to medicalize gender nonconformity first began in the early 1900's in an effort to legitimate gender nonconformity as biologically innate, rather than a choice (Bockting, 2014). The movement eventually led to the development of surgical and hormonal treatments to assist transgender individuals in altering their bodies to align with their gender identities. While medical gender affirmation (e.g., sex change) procedures were opposed by

most of the mainstream medical community well into the 1960's (Green, 1969; Worden & Marsh, 1955), mounting data demonstrating the apparent success of medical interventions (i.e., patient satisfaction, improved quality of life), paired with the failure of psychoanalytic interventions to alter a person's gender identity, eventually led more medical and mental health providers to support these surgeries in the later half of the 20th century (Meyerowitz & Meyerowitz, 2009). Although shifting attitudes provided potential surgical access for transgender people seeking to masculinize or feminize their body, the movement towards medicalized gender conformity maintained the rigid binary construction of gender, making gender conforming transgender people invisible, and further stigmatizing those who do not conform to socially sanctioned expressions of gender (Bockting, 2014; Conrad & Schneider, 2010; Meyerowitz & Meyerowitz, 2009; Namaste, 2000). Moreover, possessing a gender identity or expression incongruent with one's assigned birth sex was viewed as *sexually deviant* or *disordered* and listed as such in the *Diagnostic and Statistical Manual of Mental Disorders* from 1968 to 2013 (APA, 1968, 2013).

Today, having a nonconforming gender identity or expression is no longer viewed as medically disordered. This notion is reflected in the change from *gender identity disorder* to *gender dysphoria* in the *DSM*, whereby *gender dysphoria* describes the distress associated with sex/gender incongruence, rather than the experience of gender variation itself (APA, 2013). Medical treatment for those experiencing distress is aimed as eliminating the state of dysphoria, rather than helping patients to conform to a binary gender expression (Coleman et al., 2012). Similar changes have also been made in the International Classification of Diseases; however, some activists argue that any formal diagnosis related to the "symptoms" of gender nonconformity serve to perpetuate stigma for transgender individuals (Drescher, 2014). Still, formal diagnoses are required for healthcare reimbursement and to access many gender affirmation procedures and thus persist (Drescher, 2014).

Structural stigma can also affect transgender health through policies and practices that restrict access to healthcare. Many transgender people lack insurance, which may be due in part to higher prevalence of unemployment among transgender people relative to the general population – a likely product of employment discrimination (Conron et al., 2012; Grant, 2011). Lack of insurance coverage restricts access to care. Although even when transgender people are insured, barriers to accessing gender affirming care often persist, as many private insurers may attempt to exclude coverage for gender affirming medical interventions claiming these procedures are, "pre-existing," "cosmetic," or "medically unnecessary" (Khan, 2013).

Transgender people who do not have access to insurance for transgender-specific care are forced to pay out of pocket for gender affirmation procedures, which may be cost prohibitive (Khan, 2013). Unable to pay for medically necessary care, some transgender people resort to the use of street hormones acquired through friends or online (Grossman & D'augelli, 2006; Sanchez et al., 2009). Street hormones can pose health risks if taken in excess of recommended doses or if hormone syringes are contaminated with HIV or other diseases. Street hormones can also pose health risks if the hormones contain a dangerous substance, which is common as street hormones are unregulated (Coleman et al., 2012; Nemoto et al., 1999; Williamson, 2010).

Due to social systems that favor masculinity over femininity (Schilt, 2010), transgender women often experience greater discrimination in employment and subsequent economic stressors relative to transgender men (Grant, 2011; Movement Advancement Project, 2013). Faced with societal pressures to conform to feminine ideals of beauty and unable to pay for surgery, some transgender women, often women of color, resort to “pumping” or using liquid silicone to enlarge their hips, breasts, butt and/or lips (Garofalo et al., 2006; Herbst et al., 2008; Sevelius, 2013; Wallace, 2010; Williamson, 2010). Pumping can pose adverse consequences as loose silicone can shift, causing permanent disfigurement, pulmonary embolism, pneumonia, renal failure, and even death (CDC, 2008; Gaber, 2004; Williamson, 2010). Lack of access to medically necessary care has also been shown to lead to depression, suicidal ideation, non-suicidal self-injury, and suicide for individuals of diverse transgender experience (Huft, 2008; Spicer, 2010).

Institutional practices that lead to inadequate access to essential resources such as healthcare represent another form of structural stigma. Indeed, lack of trained healthcare providers can limit access to care (Khan, 2013). Lack of trained providers is driven in part by the failure of most medical schools and healthcare institutions to train their students and staff in transgender care (Makadon, 2008; Obedin-Maliver et al., 2011; Solursh et al., 2003). In fact, a 2011 study of deans of medical education in North America found that the median number of hours dedicated to LGBT-related curricular content was five (Obedin-Maliver et al., 2011). Insufficient education in medical school translates into lack of knowledge on the job, as medical providers report lack of sufficient training and exposure to transgender patients, impacting their ability to provide medically competent and sensitive care to transgender patients (Lurie, 2005; Poteat et al., 2013). The limited availability of trained providers forces some transgender people to travel long distances to receive care, pay out of pocket for a trained provider not covered under one’s insurance, or postpone care altogether – an outcome of structural stigma with direct health implications (see interpersonal stigma section below) (Cruz, 2014; Dewey, 2008).

Policies that favor one group over another represent another form of structural stigma which produce and reflect community beliefs that stigmatized groups (e.g., transgender people) are unworthy of equal protections under the law (Westbrook & Schilt, 2013). For example, as recently as 2000, state-level anti-discrimination policies excluded transgender individuals as a protected class (National Gay and Lesbian Task Force, 2008); as a result, transgender people could be victimized without legal recourse. In 2012 Massachusetts passed a non-discrimination law providing protections for transgender people in employment, education, and housing; however, the policy failed to include public accommodation protections despite activists efforts to include them. Exclusion of public accommodation protections means that, as of 2015, transgender people in Massachusetts can legally be refused access to public bathrooms, denied healthcare, and removed from public transportation among other spaces - discrimination experiences associated with increased risk of adverse physical symptoms (such as headache, upset stomach, tensing of muscles, or pounding heart) and emotional symptoms (feeling emotionally upset, sad, or frustrated) (Reisner et al., 2015b). While the original bill had included public accommodations, the protections were removed due to stigma-driven concerns from conservative groups that individuals who were not actually transgender would gain access to women’s bathrooms, posing a threat to women

and children (Massachusetts Family Institute, 2011; MassResistance, 2008; Westbrook & Schilt, 2013). As of 2015, efforts to pass a state-wide public accommodations bill remain stalled in the Massachusetts legislature and other states where supporting the unsubstantiated claims of some members of the cisgender minority is of greater importance than providing transgender people with access to essential resources such as bathrooms and other public spaces (Westbrook & Schilt, 2013).

Level 2: Interpersonal Stigma

Societal norms and beliefs often translate into enacted stigma at the interpersonal level, which can produce negative consequences for transgender people. Indeed, individuals may hold the same community-level biases around gender nonconformity, which may be explicit (known to the individual and within their control) or implicit (automatically activated, often subconscious biases for which people have limited control) (Major et al., 2013). However, in order for a person to enact their biases towards a transgender person, they must first be aware that the individual is transgender.

Goffman (1963) described those with visible stigmas as the discredited, as their stigmatized condition is readily apparent and therefore more susceptible to mistreatment. Conversely, the discreditable are those whose stigma is invisible, but who would experience stigma should their stigma become known. To that end, transgender people with low visual conformity (other people can tell they are transgender) experience more discrimination and worse health outcomes than those with high visual conformity (Grant, 2011; Reisner et al., 2015b). Transgender individuals who are unable to access gender affirmation procedures (e.g., due to cost, familial rejection, or health concerns), those who have socially transitioned, but never plan to medically transition, and individuals for whom medical interventions are less effective in producing gender conformity (e.g., those transitioning post-puberty, transgender women on estrogen relative to transgender men on testosterone) may therefore be particularly at risk of experiencing enacted forms of stigma as their nonconforming appearance is visible to others (Bockting et al., 2013; Grant, 2011; Reisner et al., 2015b).

Transgender individuals whose gender/sex incongruence becomes known to others are at risk for enacted forms of stigma such as physical and sexual assault (Grant et al., 2011; see Stotzer, 2009 for a review). Indeed, a review of violence against US transgender people found that prevalence of lifetime physical assault due to gender identity ranged from 33–53% (Stotzer, 2009). It is theorized that gender nonconformity causes perpetrators of violence to become anxious and angry, ultimately enacting violence against transgender people as a means of rejecting and diminishing that which they fear (Westbrook & Schilt, 2013). Gender, race and class also shape violence against transgender people. According to the US National Coalition of Anti-Violence Programs, of the 18 anti-LGBT or HIV-related homicides in 2013, 72% of victims were transgender women, and 67% were transgender women of color (Ahmed & Jindasurat, 2014). Sexual assault is also highly prevalent (13–86%) among transgender individuals independent of gender (Stotzer, 2009), though specific subgroups, including sex workers and transgender women of color, may be particularly vulnerable (Ahmed & Jindasurat, 2014; Stotzer, 2009) due to interlocking systems of

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oppression (e.g., racism, sexism) (Crenshaw, 1991; Grollman, 2014). Physical and sexual assault is most frequently perpetrated by cisgender males (Stotzer, 2009) and used to exert power over devalued individuals (Schilt, 2009). In the case of sexualized interactions between cisgender men and transgender women, it has been argued that cisgender men feel threatened when they learn a woman is transgender, and react violently in an effort to prove their heterosexuality and reclaim their masculinity and power (Schilt, 2009). Studies also show high levels of reported violence among young and low-income transgender people (Stotzer, 2009), suggesting that violence on the basis of transgender identity or expression often affects the most marginalized transgender subpopulations.

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Violence against transgender people is often perpetuated by someone known to the victim, including family members (Stotzer, 2009). Indeed, rejection by one's family of origin is common among transgender people and may be enacted through physical assault as well as through less overt means such as lack of support around gender expression or barring access to medical gender affirmation procedures (Factor & Rothblum, 2008; Grossman & D'augelli, 2006; Wren, 2002). Familial rejection can occur at any age, although it may be particularly distressful for transgender youth who not only rely on their parents for emotional support (Garofalo et al., 2006), but may become homeless as a result familial rejection (Grant, 2011; Grossman & D'augelli, 2006; Sullivan et al., 2001). For both transgender youth and adults, lack of support is associated with isolation, low self-esteem, depression, and other negative health outcomes (Grossman & D'augelli, 2006; Koken et al., 2009; Nemoto et al., 2011; Simons et al., 2013). Lack of support may also lead some transgender individuals to transition later in life (Fabbre, 2014; Gagné & Tewksbury, 1998). Transitioning later in life may confer economic benefits (particularly for transgender women who are able to earn more as men), while avoiding discrimination in workplace settings (Schilt & Wiswall, 2008). However, delaying one's transition and concealing one's transgender identity may cause psychological distress in adolescents and adults (Bryant & Schilt, 2008; Gagné & Tewksbury, 1998). Moreover, delaying transition until adulthood can present transition barriers for those who wish to visually conform to a stereotypically masculine or feminine gender expression as one's secondary sex characteristics are already formed and therefore may be difficult to reverse or minimize later (Cohen-Kettenis & van Goozen, 2002).

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Mistreatment in everyday settings such as healthcare is another form of interpersonal stigma commonly experienced by transgender people. A national study of over 6,000 transgender adults found that 28% had experienced harassment in medical settings, 19% were refused care, and 2% experienced violence in their doctor's office (Grant, 2011). The prevalence of discrimination was even higher among people of color as 17% of White respondents reported healthcare discrimination compared to 36% of Native Americans, 27% of multi-racial individuals, 22% of Hispanics and 19% of Black respondents (Grant, 2011). In some cases, provider discrimination may be explicit and grounded in stigma-related beliefs (Dewey, 2008; Lurie, 2005; Poteat et al., 2013; Snelgrove et al., 2012). In other cases, provider mistreatment, such as the use of outdated or incorrect language (e.g., wrong pronoun), may be the result of structural factors such as lack of training or implicit biases unknown to the provider (Major et al., 2013). To that end, qualitative research shows that insufficient provider training creates uneasiness and discomfort for both patients and

providers, and even hostile treatment for transgender patients (Lurie, 2005; Poteat et al., 2013). Stigma in healthcare settings has individual behavioral implications, including the anticipation and avoidance of stigma in future healthcare interactions (see below) (Grant, 2011; Poteat et al., 2013; Reisner et al., 2015b; Schilder et al., 2001).

Level 3: Individual Stigma

Stigma at the interpersonal level can shape stigmatized individuals' cognitive, affective, and behavioral processes. Thus, at the individual level, stigmatized individuals' psychological processes are affected by stigma, which powerfully shapes their basic orientation to themselves, others, and their environmental circumstances. These processes include anxious expectations of rejection and stigma avoidance, stigma concealment, and reduced self-efficacy to cope with stigma-related stressors.

Experiencing stigma at the interpersonal level can affect how transgender people evaluate and approach future situations. Anxiously expecting discrimination can lead to avoidance of interpersonal situations, which can take a toll on one's mental and physical health (Reisner et al., 2015a; Reisner et al., 2015b). For example, many transgender people report experiencing mistreatment in healthcare settings, which is associated with postponing necessary care and the development of conditions requiring emergency care (Cruz, 2014; Dewey, 2008; Grant, 2011; Reisner et al., 2015b; Xavier et al., 2013). Transgender individuals' avoidance of healthcare due to mistreatment supports the stigma-based rejection sensitivity model proposed by Mendoza-Denton et al., (2002), in which stigmatized individuals nervously anticipate (hypervigilance), routinely observe (perceived stigma), and anxiously react to rejection with important health costs (e.g., the onset of otherwise preventable health conditions).

Transgender individuals who are visually conforming may choose not to disclose their transgender identity as a form of stigma management (Cruz, 2014; Dewey, 2008; Goffman, 1963; Mizock & Mueser, 2014). To that end, visually conforming transgender individuals are said to have "passing privilege" as their stigma is hidden and they are able to avoid mistreatment (Sevelius, 2013; Xavier, 1999). While the ability to *pass* may help transgender individuals avoid stigma, concealing a core aspect of one's self can impart profound stress on individuals who question when their stigma will be discovered and whether they should disclose their stigma to others (Smart & Wegner, 1999). Concealing one's transgender status can also limit the extent to which *stealth* individuals (those who do not disclose their transgender history to anyone) are able to access support from the transgender community or medical and mental health interventions. Additionally, concealment by those who have not transitioned can restrict access to transition-related care for those who desire it, as well as prevent those who have transitioned from receiving appropriate preventative care for anatomy they may still possess (e.g., pap tests for transgender men, prostate exams for transgender women) (Alegria, 2011; Samuel & Zaritsky, 2008).

The internalization of stigma can also impact an individual's ability to cope with external stressors, erode self-efficacy for enacting health-promoting behaviors, and eventually diminish an individual's ability to remain resilient in the face of negative events (Hendricks & Testa, 2012; Meyer, 2003b; Mizock & Mueser, 2014). In fact, high levels of internalized

transgender stigma is associated with increased probability of lifetime suicide attempts (Perez-Brumer et al., 2015). Additionally, internalized stigma in transgender people may reduce self-care and help-seeking behaviors for mental health problems resulting in a failure to access mental health services when needed (Hellman & Klein, 2004; Zigas et al., 2003).

Direct Health Effects of Stigma

The negative health impact of multiple forms of stigma are summarized in the gender minority stress theory (Hendricks & Testa, 2012). Derived from minority stress theories applied to other stigmatized statuses (e.g., SES, Dohrenwend, 2000; race, Williams, 2001; sexual minority status, Meyer, 2003b), gender minority stress theory proposes that added stressors related to the stigma attached to one's discordant gender identity/expression adversely affect health and accounts for health differences between transgender and cisgender individuals on a population level. In this model, structural forms of stigma establish stressful environments for stigmatized populations, which then generate the cognitive, affective, and behavioral stress processes with health consequences reviewed here.

Experimental studies among diverse populations show that stressors have immediate effects on the body including diastolic blood pressure reactivity, increased cortisol output, and elevated cardiometabolic risk (Gyll et al., 2001; Hatzenbuehler et al., 2014b; Townsend et al., 2011). Chronic activation of the body's stress response system can compromise health over time, a phenomenon termed *allostatic load* (McEwen & Stellar, 1993). For many, chronic stress is associated with adverse health outcomes, such as hypertension, diabetes, and even death (Anderson, 1989; Hatzenbuehler et al., 2014a; Taylor et al., 2006). Persistent stress has also been linked to anxiety, depression, suicidality, and substance use to cope (Clements-Nolle et al., 2006; Hatzenbuehler et al., 2008; Reisner et al., 2014b). While a dearth of research has explored the long-term physical health effects of stigma-related stress in transgender people, studies among other stigmatized groups reveal that stigma can affect health over the life-course, as middle age Black women in one study, were found to be 7.5 years biologically older than their white peers (Geronimus et al., 2010). Given that transgender people experience stigma in numerous contexts throughout their lives, it is likely that these experiences take a similarly additive toll on their health, yet this remains understudied. Further, adults with multiple disadvantaged statuses are more likely to experience poor physical and mental health than those with a single stigmatized identity (Grollman, 2014). Thus, transgender individuals with multiple disadvantaged statuses (e.g., low income, transgender women of color) may be at particularly increased risk of poor health due the chronic stress associated with experiencing discrimination through multiple pathways.

Interventions to Reduce Stigma and Its Negative Health Impact

To prevent the onset of adverse health outcomes in diverse transgender populations, interventionists need to reduce the factors that cause stress and intervene directly to help transgender people mitigate stress responses. Stigma interventions have been developed to change attitudes and improve coping at the individual-level, reduce the perpetration of stigma at the interpersonal-level, and change the norms, policies, and systems that

perpetuate stigma at the structural-level. This section reviews interventions relevant to transgender populations at each level, and across multiple levels, providing potential intervention strategies for future development and testing.

Individual and Interpersonal Stigma Interventions

Clinicians have long recognized the need to intervene to reduce the effects of stigma in transgender people. A primary focus of counseling for transgender individuals involves reducing the shame around one's transgender identity and helping individuals to cope with the effects of stigma (Coleman et al., 2012; Johnson & Yarhouse, 2013). While the success of these therapeutic strategies have largely been reported through qualitative reports (Bockting et al., 2006; Byne et al., 2012), more recently researchers have attempted to measure the effects of individual-level coping interventions that target the psychological, emotional, and behavioral responses to stigma. A 2014 study of lesbian, gay, bisexual, transgender, and queer or questioning college students and allies (LGBTQA) aimed to build collective self-esteem and reduce the effects of stigma by having participants listen to a presentation on positive LGBTQA identities and write narratives related to their own positive identity experiences (Riggle et al., 2014). Post-intervention, participants showed an increase in positive LGBTQA identity, collective self-esteem, and individual self-esteem; however, these results were not maintained one month later. More intensive interventions (e.g., more sessions, multiple components) aimed at building identity-related self-esteem have been conducted in non-transgender sexual minority populations with more sustained positive results (Pachankis & Goldfried, 2010; Pachankis et al., 2015). While individual-level coping interventions tend to be feasible to implement, they are limited in their ability to reach all stigmatized individuals in need of support. Thus, efforts that reach a larger audience of stigmatized people may yield more sustainable and far-reaching results.

While clinical interventions can be useful in addressing individual challenges, interventions that help transgender individuals to connect and share strategies for resilience can be effective in managing stigma (Schrock et al., 2004). In fact, awareness and engagement with other transgender people significantly influences risk and resilience during early gender identity development as both prior awareness and engagement with other transgender people are related to less fearfulness, less suicidality, and more comfort (Testa et al., 2014). Recognizing the utility of community support, groups have been developed to provide transgender people with the opportunity to connect with one another and manage the effects of stigma (Bradford et al., 2013; Schrock et al., 2004). In evaluating the effects of a transgender support groups, Schrock et al., (2004) found that participants were able to "find relief from shame, fear, powerlessness, alienation, and inauthenticity" (p. 76). Moreover, transgender social support and community involvement have been shown to protectively moderate the association between stigma and psychological distress (Bockting et al., 2013) and physical health outcomes (i.e. HIV/STI infection) (Nuttbrock et al., 2015). One limitation of social support interventions, however, is that they teach individuals to behaviorally manage the effects of stigma without addressing the structural forces that create and perpetuate stigma (Schrock et al., 2004). Thus, individual interventions that foster social change may be more effective and sustainable.

Collective activism serves as a means to combat the effects of stigma. Activism around a shared cause can create a sense of unity and collective identity and help individuals to feel empowered against stigma (Ashmore et al., 2004; Testa et al., 2014). Activism generally requires an individual to be out about their transgender identity. Through their visibility, out activists reject societal efforts to keep transgender people down and concealed (Bornstein & Bergman, 2010), while also avoiding the psychiatric distress associated with concealing a stigmatized aspect of one's self (Schrock et al., 2004). Activism may be particularly empowering for transgender people as it simultaneously yields personal fulfillment and fights systems of oppression (Mizock & Mueser, 2014; Schrock et al., 2004).

Interventions to reduce transgender stigma and its effects need not be limited to transgender people, but also individuals who hold the power to constrain the opportunities and resources of transgender people, such as family members, peers, and providers. Interventions aimed at family members can have positive effects, including fostering understanding and acceptance of transgender loved ones as well as recognizing one is not alone (Broad, 2011; Menvielle & Hill, 2010; Menvielle & Tuerk, 2002). A central component of many family support groups is education about transgender experiences which allows non-transgender participants to develop a humanizing perspective of their transgender family member and no longer see them as the "other" (MacNish & Gold-Peifer, 2014; Menvielle & Hill, 2010). Support groups can also aid family members in coping with the loss of their transgender family member as they knew them, as well as combating the stigma that families also face due to having a transgender loved one (MacNish & Gold-Peifer, 2014; Menvielle & Tuerk, 2002). Such interventions can also help to create allies who can educate the broader community about transgender issues in order to reduce structural and interpersonal stigma (Broad, 2011; Broad et al., 2008).

Many providers lack training in transgender care and are in need of interventions to prevent enacted stigma in healthcare settings (Lurie, 2005; Poteat et al., 2013; Snelgrove et al., 2012). Educational efforts to increase transgender cultural competency (e.g., "Transgender 101" trainings) are often successful in improving healthcare provider awareness and understanding of transgender patients by exposing them to the healthcare barriers that transgender people encounter and improving their skills in caring for transgender patients (Hanssmann et al., 2008). Empirical interventions to improve providers' transgender medical knowledge have also demonstrated success, as a lecture covering the durability of gender identity and hormonal treatment regimens significantly increased physician-residents' knowledge and willingness to provide hormonal therapy for transgender patients (Thomas & Safer, 2015). An intervention to reduce providers' implicit racial biases was also successful (Burgess et al., 2007) and could be adapted to reduce providers' implicit transgender bias in healthcare settings. While education is important, lack of exposure to transgender people represents a barrier to provider comfort and expertise (Lurie, 2005). Inter-group contact is effective in reducing prejudice among diverse populations (Pettigrew & Tropp, 2006). Thus, interventions aimed at increasing provider contact with transgender people may be beneficial in eliminating biases and discomfort (Pettigrew & Tropp, 2006; Walch et al., 2012); although such interventions could prove burdensome to transgender people.

To our knowledge no empirical studies testing the efficacy of provider contact interventions exist for transgender patients; however, a recent study with college students showed that exposure to a transgender speaker panel on transgender stigma yielded greater immediate decreases in stigma compared to a lecture led by non-transgender people (Walch et al., 2012). Healthcare entities have also begun to institute training programs aimed at increasing transgender medical and cultural competency through exposure to transgender patients and trainings led by transgender people (Hanssmann et al., 2008; Makadon, 2008). While these interventions represent efforts to reduce transgender stigma in healthcare settings, they require significant time and resources, with positive effects only extending to those who participate in the intervention and often only sustained for a limited time (Hanssmann et al., 2008). Given that stigma is socially constructed, efforts to reduce transgender stigma at the population-level and improve health outcomes for all transgender people are needed.

Structural Stigma Interventions

Changes to policies that reduce stigma and provide equal opportunities for transgender people have the potential to improve the health of transgender individuals. Recent years have witnessed a movement to be more inclusive of transgender people in non-discrimination policies, with numerous states having passed laws to provide transgender people with equal protections in employment, housing, and education (Transgender Law and Policy Institute, 2012). While empirical work has not assessed whether these policies had an effect on the lived realities of transgender people, studies in other populations suggest that even changes to distal stigma structures (i.e., state-level policies) can improve the health of stigmatized groups (Hatzenbuehler & Keyes, 2013; Hatzenbuehler et al., 2009). For example, Hatzenbuehler et al. (2009) examined state-level policies that provided protections against hate crimes and employment discrimination based on sexual orientation and found that state-level protective policies led to a reduction in the association between LGB status and mood disorders. Similarly, a study of anti-bullying laws in Oregon found that inclusive anti-bullying policies were significantly associated with a reduced risk for suicide attempts and exposure to peer victimization among gay youth (Hatzenbuehler & Keyes, 2013). These findings suggest that policies can positively impact the lives of stigmatized individuals by providing greater protections and access to resources under the law.

As noted previously, access to gender transition-related care represents an important structural factor that can impact the mental and physical health of transgender people. In 2010, the Affordable Care Act made it illegal for insurance companies to deny individuals on the basis of pre-existing conditions and gender identity (ACA, 2010). The law also provides low-income people with access to gender affirmation therapies through Medicaid. Protections for older and disabled adults came with the 2014 repeal of the Medicare policy of excluding coverage for transition-related surgery, thus allowing care decisions to be made on an individual basis (NCTE, 2015). While other structural factors, such as untrained providers could still bar access to care for transgender patients, extended coverage under the law may encourage medical schools and healthcare institutions to increase training for transgender care as gender affirmation surgeries will become reimbursable (Khan, 2013). Such policy changes serve as structural interventions that engender immediate health

benefits through increased access to care and also have the potential to shift societal attitudes by increasing public awareness of transgender issues.

Multi-Level Community-Based Stigma Interventions

As shown in this review, stigma works at multiple levels to impact the health of transgender people; thus, interventions that target stigma at multiple levels are likely to achieve the maximum benefit (Cook et al., 2014). One such campaign is the *I AM Trans People Speak* campaign developed by the Massachusetts Transgender Political Association (MTPC, 2013), which features videos of transgender people sharing their stories and the multiple identities they hold. The videos act as a self-affirmation intervention (Walton & Cohen, 2011) that aids transgender people in coping with stigma. The campaign also features videos of family members, partners, and other transgender allies telling their narratives of heartbreak, acceptance, and unconditional love. While the project has not been rigorously evaluated, dissemination of the videos to non-transgender audiences aims to reduce transgender stigma by educating the public about transgender people's lives and eliminating stereotypes through exposure. Similar programs have also been developed to address mental illness stigma and homophobia with positive results (Corrigan & Gelb, 2006; Vinney, 2014). The *I Am* campaign is just one strategy MTPC uses to combat transgender stigma and discrimination at multiple levels. The organization also advocates for the passage of supportive legislation, engages in community education by delivering "Transgender 101" trainings, supports transgender people in responding to discrimination, and encourages community empowerment through collective action. Interventionists looking to reduce transgender stigma should consider collaboratively engaging in research with community-based organizations, as community-based participatory research can yield measurable, significant, and sustainable results (Corrigan & Shapiro, 2010).

Summary and Future Directions

Changing attitudes have allowed transgender people to become more visible in society. However, the increased visibility of transgender people also highlights the high prevalence of adverse health outcomes that exist in some transgender communities – health inequities linked to the societal stigma attached to gender nonconforming identities and expressions. While recent US non-discrimination policies may reflect greater acceptance of transgender people, widespread interpersonal stigma ultimately impacts the health of transgender individuals.

This review paves a path for a transgender health research agenda that includes three primary domains: 1) Stigma Determinants: Stronger evidence—using population-based, longitudinal, and experimental designs—is needed to document the causal relationship between stigma and adverse health in US transgender populations. 2) Stigma Mechanisms and Moderators: Future studies should simultaneously and interactively examine the structural, interpersonal, and individual pathways through which stigma operates to jeopardize the health of transgender people in the US. Such research will permit examination of the pathways that mediate the stigma-health relationship for this population and the investigation of moderators that may help to identify subgroups at greatest risk for poor health (e.g., by age, race/ethnicity, poverty) or protective factors that can be levied as

future modifiable intervention targets (e.g., transgender peer support, community involvement). 3) Stigma Interventions: Interventions are needed to reduce stigma toward transgender people at the individual, interpersonal, and structural levels. Multi-level interventions that concurrently address individual responses to stigma (e.g., stigma management and coping), implicit and explicit biases that contribute to enacted stigma at the interpersonal level (e.g., provider attitudes), and systems that restrict access to essential resources as the structural level (e.g., restrictive policies) also warrant future development and testing. Regardless of intervention level, these approaches should meaningfully enlist the input of transgender communities to ensure intervention acceptability, engagement, and long-term implementation.

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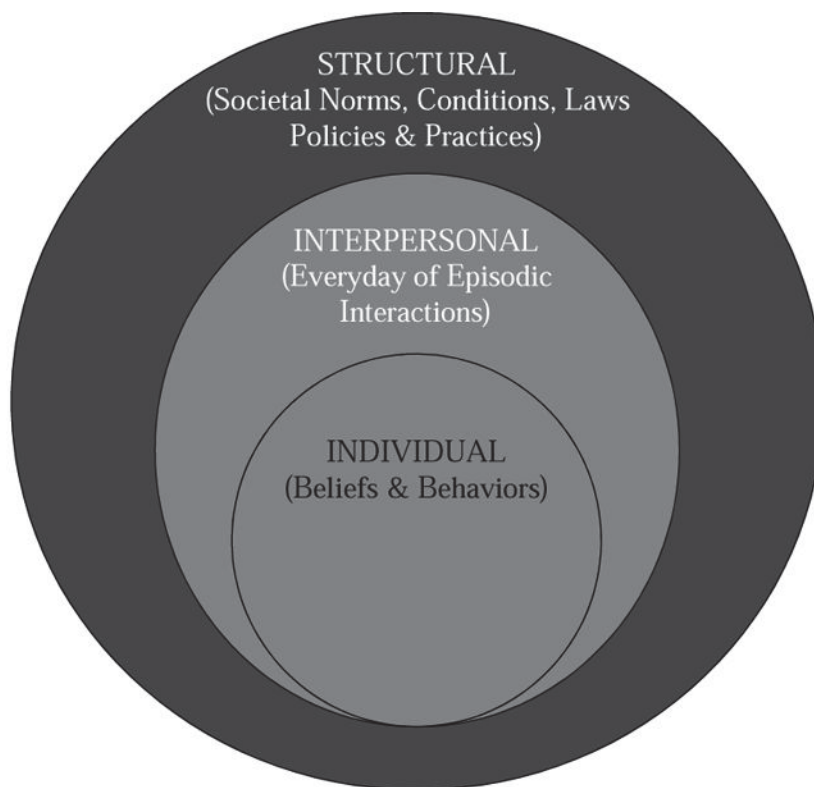
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Research Highlights

- Stigma contributes to widespread health inequities in US transgender communities.
- We review the multiple levels at which stigma towards transgender people operates.
- The stress mechanisms through which stigma contributes to health are discussed.
- Intervention strategies to reduce transgender stigma are outlined at each level.
- Multi-level interventions are needed to reduce transgender stigma in the US.

**Structural**Types of Stigma

- Gender conformity to natal sex norms
- Stigmatizing policies and enforcement practices
- Lack of provider training and education
- Healthcare access barriers
- Economic inequality
- Gender inequality

Interventions

- Non-discrimination policies
- Access to care policies
- Transgender health content in medical school curricula

InterpersonalTypes of Stigma

- Healthcare discrimination
- Workplace discrimination
- Family rejection
- Hate crimes
- Sexual assault
- Physical assault

Interventions

- Family/partner support groups
- Healthcare provider trainings
- Intergroup contact

IndividualTypes of Stigma

- Concealment of stigma
- Avoidance of stigma
- Internalization of stigma

Interventions

- Counseling/therapy
- Self-affirmation
- Transgender support groups
- Collective activism

Figure 1.

Modified Social-Ecological Model of Transgender Stigma & Stigma Interventions

Gender and health

Credits

Overview

WHO's role

Gender refers to the characteristics of women, men, girls and boys that are socially constructed. This includes norms, behaviours and roles associated with being a woman, man, girl or boy, as well as relationships with each other. As a social construct, gender varies from society to society and can change over time.

Gender is hierarchical and produces inequalities that intersect with other social and economic inequalities. Gender-based discrimination intersects with other factors of discrimination, such as ethnicity, socioeconomic status, disability, age, geographic location, gender identity and sexual orientation, among others. This is referred to as intersectionality.

Gender interacts with but is different from sex, which refers to the different biological and physiological characteristics of females, males and intersex persons, such as chromosomes, hormones and reproductive organs. Gender and sex are related to but different from gender identity. Gender identity refers to a person's deeply felt, internal and individual experience of gender, which may or may not correspond to the person's physiology or designated sex at birth.

Gender influences people's experience of and access to healthcare. The way that health services are organized and provided can either limit or enable a person's access to healthcare information, support and services, and the outcome of those encounters. Health services should be affordable, accessible and acceptable to all, and they should be provided with quality, equity and dignity.

Gender inequality and discrimination faced by women and girls puts their health and well-being at risk. Women and girls often face greater barriers than men and boys to accessing health information and services. These barriers include restrictions on mobility; lack of access to decision-making power; lower literacy rates; discriminatory attitudes of communities and healthcare providers; and lack of training and awareness amongst healthcare providers and health systems of the specific health needs and challenges of women and girls.

Consequently, women and girls face greater risks of unintended pregnancies, sexually transmitted infections including HIV, cervical cancer, malnutrition, lower vision, respiratory infections, malnutrition and elder abuse, amongst others. Women and girls also face unacceptably high levels of violence rooted in gender inequality and are at grave risk of harmful practices such as female genital mutilation, and child, early and forced marriage. WHO figures show that about 1 in 3 women worldwide have experienced either physical and/or sexual intimate partner violence or non-partner sexual violence in their lifetime.

Harmful gender norms – especially those related to rigid notions of masculinity – can also affect boys and men's health and wellbeing negatively. For example, specific notions of masculinity may encourage boys and men to smoke, take sexual and other health risks, misuse alcohol and not seek help or health care. Such gender norms also contribute to boys and men perpetrating violence – as well as being subjected to violence themselves. They can also have grave implications for their mental health.

Rigid gender norms also negatively affect people with diverse gender identities, who often face violence, stigma and discrimination as a result, including in healthcare settings. Consequently, they are at higher risk of HIV and mental health problems, including suicide.

Fact sheets



Data



Tools



WHO Resolutions



Q & A



WHO teams





Standards of Care for the Health of Transsexual, Transgender, and Gender- Nonconforming People

The World Professional Association for Transgender Health



Standards of Care

for the Health of Transsexual, Transgender, and Gender- Nonconforming People

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Purpose and Use of the *Standards of Care*

The World Professional Association for Transgender Health (WPATH)^I is an international, multidisciplinary, professional association whose mission is to promote evidence-based care, education, research, advocacy, public policy, and respect in transsexual and transgender health. The vision of WPATH is a world wherein transsexual, transgender, and gender-nonconforming people benefit from access to evidence-based health care, social services, justice, and equality.

One of the main functions of WPATH is to promote the highest standards of health care for individuals through the articulation of *Standards of Care (SOC) for the Health of Transsexual, Transgender, and Gender Nonconforming People*. The SOC are based on the best available science and expert professional consensus.^{II} Most of the research and experience in this field comes from a North American and Western European perspective; thus, adaptations of the SOC to other parts of the world are necessary. Suggestions for ways of thinking about cultural relativity and cultural competence are included in this version of the SOC.

The overall goal of the SOC is to provide clinical guidance for health professionals to assist transsexual, transgender, and gender-nonconforming people with safe and effective pathways to achieving lasting personal comfort with their gendered selves, in order to maximize their overall health, psychological well-being, and self-fulfillment. This assistance may include primary care, gynecologic and urologic care, reproductive options, voice and communication therapy, mental health services (e.g., assessment, counseling, psychotherapy), and hormonal and surgical treatments. While this is primarily a document for health professionals, the SOC may also be used by individuals, their families, and social institutions to understand how they can assist with promoting optimal health for members of this diverse population.

WPATH recognizes that health is dependent upon not only good clinical care but also social and political climates that provide and ensure social tolerance, equality, and the full rights of citizenship. Health is promoted through public policies and legal reforms that promote tolerance and equity

^I Formerly the Harry Benjamin International Gender Dysphoria Association

^{II} The *Standards of Care (SOC)*, Version 7, represents a significant departure from previous versions. Changes in this version are based upon significant cultural shifts, advances in clinical knowledge, and appreciation of the many health care issues that can arise for transsexual, transgender, and gender-nonconforming people beyond hormone therapy and surgery (Coleman, 2009a, b, c, d).

for gender and sexual diversity and that eliminate prejudice, discrimination, and stigma. WPATH is committed to advocacy for these changes in public policies and legal reforms.

The *Standards of Care* Are Flexible Clinical Guidelines

The SOC are intended to be flexible in order to meet the diverse health care needs of transsexual, transgender, and gender-nonconforming people. While flexible, they offer standards for promoting optimal health care and guiding the treatment of people experiencing gender dysphoria—broadly defined as discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b).

As in all previous versions of the SOC, the criteria put forth in this document for hormone therapy and surgical treatments for gender dysphoria are clinical guidelines; individual health professionals and programs may modify them. Clinical departures from the SOC may come about because of a patient's unique anatomic, social, or psychological situation; an experienced health professional's evolving method of handling a common situation; a research protocol; lack of resources in various parts of the world; or the need for specific harm-reduction strategies. These departures should be recognized as such, explained to the patient, and documented through informed consent for quality patient care and legal protection. This documentation is also valuable for the accumulation of new data, which can be retrospectively examined to allow for health care—and the SOC—to evolve.

The SOC articulate standards of care but also acknowledge the role of making informed choices and the value of harm-reduction approaches. In addition, this version of the SOC recognizes and validates various expressions of gender that may not necessitate psychological, hormonal, or surgical treatments. Some patients who present for care will have made significant self-directed progress towards gender role changes, transition, or other resolutions regarding their gender identity or gender dysphoria. Other patients will require more intensive services. Health professionals can use the SOC to help patients consider the full range of health services open to them, in accordance with their clinical needs and goals for gender expression.



Global Applicability of the *Standards of Care*

While the SOC are intended for worldwide use, WPATH acknowledges that much of the recorded clinical experience and knowledge in this area of health care is derived from North American and Western European sources. From place to place, both across and within nations, there are differences in all of the following: social attitudes towards transsexual, transgender, and gender-nonconforming people; constructions of gender roles and identities; language used to describe different gender identities; epidemiology of gender dysphoria; access to and cost of treatment; therapies offered; number and type of professionals who provide care; and legal and policy issues related to this area of health care (Winter, 2009).

It is impossible for the SOC to reflect all of these differences. In applying these standards to other cultural contexts, health professionals must be sensitive to these differences and adapt the SOC according to local realities. For example, in a number of cultures, gender-nonconforming people are found in such numbers and living in such ways as to make them highly socially visible (Peletz, 2006). In settings such as these, it is common for people to initiate a change in their gender expression and physical characteristics while in their teens or even earlier. Many grow up and live in a social, cultural, and even linguistic context quite unlike that of Western cultures. Yet almost all experience prejudice (Peletz, 2006; Winter, 2009). In many cultures, social stigma towards gender nonconformity is widespread and gender roles are highly prescriptive (Winter et al., 2009). Gender-nonconforming people in these settings are forced to be hidden and, therefore, may lack opportunities for adequate health care (Winter, 2009).

The SOC are not intended to limit efforts to provide the best available care to all individuals. Health professionals throughout the world—even in areas with limited resources and training opportunities—can apply the many core principles that undergird the SOC. These principles include the following: Exhibit respect for patients with nonconforming gender identities (do not pathologize differences in gender identity or expression); provide care (or refer to knowledgeable colleagues) that affirms patients' gender identities and reduces the distress of gender dysphoria, when present; become knowledgeable about the health care needs of transsexual, transgender, and gender-nonconforming people, including the benefits and risks of treatment options for gender dysphoria; match the treatment approach to the specific needs of patients, particularly their goals for gender expression and need for relief from gender dysphoria; facilitate access to appropriate care; seek patients' informed consent before providing treatment; offer continuity of care; and be prepared to support and advocate for patients within their families and communities (schools, workplaces, and other settings).

Terminology is culture- and time-dependent and is rapidly evolving. It is important to use respectful language in different places and times, and among different people. As the SOC are translated into other languages, great care must be taken to ensure that the meanings of terms are accurately translated. Terminology in English may not be easily translated into other languages, and vice versa. Some languages do not have equivalent words to describe the various terms within this document; hence, translators should be cognizant of the underlying goals of treatment and articulate culturally applicable guidance for reaching those goals.



The Difference Between Gender Nonconformity and Gender Dysphoria

Being Transsexual, Transgender, or Gender-Nonconforming Is a Matter of Diversity, Not Pathology

WPATH released a statement in May 2010 urging the de-psychopathologization of gender nonconformity worldwide (WPATH Board of Directors, 2010). This statement noted that “the expression of gender characteristics, including identities, that are not stereotypically associated with one’s assigned sex at birth is a common and culturally diverse human phenomenon [that] should not be judged as inherently pathological or negative.”

Unfortunately, there is stigma attached to gender nonconformity in many societies around the world. Such stigma can lead to prejudice and discrimination, resulting in “minority stress” (I. H. Meyer, 2003). Minority stress is unique (additive to general stressors experienced by all people), socially based, and chronic, and may make transsexual, transgender, and gender-nonconforming individuals more vulnerable to developing mental health concerns such as anxiety and depression (Institute of Medicine, 2011). In addition to prejudice and discrimination in society at large, stigma can contribute to abuse and neglect in one’s relationships with peers and family members, which in turn can lead to psychological distress. However, these symptoms are socially induced and are not inherent to being transsexual, transgender, or gender-nonconforming.

Gender Nonconformity Is Not the Same as Gender Dysphoria

Gender nonconformity refers to the extent to which a person's gender identity, role, or expression differs from the cultural norms prescribed for people of a particular sex (Institute of Medicine, 2011). *Gender dysphoria* refers to discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b). Only *some* gender-nonconforming people experience gender dysphoria at *some* point in their lives.

Treatment is available to assist people with such distress to explore their gender identity and find a gender role that is comfortable for them (Bockting & Goldberg, 2006). Treatment is individualized: What helps one person alleviate gender dysphoria might be very different from what helps another person. This process may or may not involve a change in gender expression or body modifications. Medical treatment options include, for example, feminization or masculinization of the body through hormone therapy and/or surgery, which are effective in alleviating gender dysphoria and are medically necessary for many people. Gender identities and expressions are diverse, and hormones and surgery are just two of many options available to assist people with achieving comfort with self and identity.

Gender dysphoria can in large part be alleviated through treatment (Murad et al., 2010). Hence, while transsexual, transgender, and gender-nonconforming people may experience gender dysphoria at some points in their lives, many individuals who receive treatment will find a gender role and expression that is comfortable for them, even if these differ from those associated with their sex assigned at birth, or from prevailing gender norms and expectations.

Diagnoses Related to Gender Dysphoria

Some people experience gender dysphoria at such a level that the distress meets criteria for a formal diagnosis that might be classified as a mental disorder. Such a diagnosis is not a license for stigmatization or for the deprivation of civil and human rights. Existing classification systems such as the *Diagnostic Statistical Manual of Mental Disorders (DSM)* (American Psychiatric Association, 2000) and the *International Classification of Diseases (ICD)* (World Health Organization, 2007) define hundreds of mental disorders that vary in onset, duration, pathogenesis, functional disability, and treatability. All of these systems attempt to classify clusters of symptoms and conditions, not the individuals themselves. A disorder is a description of something with which a person might struggle, not a description of the person or the person's identity.

Thus, transsexual, transgender, and gender-nonconforming individuals are not inherently disordered. Rather, the distress of gender dysphoria, when present, is the concern that might be diagnosable and for which various treatment options are available. The existence of a diagnosis for such dysphoria often facilitates access to health care and can guide further research into effective treatments.

Research is leading to new diagnostic nomenclatures, and terms are changing in both the *DSM* (Cohen-Kettenis & Pfäfflin, 2010; Knudson, De Cuypere, & Bockting, 2010b; Meyer-Bahlburg, 2010; Zucker, 2010) and the *ICD*. For this reason, familiar terms are employed in the *SOC* and definitions are provided for terms that may be emerging. Health professionals should refer to the most current diagnostic criteria and appropriate codes to apply in their practice areas.

IV Epidemiologic Considerations

Formal epidemiologic studies on the incidence^{III} and prevalence^{IV} of transsexualism specifically or transgender and gender-nonconforming identities in general have not been conducted, and efforts to achieve realistic estimates are fraught with enormous difficulties (Institute of Medicine, 2011; Zucker & Lawrence, 2009). Even if epidemiologic studies established that a similar proportion of transsexual, transgender, or gender-nonconforming people existed all over the world, it is likely that cultural differences from one country to another would alter both the behavioral expressions of different gender identities and the extent to which gender dysphoria—distinct from one's gender identity—is actually occurring in a population. While in most countries, crossing normative gender boundaries generates moral censure rather than compassion, there are examples in certain cultures of gender-nonconforming behaviors (e.g., in spiritual leaders) that are less stigmatized and even revered (Besnier, 1994; Bolin, 1988; Chiñas, 1995; Coleman, Colgan, & Gooren, 1992; Costa & Matzner, 2007; Jackson & Sullivan, 1999; Nanda, 1998; Taywaditap, Coleman, & Dumronggittigule, 1997).

For various reasons, researchers who have studied incidence and prevalence have tended to focus on the most easily counted subgroup of gender-nonconforming individuals: transsexual individuals who experience gender dysphoria and who present for gender-transition-related care at specialist gender clinics (Zucker & Lawrence, 2009). Most studies have been conducted in European countries such as Sweden (Wålinder, 1968, 1971), the United Kingdom (Hoenig & Kenna, 1974),

III **incidence**—the number of new cases arising in a given period (e.g., a year)

IV **prevalence**—the number of individuals having a condition, divided by the number of people in the general population

the Netherlands (Bakker, Van Kesteren, Gooren, & Bezemer, 1993; Eklund, Gooren, & Bezemer, 1988; van Kesteren, Gooren, & Megens, 1996), Germany (Weitze & Osburg, 1996), and Belgium (De Cuypere et al., 2007). One was conducted in Singapore (Tsoi, 1988).

De Cuypere and colleagues (2007) reviewed such studies, as well as conducted their own. Together, those studies span 39 years. Leaving aside two outlier findings from Pauly in 1965 and Tsoi in 1988, ten studies involving eight countries remain. The prevalence figures reported in these ten studies range from 1:11,900 to 1:45,000 for male-to-female individuals (MtF) and 1:30,400 to 1:200,000 for female-to-male (FtM) individuals. Some scholars have suggested that the prevalence is much higher, depending on the methodology used in the research (e.g., Olyslager & Conway, 2007).

Direct comparisons across studies are impossible, as each differed in their data collection methods and in their criteria for documenting a person as transsexual (e.g., whether or not a person had undergone genital reconstruction, versus had initiated hormone therapy, versus had come to the clinic seeking medically supervised transition services). The trend appears to be towards higher prevalence rates in the more recent studies, possibly indicating increasing numbers of people seeking clinical care. Support for this interpretation comes from research by Reed and colleagues (2009), who reported a doubling of the numbers of people accessing care at gender clinics in the United Kingdom every five or six years. Similarly, Zucker and colleagues (2008) reported a four- to five-fold increase in child and adolescent referrals to their Toronto, Canada clinic over a 30-year period.

The numbers yielded by studies such as these can be considered minimum estimates at best. The published figures are mostly derived from clinics where patients met criteria for severe gender dysphoria and had access to health care at those clinics. These estimates do not take into account that treatments offered in a particular clinic setting might not be perceived as affordable, useful, or acceptable by all self-identified gender dysphoric individuals in a given area. By counting only those people who present at clinics for a specific type of treatment, an unspecified number of gender dysphoric individuals are overlooked.

Other clinical observations (not yet firmly supported by systematic study) support the likelihood of a higher prevalence of gender dysphoria: (i) Previously unrecognized gender dysphoria is occasionally diagnosed when patients are seen with anxiety, depression, conduct disorder, substance abuse, dissociative identity disorders, borderline personality disorder, sexual disorders, and disorders of sex development (Cole, O'Boyle, Emory, & Meyer III, 1997). (ii) Some crossdressers, drag queens/kings or female/male impersonators, and gay and lesbian individuals may be experiencing gender dysphoria (Bullough & Bullough, 1993). (iii) The intensity of some people's gender dysphoria fluctuates below and above a clinical threshold (Docter, 1988). (iv) Gender nonconformity among FtM individuals tends to be relatively invisible in many cultures, particularly to Western health

professionals and researchers who have conducted most of the studies on which the current estimates of prevalence and incidence are based (Winter, 2009).

Overall, the existing data should be considered a starting point, and health care would benefit from more rigorous epidemiologic study in different locations worldwide.



Overview of Therapeutic Approaches for Gender Dysphoria

Advancements in the Knowledge and Treatment of Gender Dysphoria

In the second half of the 20th century, awareness of the phenomenon of gender dysphoria increased when health professionals began to provide assistance to alleviate gender dysphoria by supporting changes in primary and secondary sex characteristics through hormone therapy and surgery, along with a change in gender role. Although Harry Benjamin already acknowledged a spectrum of gender nonconformity (Benjamin, 1966), the initial clinical approach largely focused on identifying who was an appropriate candidate for sex reassignment to facilitate a physical change from male to female or female to male as completely as possible (e.g., Green & Fleming, 1990; Hastings, 1974). This approach was extensively evaluated and proved to be highly effective. Satisfaction rates across studies ranged from 87% of MtF patients to 97% of FtM patients (Green & Fleming, 1990), and regrets were extremely rare (1–1.5% of MtF patients and <1% of FtM patients; Pfäfflin, 1993). Indeed, hormone therapy and surgery have been found to be medically necessary to alleviate gender dysphoria in many people (American Medical Association, 2008; Anton, 2009; World Professional Association for Transgender Health, 2008).

As the field matured, health professionals recognized that while many individuals need both hormone therapy and surgery to alleviate their gender dysphoria, others need only one of these treatment options and some need neither (Bockting & Goldberg, 2006; Bockting, 2008; Lev, 2004). Often with the help of psychotherapy, some individuals integrate their trans- or cross-gender feelings into the gender role they were assigned at birth and do not feel the need to feminize or masculinize their body. For others, changes in gender role and expression are sufficient to alleviate

gender dysphoria. Some patients may need hormones, a possible change in gender role, but not surgery; others may need a change in gender role along with surgery, but not hormones. In other words, treatment for gender dysphoria has become more individualized.

As a generation of transsexual, transgender, and gender-nonconforming individuals has come of age—many of whom have benefitted from different therapeutic approaches—they have become more visible as a community and demonstrated considerable diversity in their gender identities, roles, and expressions. Some individuals describe themselves not as gender-nonconforming but as unambiguously cross-sexed (i.e., as a member of the other sex; Bockting, 2008). Other individuals affirm their unique gender identity and no longer consider themselves to be either male or female (Bornstein, 1994; Kimberly, 1997; Stone, 1991; Warren, 1993). Instead, they may describe their gender identity in specific terms such as transgender, bigender, or genderqueer, affirming their unique experiences that may transcend a male/female binary understanding of gender (Bockting, 2008; Ekins & King, 2006; Nestle, Wilchins, & Howell, 2002). They may not experience their process of identity affirmation as a “transition,” because they never fully embraced the gender role they were assigned at birth or because they actualize their gender identity, role, and expression in a way that does not involve a change from one gender role to another. For example, some youth identifying as genderqueer have always experienced their gender identity and role as such (genderqueer). Greater public visibility and awareness of gender diversity (Feinberg, 1996) has further expanded options for people with gender dysphoria to actualize an identity and find a gender role and expression that are comfortable for them.

Health professionals can assist gender dysphoric individuals with affirming their gender identity, exploring different options for expression of that identity, and making decisions about medical treatment options for alleviating gender dysphoria.

Options for Psychological and Medical Treatment of Gender Dysphoria

For individuals seeking care for gender dysphoria, a variety of therapeutic options can be considered. The number and type of interventions applied and the order in which these take place may differ from person to person (e.g., Bockting, Knudson, & Goldberg, 2006; Bolin, 1994; Rachlin, 1999; Rachlin, Green, & Lombardi, 2008; Rachlin, Hansbury, & Pardo, 2010). Treatment options include the following:

- Changes in gender expression and role (which may involve living part time or full time in another gender role, consistent with one’s gender identity);
- Hormone therapy to feminize or masculinize the body;

- Surgery to change primary and/or secondary sex characteristics (e.g., breasts/chest, external and/or internal genitalia, facial features, body contouring);
- Psychotherapy (individual, couple, family, or group) for purposes such as exploring gender identity, role, and expression; addressing the negative impact of gender dysphoria and stigma on mental health; alleviating internalized transphobia; enhancing social and peer support; improving body image; or promoting resilience.

Options for Social Support and Changes in Gender Expression

In addition (or as an alternative) to the psychological- and medical-treatment options described above, other options can be considered to help alleviate gender dysphoria, for example:

- In-person and online peer support resources, groups, or community organizations that provide avenues for social support and advocacy;
- In-person and online support resources for families and friends;
- Voice and communication therapy to help individuals develop verbal and non-verbal communication skills that facilitate comfort with their gender identity;
- Hair removal through electrolysis, laser treatment, or waxing;
- Breast binding or padding, genital tucking or penile prostheses, padding of hips or buttocks;
- Changes in name and gender marker on identity documents.

VI

Assessment and Treatment of Children and Adolescents With Gender Dysphoria

There are a number of differences in the phenomenology, developmental course, and treatment approaches for gender dysphoria in children, adolescents, and adults. In children and adolescents, a rapid and dramatic developmental process (physical, psychological, and sexual) is involved and

there is greater fluidity and variability in outcomes, particularly in prepubertal children. Accordingly, this section of the SOC offers specific clinical guidelines for the assessment and treatment of gender dysphoric children and adolescents.

Differences Between Children and Adolescents with Gender Dysphoria

An important difference between gender dysphoric children and adolescents is in the proportion for whom dysphoria persists into adulthood. Gender dysphoria during childhood does not inevitably continue into adulthood.^V Rather, in follow-up studies of prepubertal children (mainly boys) who were referred to clinics for assessment of gender dysphoria, the dysphoria persisted into adulthood for only 6–23% of children (Cohen-Kettenis, 2001; Zucker & Bradley, 1995). Boys in these studies were more likely to identify as gay in adulthood than as transgender (Green, 1987; Money & Russo, 1979; Zucker & Bradley, 1995; Zuger, 1984). Newer studies, also including girls, showed a 12–27% persistence rate of gender dysphoria into adulthood (Drummond, Bradley, Peterson-Badali, & Zucker, 2008; Wallien & Cohen-Kettenis, 2008).

In contrast, the persistence of gender dysphoria into adulthood appears to be much higher for adolescents. No formal prospective studies exist. However, in a follow-up study of 70 adolescents who were diagnosed with gender dysphoria and given puberty-suppressing hormones, all continued with actual sex reassignment, beginning with feminizing/masculinizing hormone therapy (de Vries, Steensma, Doreleijers, & Cohen-Kettenis, 2010).

Another difference between gender dysphoric children and adolescents is in the sex ratios for each age group. In clinically referred, gender dysphoric children under age 12, the male/female ratio ranges from 6:1 to 3:1 (Zucker, 2004). In clinically referred, gender dysphoric adolescents older than age 12, the male/female ratio is close to 1:1 (Cohen-Kettenis & Pfäfflin, 2003).

As discussed in section IV and by Zucker and Lawrence (2009), formal epidemiologic studies on gender dysphoria—in children, adolescents, and adults—are lacking. Additional research is needed to refine estimates of its prevalence and persistence in different populations worldwide.

^V Gender-nonconforming behaviors in children may continue into adulthood, but such behaviors are not necessarily indicative of gender dysphoria and a need for treatment. As described in section III, gender dysphoria is not synonymous with diversity in gender expression.

Phenomenology in Children

Children as young as age two may show features that could indicate gender dysphoria. They may express a wish to be of the other sex and be unhappy about their physical sex characteristics and functions. In addition, they may prefer clothes, toys, and games that are commonly associated with the other sex and prefer playing with other-sex peers. There appears to be heterogeneity in these features: Some children demonstrate extremely gender-nonconforming behavior and wishes, accompanied by persistent and severe discomfort with their primary sex characteristics. In other children, these characteristics are less intense or only partially present (Cohen-Kettenis et al., 2006; Knudson, De Cuypere, & Bockting, 2010a).

It is relatively common for gender dysphoric children to have coexisting internalizing disorders such as anxiety and depression (Cohen-Kettenis, Owen, Kaijser, Bradley, & Zucker, 2003; Wallien, Swaab, & Cohen-Kettenis, 2007; Zucker, Owen, Bradley, & Ameeriar, 2002). The prevalence of autism spectrum disorders seems to be higher in clinically referred, gender dysphoric children than in the general population (de Vries, Noens, Cohen-Kettenis, van Berckelaer-Onnes, & Doreleijers, 2010).

Phenomenology in Adolescents

In most children, gender dysphoria will disappear before, or early in, puberty. However, in some children these feelings will intensify and body aversion will develop or increase as they become adolescents and their secondary sex characteristics develop (Cohen-Kettenis, 2001; Cohen-Kettenis & Pfäfflin, 2003; Drummond et al., 2008; Wallien & Cohen-Kettenis, 2008; Zucker & Bradley, 1995). Data from one study suggest that more extreme gender nonconformity in childhood is associated with persistence of gender dysphoria into late adolescence and early adulthood (Wallien & Cohen-Kettenis, 2008). Yet many adolescents and adults presenting with gender dysphoria do not report a history of childhood gender-nonconforming behaviors (Docter, 1988; Landén, Wälinder, & Lundström, 1998). Therefore, it may come as a surprise to others (parents, other family members, friends, and community members) when a youth's gender dysphoria first becomes evident in adolescence.

Adolescents who experience their primary and/or secondary sex characteristics and their sex assigned at birth as inconsistent with their gender identity may be intensely distressed about it. Many, but not all, gender dysphoric adolescents have a strong wish for hormones and surgery. Increasing numbers of adolescents have already started living in their desired gender role upon entering high school (Cohen-Kettenis & Pfäfflin, 2003).

Among adolescents who are referred to gender identity clinics, the number considered eligible for early medical treatment—starting with GnRH analogues to suppress puberty in the first Tanner stages—differs among countries and centers. Not all clinics offer puberty suppression. If such treatment is offered, the pubertal stage at which adolescents are allowed to start varies from Tanner stage 2 to stage 4 (Delemarre-van de Waal & Cohen-Kettenis, 2006; Zucker et al., 2012). The percentages of treated adolescents are likely influenced by the organization of health care, insurance aspects, cultural differences, opinions of health professionals, and diagnostic procedures offered in different settings.

Inexperienced clinicians may mistake indications of gender dysphoria for delusions. Phenomenologically, there is a qualitative difference between the presentation of gender dysphoria and the presentation of delusions or other psychotic symptoms. The vast majority of children and adolescents with gender dysphoria are not suffering from underlying severe psychiatric illness such as psychotic disorders (Steensma, Biemond, de Boer, & Cohen-Kettenis, published online ahead of print January 7, 2011).

It is more common for adolescents with gender dysphoria to have coexisting internalizing disorders such as anxiety and depression, and/or externalizing disorders such as oppositional defiant disorder (de Vries et al., 2010). As in children, there seems to be a higher prevalence of autistic spectrum disorders in clinically referred, gender dysphoric adolescents than in the general adolescent population (de Vries et al., 2010).

Competency of Mental Health Professionals Working with Children or Adolescents with Gender Dysphoria

The following are recommended minimum credentials for mental health professionals who assess, refer, and offer therapy to children and adolescents presenting with gender dysphoria:

1. Meet the competency requirements for mental health professionals working with adults, as outlined in section VII;
2. Trained in childhood and adolescent developmental psychopathology;
3. Competent in diagnosing and treating the ordinary problems of children and adolescents.

Roles of Mental Health Professionals Working with Children and Adolescents with Gender Dysphoria

The roles of mental health professionals working with gender dysphoric children and adolescents may include the following:

1. Directly assess gender dysphoria in children and adolescents (see general guidelines for assessment, below).
2. Provide family counseling and supportive psychotherapy to assist children and adolescents with exploring their gender identity, alleviating distress related to their gender dysphoria, and ameliorating any other psychosocial difficulties.
3. Assess and treat any coexisting mental health concerns of children or adolescents (or refer to another mental health professional for treatment). Such concerns should be addressed as part of the overall treatment plan.
4. Refer adolescents for additional physical interventions (such as puberty-suppressing hormones) to alleviate gender dysphoria. The referral should include documentation of an assessment of gender dysphoria and mental health, the adolescent's eligibility for physical interventions (outlined below), the mental health professional's relevant expertise, and any other information pertinent to the youth's health and referral for specific treatments.
5. Educate and advocate on behalf of gender dysphoric children, adolescents, and their families in their community (e.g., day care centers, schools, camps, other organizations). This is particularly important in light of evidence that children and adolescents who do not conform to socially prescribed gender norms may experience harassment in school (Grossman, D'Augelli, & Salter, 2006; Grossman, D'Augelli, Howell, & Hubbard, 2006; Sausa, 2005), putting them at risk for social isolation, depression, and other negative sequelae (Nuttbrock et al., 2010).
6. Provide children, youth, and their families with information and referral for peer support, such as support groups for parents of gender-nonconforming and transgender children (Gold & MacNish, 2011; Pleak, 1999; Rosenberg, 2002).

Assessment and psychosocial interventions for children and adolescents are often provided within a multidisciplinary gender identity specialty service. If such a multidisciplinary service is not available, a mental health professional should provide consultation and liaison arrangements with a pediatric endocrinologist for the purpose of assessment, education, and involvement in any decisions about physical interventions.

Psychological Assessment of Children and Adolescents

When assessing children and adolescents who present with gender dysphoria, mental health professionals should broadly conform to the following guidelines:

1. Mental health professionals should not dismiss or express a negative attitude towards nonconforming gender identities or indications of gender dysphoria. Rather, they should acknowledge the presenting concerns of children, adolescents, and their families; offer a thorough assessment for gender dysphoria and any coexisting mental health concerns; and educate clients and their families about therapeutic options, if needed. Acceptance, and alleviation of secrecy, can bring considerable relief to gender dysphoric children/adolescents and their families.
2. Assessment of gender dysphoria and mental health should explore the nature and characteristics of a child's or adolescent's gender identity. A psychodiagnostic and psychiatric assessment—covering the areas of emotional functioning, peer and other social relationships, and intellectual functioning/school achievement—should be performed. Assessment should include an evaluation of the strengths and weaknesses of family functioning. Emotional and behavioral problems are relatively common, and unresolved issues in a child's or youth's environment may be present (de Vries, Doreleijers, Steensma, & Cohen-Kettenis, 2011; Di Ceglie & Thümmel, 2006; Wallien et al., 2007).
3. For adolescents, the assessment phase should also be used to inform youth and their families about the possibilities and limitations of different treatments. This is necessary for informed consent, but also important for assessment. The way that adolescents respond to information about the reality of sex reassignment can be diagnostically informative. Correct information may alter a youth's desire for certain treatment, if the desire was based on unrealistic expectations of its possibilities.

Psychological and Social Interventions for Children and Adolescents

When supporting and treating children and adolescents with gender dysphoria, health professionals should broadly conform to the following guidelines:

1. Mental health professionals should help families to have an accepting and nurturing response to the concerns of their gender dysphoric child or adolescent. Families play an important role in the psychological health and well-being of youth (Brill & Pepper, 2008; Lev, 2004). This also applies to peers and mentors from the community, who can be another source of social support.

2. Psychotherapy should focus on reducing a child's or adolescent's distress related to the gender dysphoria and on ameliorating any other psychosocial difficulties. For youth pursuing sex reassignment, psychotherapy may focus on supporting them before, during, and after reassignment. Formal evaluations of different psychotherapeutic approaches for this situation have not been published, but several counseling methods have been described (Cohen-Kettenis, 2006; de Vries, Cohen-Kettenis, & Delemarre-van de Waal, 2006; Di Ceglie & Thümmel, 2006; Hill, Menvielle, Sica, & Johnson, 2010; Malpas, in press; Menvielle & Tuerk, 2002; Rosenberg, 2002; Vanderburgh, 2009; Zucker, 2006).

Treatment aimed at trying to change a person's gender identity and expression to become more congruent with sex assigned at birth has been attempted in the past without success (Gelder & Marks, 1969; Greenson, 1964), particularly in the long term (Cohen-Kettenis & Kuiper, 1984; Pauly, 1965). Such treatment is no longer considered ethical.

3. Families should be supported in managing uncertainty and anxiety about their child's or adolescent's psychosexual outcomes and in helping youth to develop a positive self-concept.
4. Mental health professionals should not impose a binary view of gender. They should give ample room for clients to explore different options for gender expression. Hormonal or surgical interventions are appropriate for some adolescents, but not for others.
5. Clients and their families should be supported in making difficult decisions regarding the extent to which clients are allowed to express a gender role that is consistent with their gender identity, as well as the timing of changes in gender role and possible social transition. For example, a client might attend school while undergoing social transition only partly (e.g., by wearing clothing and having a hairstyle that reflects gender identity) or completely (e.g., by also using a name and pronouns congruent with gender identity). Difficult issues include whether and when to inform other people of the client's situation, and how others in their lives might respond.
6. Health professionals should support clients and their families as educators and advocates in their interactions with community members and authorities such as teachers, school boards, and courts.
7. Mental health professionals should strive to maintain a therapeutic relationship with gender-nonconforming children/adolescents and their families throughout any subsequent social changes or physical interventions. This ensures that decisions about gender expression and the treatment of gender dysphoria are thoughtfully and recurrently considered. The same reasoning applies if a child or adolescent has already socially changed gender role prior to being seen by a mental health professional.

Social Transition in Early Childhood

Some children state that they want to make a social transition to a different gender role long before puberty. For some children, this may reflect an expression of their gender identity. For others, this could be motivated by other forces. Families vary in the extent to which they allow their young children to make a social transition to another gender role. Social transitions in early childhood do occur within some families with early success. This is a controversial issue, and divergent views are held by health professionals. The current evidence base is insufficient to predict the long-term outcomes of completing a gender role transition during early childhood. Outcomes research with children who completed early social transitions would greatly inform future clinical recommendations.

Mental health professionals can help families to make decisions regarding the timing and process of any gender role changes for their young children. They should provide information and help parents to weigh the potential benefits and challenges of particular choices. Relevant in this respect are the previously described relatively low persistence rates of childhood gender dysphoria (Drummond et al., 2008; Wallien & Cohen-Kettenis, 2008). A change back to the original gender role can be highly distressing and even result in postponement of this second social transition on the child's part (Steensma & Cohen-Kettenis, 2011). For reasons such as these, parents may want to present this role change as an exploration of living in another gender role rather than an irreversible situation. Mental health professionals can assist parents in identifying potential in-between solutions or compromises (e.g., only when on vacation). It is also important that parents explicitly let the child know that there is a way back.

Regardless of a family's decisions regarding transition (timing, extent), professionals should counsel and support them as they work through the options and implications. If parents do not allow their young child to make a gender-role transition, they may need counseling to assist them with meeting their child's needs in a sensitive and nurturing way, ensuring that the child has ample possibilities to explore gender feelings and behavior in a safe environment. If parents do allow their young child to make a gender role transition, they may need counseling to facilitate a positive experience for their child. For example, they may need support in using correct pronouns, maintaining a safe and supportive environment for their transitioning child (e.g., in school, peer group settings), and communicating with other people in their child's life. In either case, as a child nears puberty, further assessment may be needed as options for physical interventions become relevant.

Physical Interventions for Adolescents

Before any physical interventions are considered for adolescents, extensive exploration of psychological, family, and social issues should be undertaken, as outlined above. The duration of this exploration may vary considerably depending on the complexity of the situation.

Physical interventions should be addressed in the context of adolescent development. Some identity beliefs in adolescents may become firmly held and strongly expressed, giving a false impression of irreversibility. An adolescent's shift towards gender conformity can occur primarily to please the parents and may not persist or reflect a permanent change in gender dysphoria (Hembree et al., 2009; Steensma et al., published online ahead of print January 7, 2011).

Physical interventions for adolescents fall into three categories or stages (Hembree et al., 2009):

1. *Fully reversible interventions.* These involve the use of GnRH analogues to suppress estrogen or testosterone production and consequently delay the physical changes of puberty. Alternative treatment options include progestins (most commonly medroxyprogesterone) or other medications (such as spironolactone) that decrease the effects of androgens secreted by the testicles of adolescents who are not receiving GnRH analogues. Continuous oral contraceptives (or depot medroxyprogesterone) may be used to suppress menses.
2. *Partially reversible interventions.* These include hormone therapy to masculinize or feminize the body. Some hormone-induced changes may need reconstructive surgery to reverse the effect (e.g., gynaecomastia caused by estrogens), while other changes are not reversible (e.g., deepening of the voice caused by testosterone).
3. *Irreversible interventions.* These are surgical procedures.

A staged process is recommended to keep options open through the first two stages. Moving from one stage to another should not occur until there has been adequate time for adolescents and their parents to assimilate fully the effects of earlier interventions.

Fully Reversible Interventions

Adolescents may be eligible for puberty-suppressing hormones as soon as pubertal changes have begun. In order for adolescents and their parents to make an informed decision about pubertal delay, it is recommended that adolescents experience the onset of puberty to at least Tanner Stage 2. Some children may arrive at this stage at very young ages (e.g., 9 years of age). Studies

evaluating this approach have only included children who were at least 12 years of age (Cohen-Kettenis, Schagen, Steensma, de Vries, & Delemarre-van de Waal, 2011; de Vries, Steensma et al., 2010; Delemarre-van de Waal, van Weissenbruch, & Cohen Kettenis, 2004; Delemarre-van de Waal & Cohen-Kettenis, 2006).

Two goals justify intervention with puberty-suppressing hormones: (i) their use gives adolescents more time to explore their gender nonconformity and other developmental issues; and (ii) their use may facilitate transition by preventing the development of sex characteristics that are difficult or impossible to reverse if adolescents continue on to pursue sex reassignment.

Puberty suppression may continue for a few years, at which time a decision is made to either discontinue all hormone therapy or transition to a feminizing/masculinizing hormone regimen. Pubertal suppression does not inevitably lead to social transition or to sex reassignment.

Criteria for Puberty-Suppressing Hormones

In order for adolescents to receive puberty-suppressing hormones, the following minimum criteria must be met:

1. The adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed);
2. Gender dysphoria emerged or worsened with the onset of puberty;
3. Any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment;
4. The adolescent has given informed consent and, particularly when the adolescent has not reached the age of medical consent, the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process.

Regimens, Monitoring, and Risks for Puberty Suppression

For puberty suppression, adolescents with male genitalia should be treated with GnRH analogues, which stop luteinizing hormone secretion and therefore testosterone secretion. Alternatively, they may be treated with progestins (such as medroxyprogesterone) or with other medications that block testosterone secretion and/or neutralize testosterone action. Adolescents with female genitalia should be treated with GnRH analogues, which stop the production of estrogens and

progesterone. Alternatively, they may be treated with progestins (such as medroxyprogesterone). Continuous oral contraceptives (or depot medroxyprogesterone) may be used to suppress menses. In both groups of adolescents, use of GnRH analogues is the preferred treatment (Hembree et al., 2009), but their high cost is prohibitive for some patients.

During pubertal suppression, an adolescent's physical development should be carefully monitored—preferably by a pediatric endocrinologist—so that any necessary interventions can occur (e.g., to establish an adequate gender appropriate height, to improve iatrogenic low bone mineral density) (Hembree et al., 2009).

Early use of puberty-suppressing hormones may avert negative social and emotional consequences of gender dysphoria more effectively than their later use would. Intervention in early adolescence should be managed with pediatric endocrinological advice, when available. Adolescents with male genitalia who start GnRH analogues early in puberty should be informed that this could result in insufficient penile tissue for penile inversion vaginoplasty techniques (alternative techniques, such as the use of a skin graft or colon tissue, are available).

Neither puberty suppression nor allowing puberty to occur is a neutral act. On the one hand, functioning in later life can be compromised by the development of irreversible secondary sex characteristics during puberty and by years spent experiencing intense gender dysphoria. On the other hand, there are concerns about negative physical side effects of GnRH analogue use (e.g., on bone development and height). Although the very first results of this approach (as assessed for adolescents followed over 10 years) are promising (Cohen-Kettenis et al., 2011; Delemarre-van de Waal & Cohen-Kettenis, 2006), the long-term effects can only be determined when the earliest-treated patients reach the appropriate age.

Partially Reversible Interventions

Adolescents may be eligible to begin feminizing/masculinizing hormone therapy, preferably with parental consent. In many countries, 16-year-olds are legal adults for medical decision-making and do not require parental consent. Ideally, treatment decisions should be made among the adolescent, the family, and the treatment team.

Regimens for hormone therapy in gender dysphoric adolescents differ substantially from those used in adults (Hembree et al., 2009). The hormone regimens for youth are adapted to account for the somatic, emotional, and mental development that occurs throughout adolescence (Hembree et al., 2009).

Irreversible Interventions

Genital surgery should not be carried out until (i) patients reach the legal age of majority to give consent for medical procedures in a given country, and (ii) patients have lived continuously for at least 12 months in the gender role that is congruent with their gender identity. The age threshold should be seen as a minimum criterion and not an indication in and of itself for active intervention.

Chest surgery in FtM patients could be carried out earlier, preferably after ample time of living in the desired gender role and after one year of testosterone treatment. The intent of this suggested sequence is to give adolescents sufficient opportunity to experience and socially adjust in a more masculine gender role, before undergoing irreversible surgery. However, different approaches may be more suitable, depending on an adolescent's specific clinical situation and goals for gender identity expression.

Risks of Withholding Medical Treatment for Adolescents

Refusing timely medical interventions for adolescents might prolong gender dysphoria and contribute to an appearance that could provoke abuse and stigmatization. As the level of gender-related abuse is strongly associated with the degree of psychiatric distress during adolescence (Nuttbrock et al., 2010), withholding puberty suppression and subsequent feminizing or masculinizing hormone therapy is not a neutral option for adolescents.

VII

Mental Health

Transsexual, transgender, and gender-nonconforming people might seek the assistance of a mental health professional for any number of reasons. Regardless of a person's reason for seeking care, mental health professionals should have familiarity with gender nonconformity, act with appropriate cultural competence, and exhibit sensitivity in providing care.

This section of the SOC focuses on the role of mental health professionals in the care of adults seeking help for gender dysphoria and related concerns. Professionals working with gender dysphoric children, adolescents, and their families should consult section VI.

Competency of Mental Health Professionals Working with Adults Who Present with Gender Dysphoria

The training of mental health professionals competent to work with gender dysphoric adults rests upon basic general clinical competence in the assessment, diagnosis, and treatment of mental health concerns. Clinical training may occur within any discipline that prepares mental health professionals for clinical practice, such as psychology, psychiatry, social work, mental health counseling, marriage and family therapy, nursing, or family medicine with specific training in behavioral health and counseling. The following are recommended minimum credentials for mental health professionals who work with adults presenting with gender dysphoria:

1. A master's degree or its equivalent in a clinical behavioral science field. This degree, or a more advanced one, should be granted by an institution accredited by the appropriate national or regional accrediting board. The mental health professional should have documented credentials from a relevant licensing board or equivalent for that country.
2. Competence in using the *Diagnostic Statistical Manual of Mental Disorders* and/or the *International Classification of Diseases* for diagnostic purposes.
3. Ability to recognize and diagnose coexisting mental health concerns and to distinguish these from gender dysphoria.
4. Documented supervised training and competence in psychotherapy or counseling.
5. Knowledgeable about gender-nonconforming identities and expressions, and the assessment and treatment of gender dysphoria.
6. Continuing education in the assessment and treatment of gender dysphoria. This may include attending relevant professional meetings, workshops, or seminars; obtaining supervision from a mental health professional with relevant experience; or participating in research related to gender nonconformity and gender dysphoria.

In addition to the minimum credentials above, it is recommended that mental health professionals develop and maintain cultural competence to facilitate their work with transsexual, transgender, and gender-nonconforming clients. This may involve, for example, becoming knowledgeable about current community, advocacy, and public policy issues relevant to these clients and their families. Additionally, knowledge about sexuality, sexual health concerns, and the assessment and treatment of sexual disorders is preferred.

Mental health professionals who are new to the field (irrespective of their level of training and other experience) should work under the supervision of a mental health professional with established competence in the assessment and treatment of gender dysphoria.

Tasks of Mental Health Professionals Working with Adults Who Present with Gender Dysphoria

Mental health professionals may serve transsexual, transgender, and gender-nonconforming individuals and their families in many ways, depending on a client's needs. For example, mental health professionals may serve as a psychotherapist, counselor, or family therapist, or as a diagnostician/assessor, advocate, or educator.

Mental health professionals should determine a client's reasons for seeking professional assistance. For example, a client may be presenting for any combination of the following health care services: psychotherapeutic assistance to explore gender identity and expression or to facilitate a coming-out process; assessment and referral for feminizing/masculinizing medical interventions; psychological support for family members (partners, children, extended family); psychotherapy unrelated to gender concerns; or other professional services.

Below are general guidelines for common tasks that mental health professionals may fulfill in working with adults who present with gender dysphoria.

Tasks Related to Assessment and Referral

1. Assess Gender Dysphoria

Mental health professionals assess clients' gender dysphoria in the context of an evaluation of their psychosocial adjustment (Bockting et al., 2006; Lev, 2004, 2009). The evaluation includes, at a minimum, assessment of gender identity and gender dysphoria, history and development of gender dysphoric feelings, the impact of stigma attached to gender nonconformity on mental health, and the availability of support from family, friends, and peers (for example, in-person or online contact with other transsexual, transgender, or gender-nonconforming individuals or groups). The evaluation may result in no diagnosis, in a formal diagnosis related to gender dysphoria, and/or in other diagnoses that describe aspects of the client's health and psychosocial adjustment. The role

of mental health professionals includes making reasonably sure that the gender dysphoria is not secondary to, or better accounted for, by other diagnoses.

Mental health professionals with the competencies described above (hereafter called “a qualified mental health professional”) are best prepared to conduct this assessment of gender dysphoria. However, this task may instead be conducted by another type of health professional who has appropriate training in behavioral health and is competent in the assessment of gender dysphoria, particularly when functioning as part of a multidisciplinary specialty team that provides access to feminizing/masculinizing hormone therapy. This professional may be the prescribing hormone therapy provider or a member of that provider’s health care team.

2. Provide Information Regarding Options for Gender Identity and Expression and Possible Medical Interventions

An important task of mental health professionals is to educate clients regarding the diversity of gender identities and expressions and the various options available to alleviate gender dysphoria. Mental health professionals then may facilitate a process (or refer elsewhere) in which clients explore these various options, with the goals of finding a comfortable gender role and expression and becoming prepared to make a fully informed decision about available medical interventions, if needed. This process may include referral for individual, family, and group therapy and/or to community resources and avenues for peer support. The professional and the client discuss the implications, both short- and long-term, of any changes in gender role and use of medical interventions. These implications can be psychological, social, physical, sexual, occupational, financial, and legal (Bockting et al., 2006; Lev, 2004).

This task is also best conducted by a qualified mental health professional, but may be conducted by another health professional with appropriate training in behavioral health and with sufficient knowledge about gender-nonconforming identities and expressions and about possible medical interventions for gender dysphoria, particularly when functioning as part of a multidisciplinary specialty team that provides access to feminizing/masculinizing hormone therapy.

3. Assess, Diagnose, and Discuss Treatment Options for Coexisting Mental Health Concerns

Clients presenting with gender dysphoria may struggle with a range of mental health concerns (Gómez-Gil, Trilla, Salamero, Godás, & Valdés, 2009; Murad et al., 2010) whether related or unrelated to what is often a long history of gender dysphoria and/or chronic minority stress. Possible concerns include anxiety, depression, self-harm, a history of abuse and neglect, compulsivity, substance abuse, sexual concerns, personality disorders, eating disorders, psychotic disorders, and autistic spectrum disorders (Bockting et al., 2006; Nuttbrock et al., 2010; Robinow, 2009). Mental health professionals should screen for these and other mental health concerns and incorporate

the identified concerns into the overall treatment plan. These concerns can be significant sources of distress and, if left untreated, can complicate the process of gender identity exploration and resolution of gender dysphoria (Bockting et al., 2006; Fraser, 2009a; Lev, 2009). Addressing these concerns can greatly facilitate the resolution of gender dysphoria, possible changes in gender role, the making of informed decisions about medical interventions, and improvements in quality of life.

Some clients may benefit from psychotropic medications to alleviate symptoms or treat coexisting mental health concerns. Mental health professionals are expected to recognize this and either provide pharmacotherapy or refer to a colleague who is qualified to do so. The presence of coexisting mental health concerns does not necessarily preclude possible changes in gender role or access to feminizing/masculinizing hormones or surgery; rather, these concerns need to be optimally managed prior to, or concurrent with, treatment of gender dysphoria. In addition, clients should be assessed for their ability to provide educated and informed consent for medical treatments.

Qualified mental health professionals are specifically trained to assess, diagnose, and treat (or refer to treatment for) these coexisting mental health concerns. Other health professionals with appropriate training in behavioral health, particularly when functioning as part of a multidisciplinary specialty team providing access to feminizing/masculinizing hormone therapy, may also screen for mental health concerns and, if indicated, provide referral for comprehensive assessment and treatment by a qualified mental health professional.

4. If Applicable, Assess Eligibility, Prepare, and Refer for Hormone Therapy

The SOC provide criteria to guide decisions regarding feminizing/masculinizing hormone therapy (outlined in section VIII and Appendix C). Mental health professionals can help clients who are considering hormone therapy to be both psychologically prepared (e.g., client has made a fully informed decision with clear and realistic expectations; is ready to receive the service in line with the overall treatment plan; has included family and community as appropriate) and practically prepared (e.g., has been evaluated by a physician to rule out or address medical contraindications to hormone use; has considered the psychosocial implications). If clients are of childbearing age, reproductive options (section IX) should be explored before initiating hormone therapy.

It is important for mental health professionals to recognize that decisions about hormones are first and foremost a client's decisions—as are all decisions regarding healthcare. However, mental health professionals have a responsibility to encourage, guide, and assist clients with making fully informed decisions and becoming adequately prepared. To best support their clients' decisions, mental health professionals need to have functioning working relationships with their clients and sufficient information about them. Clients should receive prompt and attentive evaluation, with the goal of alleviating their gender dysphoria and providing them with appropriate medical services.

Referral for feminizing/masculinizing hormone therapy

People may approach a specialized provider in any discipline to pursue feminizing/masculinizing hormone therapy. However, transgender health care is an interdisciplinary field, and coordination of care and referral among a client's overall care team is recommended.

Hormone therapy can be initiated with a referral from a qualified mental health professional. Alternatively, a health professional who is appropriately trained in behavioral health and competent in the assessment of gender dysphoria may assess eligibility, prepare, and refer the patient for hormone therapy, particularly in the absence of significant coexisting mental health concerns and when working in the context of a multidisciplinary specialty team. The referring health professional should provide documentation—in the chart and/or referral letter—of the patient's personal and treatment history, progress, and eligibility. Health professionals who recommend hormone therapy share the ethical and legal responsibility for that decision with the physician who provides the service.

The recommended content of the referral letter for feminizing/masculinizing hormone therapy is as follows:

1. The client's general identifying characteristics;
2. Results of the client's psychosocial assessment, including any diagnoses;
3. The duration of the referring health professional's relationship with the client, including the type of evaluation and therapy or counseling to date;
4. An explanation that the criteria for hormone therapy have been met, and a brief description of the clinical rationale for supporting the client's request for hormone therapy;
5. A statement that informed consent has been obtained from the patient;
6. A statement that the referring health professional is available for coordination of care and welcomes a phone call to establish this.

For providers working within a multidisciplinary specialty team, a letter may not be necessary; rather, the assessment and recommendation can be documented in the patient's chart.

5. If Applicable, Assess Eligibility, Prepare, and Refer for Surgery

The SOC also provide criteria to guide decisions regarding breast/chest surgery and genital surgery (outlined in section XI and Appendix C). Mental health professionals can help clients who are

considering surgery to be both psychologically prepared (e.g., has made a fully informed decision with clear and realistic expectations; is ready to receive the service in line with the overall treatment plan; has included family and community as appropriate) and practically prepared (e.g., has made an informed choice about a surgeon to perform the procedure; has arranged aftercare). If clients are of childbearing age, reproductive options (section IX) should be explored before undergoing genital surgery.

The SOC do not state criteria for other surgical procedures, such as feminizing or masculinizing facial surgery; however, mental health professionals can play an important role in helping their clients to make fully informed decisions about the timing and implications of such procedures in the context of the overall coming-out or transition process.

It is important for mental health professionals to recognize that decisions about surgery are first and foremost a client's decisions—as are all decisions regarding healthcare. However, mental health professionals have a responsibility to encourage, guide, and assist clients with making fully informed decisions and becoming adequately prepared. To best support their clients' decisions, mental health professionals need to have functioning working relationships with their clients and sufficient information about them. Clients should receive prompt and attentive evaluation, with the goal of alleviating their gender dysphoria and providing them with appropriate medical services.

Referral for surgery

Surgical treatments for gender dysphoria can be initiated by a referral (one or two, depending on the type of surgery) from a qualified mental health professional. The mental health professional provides documentation—in the chart and/or referral letter—of the patient's personal and treatment history, progress, and eligibility. Mental health professionals who recommend surgery share the ethical and legal responsibility for that decision with the surgeon.

- One referral from a qualified mental health professional is needed for breast/chest surgery (e.g., mastectomy, chest reconstruction, or augmentation mammoplasty).
- Two referrals—from qualified mental health professionals who have independently assessed the patient—are needed for genital surgery (i.e., hysterectomy/salpingo-oophorectomy, orchiectomy, genital reconstructive surgeries). If the first referral is from the patient's psychotherapist, the second referral should be from a person who has only had an evaluative role with the patient. Two separate letters, or one letter signed by both (e.g., if practicing within the same clinic) may be sent. Each referral letter, however, is expected to cover the same topics in the areas outlined below.

The recommended content of the referral letters for surgery is as follows:

1. The client's general identifying characteristics;
2. Results of the client's psychosocial assessment, including any diagnoses;
3. The duration of the mental health professional's relationship with the client, including the type of evaluation and therapy or counseling to date;
4. An explanation that the criteria for surgery have been met, and a brief description of the clinical rationale for supporting the patient's request for surgery;
5. A statement about the fact that informed consent has been obtained from the patient;
6. A statement that the mental health professional is available for coordination of care and welcomes a phone call to establish this.

For providers working within a multidisciplinary specialty team, a letter may not be necessary, rather, the assessment and recommendation can be documented in the patient's chart.

Relationship of Mental Health Professionals with Hormone-Prescribing Physicians, Surgeons, and Other Health Professionals

It is ideal for mental health professionals to perform their work and periodically discuss progress and obtain peer consultation from other professionals (both in mental health care and other health disciplines) who are competent in the assessment and treatment of gender dysphoria. The relationship among professionals involved in a client's health care should remain collaborative, with coordination and clinical dialogue taking place as needed. Open and consistent communication may be necessary for consultation, referral, and management of postoperative concerns.

Tasks Related to Psychotherapy

1. Psychotherapy Is Not an Absolute Requirement for Hormone Therapy and Surgery

A mental health screening and/or assessment as outlined above is needed for referral to hormonal and surgical treatments for gender dysphoria. In contrast, psychotherapy—although highly recommended—is not a requirement.

The SOC do not recommend a minimum number of psychotherapy sessions prior to hormone therapy or surgery. The reasons for this are multifaceted (Lev, 2009). First, a minimum number of sessions tends to be construed as a hurdle, which discourages the genuine opportunity for personal growth. Second, mental health professionals can offer important support to clients throughout all phases of exploration of gender identity, gender expression, and possible transition—not just prior to any possible medical interventions. Third, clients and their psychotherapists differ in their abilities to attain similar goals in a specified time period.

2. Goals of Psychotherapy for Adults with Gender Concerns

The general goal of psychotherapy is to find ways to maximize a person's overall psychological well-being, quality of life, and self-fulfillment. Psychotherapy is not intended to alter a person's gender identity; rather, psychotherapy can help an individual to explore gender concerns and find ways to alleviate gender dysphoria, if present (Bockting et al., 2006; Bockting & Coleman, 2007; Fraser, 2009a; Lev, 2004). Typically, the overarching treatment goal is to help transsexual, transgender, and gender-nonconforming individuals achieve long-term comfort in their gender identity expression, with realistic chances for success in their relationships, education, and work. For additional details, see Fraser (Fraser, 2009c).

Therapy may consist of individual, couple, family, or group psychotherapy, the latter being particularly important to foster peer support.

3. Psychotherapy for Transsexual, Transgender, and Gender-Nonconforming Clients, Including Counseling and Support for Changes in Gender Role

Finding a comfortable gender role is, first and foremost, a psychosocial process. Psychotherapy can be invaluable in assisting transsexual, transgender, and gender-nonconforming individuals with all of the following: (i) clarifying and exploring gender identity and role, (ii) addressing the impact of stigma and minority stress on one's mental health and human development, and (iii) facilitating a coming-out process (Bockting & Coleman, 2007; Devor, 2004; Lev, 2004), which for some individuals may include changes in gender role expression and the use of feminizing/masculinizing medical interventions.

Mental health professionals can provide support and promote interpersonal skills and resilience in individuals and their families as they navigate a world that often is ill-prepared to accommodate and respect transgender, transsexual, and gender-nonconforming people. Psychotherapy can also aid in alleviating any coexisting mental health concerns (e.g., anxiety, depression) identified during screening and assessment.

For transsexual, transgender, and gender-nonconforming individuals who plan to change gender roles permanently and make a social gender role transition, mental health professionals can facilitate the development of an individualized plan with specific goals and timelines. While the experience of changing one's gender role differs from person to person, the social aspects of the experience are usually challenging—often more so than the physical aspects. Because changing gender role can have profound personal and social consequences, the decision to do so should include an awareness of what the familial, interpersonal, educational, vocational, economic, and legal challenges are likely to be, so that people can function successfully in their gender role.

Many transsexual, transgender, and gender-nonconforming people will present for care without ever having been related to, or accepted in, the gender role that is most congruent with their gender identity. Mental health professionals can help these clients to explore and anticipate the implications of changes in gender role, and to pace the process of implementing these changes. Psychotherapy can provide a space for clients to begin to express themselves in ways that are congruent with their gender identity and, for some clients, overcome fears about changes in gender expression. Calculated risks can be taken outside of therapy to gain experience and build confidence in the new role. Assistance with coming out to family and community (friends, school, workplace) can be provided.

Other transsexual, transgender, and gender-nonconforming individuals will present for care already having acquired experience (minimal, moderate, or extensive) living in a gender role that differs from that associated with their birth-assigned sex. Mental health professionals can help these clients to identify and work through potential challenges and foster optimal adjustment as they continue to express changes in their gender role.

4. Family Therapy or Support for Family Members

Decisions about changes in gender role and medical interventions for gender dysphoria have implications for, not only clients, but also their families (Emerson & Rosenfeld, 1996; Fraser, 2009a; Lev, 2004). Mental health professionals can assist clients with making thoughtful decisions about communicating with family members and others about their gender identity and treatment decisions. Family therapy may include work with spouses or partners, as well as with children and other members of a client's extended family.

Clients may also request assistance with their relationships and sexual health. For example, they may want to explore their sexuality and intimacy-related concerns.

Family therapy might be offered as part of the client's individual therapy and, if clinically appropriate, by the same provider. Alternatively, referrals can be made to other therapists with relevant expertise

for working with family members or to sources of peer support (e.g., in-person or offline support networks of partners or families).

5. Follow-Up Care Throughout Life

Mental health professionals may work with clients and their families at many stages of their lives. Psychotherapy may be helpful at different times and for various issues throughout the life cycle.

6. E-Therapy, Online Counseling, or Distance Counseling

Online or e-therapy has been shown to be particularly useful for people who have difficulty accessing competent in-person psychotherapeutic treatment and who may experience isolation and stigma (Derrig-Palumbo & Zeine, 2005; Fenichel et al., 2004; Fraser, 2009b). By extrapolation, e-therapy may be a useful modality for psychotherapy with transsexual, transgender, and gender-nonconforming people. E-therapy offers opportunities for potentially enhanced, expanded, creative, and tailored delivery of services; however, as a developing modality it may also carry unexpected risk. Telemedicine guidelines are clear in some disciplines in some parts of the United States (Fraser, 2009b; Maheu, Pulier, Wilhelm, McMenamin, & Brown-Connolly, 2005) but not all; the international situation is even less well-defined (Maheu et al., 2005). Until sufficient evidence-based data on this use of e-therapy is available, caution in its use is advised.

Mental health professionals engaging in e-therapy are advised to stay current with their particular licensing board, professional association, and country's regulations, as well as the most recent literature pertaining to this rapidly evolving medium. A more thorough description of the potential uses, processes, and ethical concerns related to e-therapy has been published (Fraser, 2009b).

Other Tasks of Mental Health Professionals

1. Educate and Advocate on Behalf of Clients Within Their Community (Schools, Workplaces, Other Organizations) and Assist Clients with Making Changes in Identity Documents

Transsexual, transgender, and gender-nonconforming people may face challenges in their professional, educational, and other types of settings as they actualize their gender identity and expression (Lev, 2004, 2009). Mental health professionals can play an important role by educating people in these settings regarding gender nonconformity and by advocating on behalf of their clients (Currah, Juang, & Minter, 2006; Currah & Minter, 2000). This role may involve consultation

with school counselors, teachers, and administrators, human resources staff, personnel managers and employers, and representatives from other organizations and institutions. In addition, health providers may be called upon to support changes in a client's name and/or gender marker on identity documents such as passports, driver's licenses, birth certificates, and diplomas.

2. Provide Information and Referral for Peer Support

For some transsexual, transgender, and gender-nonconforming people, an experience in peer support groups may be more instructive regarding options for gender expression than anything individual psychotherapy could offer (Rachlin, 2002). Both experiences are potentially valuable, and all people exploring gender issues should be encouraged to participate in community activities, if possible. Resources for peer support and information should be made available.

Culture and Its Ramifications for Assessment and Psychotherapy

Health professionals work in enormously different environments across the world. Forms of distress that cause people to seek professional assistance in any culture are understood and classified by people in terms that are products of their own cultures (Frank & Frank, 1993). Cultural settings also largely determine how such conditions are understood by mental health professionals. Cultural differences related to gender identity and expression can affect patients, mental health professionals, and accepted psychotherapy practice. WPATH recognizes that the SOC have grown out of a Western tradition and may need to be adapted depending on the cultural context.

Ethical Guidelines Related to Mental Health Care

Mental health professionals need to be certified or licensed to practice in a given country according to that country's professional regulations (Fraser, 2009b; Pope & Vasquez, 2011). Professionals must adhere to the ethical codes of their professional licensing or certifying organizations in all of their work with transsexual, transgender, and gender-nonconforming clients.

Treatment aimed at trying to change a person's gender identity and lived gender expression to become more congruent with sex assigned at birth has been attempted in the past (Gelder & Marks, 1969; Greenson, 1964), yet without success, particularly in the long-term (Cohen-Kettenis & Kuiper, 1984; Pauly, 1965). Such treatment is no longer considered ethical.

If mental health professionals are uncomfortable with, or inexperienced in, working with transsexual, transgender, and gender-nonconforming individuals and their families, they should refer clients to a competent provider or, at minimum, consult with an expert peer. If no local practitioners are available, consultation may be done via telehealth methods, assuming local requirements for distance consultation are met.

Issues of Access to Care

Qualified mental health professionals are not universally available; thus, access to quality care might be limited. WPATH aims to improve access and provides regular continuing education opportunities to train professionals from various disciplines to provide quality, transgender-specific health care. Providing mental health care from a distance through the use of technology may be one way to improve access (Fraser, 2009b).

In many places around the world, access to health care for transsexual, transgender, and gender-nonconforming people is also limited by a lack of health insurance or other means to pay for needed care. WPATH urges health insurance companies and other third-party payers to cover the medically necessary treatments to alleviate gender dysphoria (American Medical Association, 2008; Anton, 2009; The World Professional Association for Transgender Health, 2008).

When faced with a client who is unable to access services, referral to available peer support resources (offline and online) is recommended. Finally, harm-reduction approaches might be indicated to assist clients with making healthy decisions to improve their lives.

VIII

Hormone Therapy

Medical Necessity of Hormone Therapy

Feminizing/masculinizing hormone therapy—the administration of exogenous endocrine agents to induce feminizing or masculinizing changes—is a medically necessary intervention for many transsexual, transgender, and gender-nonconforming individuals with gender dysphoria

(Newfield, Hart, Dibble, & Kohler, 2006; Pfäfflin & Junge, 1998). Some people seek maximum feminization/masculinization, while others experience relief with an androgynous presentation resulting from hormonal minimization of existing secondary sex characteristics (Factor & Rothblum, 2008). Evidence for the psychosocial outcomes of hormone therapy is summarized in Appendix D.

Hormone therapy must be individualized based on a patient's goals, the risk/benefit ratio of medications, the presence of other medical conditions, and consideration of social and economic issues. Hormone therapy can provide significant comfort to patients who do not wish to make a social gender role transition or undergo surgery, or who are unable to do so (Meyer III, 2009). Hormone therapy is a recommended criterion for some, but not all, surgical treatments for gender dysphoria (see section XI and Appendix C).

Criteria for Hormone Therapy

Initiation of hormone therapy may be undertaken after a psychosocial assessment has been conducted and informed consent has been obtained by a qualified health professional, as outlined in section VII of the SOC. A referral is required from the mental health professional who performed the assessment, unless the assessment was done by a hormone provider who is also qualified in this area.

The criteria for hormone therapy are as follows:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC outlined in section VI);
4. If significant medical or mental health concerns are present, they must be reasonably well-controlled.

As noted in section VII of the SOC, the presence of coexisting mental health concerns does not necessarily preclude access to feminizing/masculinizing hormones; rather, these concerns need to be managed prior to, or concurrent with, treatment of gender dysphoria.

In selected circumstances, it can be acceptable practice to provide hormones to patients who have not fulfilled these criteria. Examples include facilitating the provision of monitored therapy using hormones of known quality as an alternative to illicit or unsupervised hormone use or to patients

who have already established themselves in their affirmed gender and who have a history of prior hormone use. It is unethical to deny availability or eligibility for hormone therapy solely on the basis of blood seropositivity for blood-borne infections such as HIV or hepatitis B or C.

In rare cases, hormone therapy may be contraindicated due to serious individual health conditions. Health professionals should assist these patients with accessing nonhormonal interventions for gender dysphoria. A qualified mental health professional familiar with the patient is an excellent resource in these circumstances.

Informed Consent

Feminizing/masculinizing hormone therapy may lead to irreversible physical changes. Thus, hormone therapy should be provided only to those who are legally able to provide informed consent. This includes people who have been declared by a court to be emancipated minors, incarcerated people, and cognitively impaired people who are considered competent to participate in their medical decisions (Bockting et al., 2006). Providers should document in the medical record that comprehensive information has been provided and understood about all relevant aspects of the hormone therapy, including both possible benefits and risks and the impact on reproductive capacity.

Relationship Between the *Standards of Care* and Informed Consent Model Protocols

A number of community health centers in the United States have developed protocols for providing hormone therapy based on an approach that has become known as the Informed Consent Model (Callen Lorde Community Health Center, 2000, 2011; Fenway Community Health Transgender Health Program, 2007; Tom Waddell Health Center, 2006). These protocols are consistent with the guidelines presented in the WPATH *Standards of Care, Version 7*. The SOC are flexible clinical guidelines; they allow for tailoring of interventions to the needs of the individual receiving services and for tailoring of protocols to the approach and setting in which these services are provided (Ehrbar & Gorton, 2010).

Obtaining informed consent for hormone therapy is an important task of providers to ensure that patients understand the psychological and physical benefits and risks of hormone therapy, as well as its psychosocial implications. Providers prescribing the hormones or health professionals recommending the hormones should have the knowledge and experience to assess gender

dysphoria. They should inform individuals of the particular benefits, limitations, and risks of hormones, given the patient's age, previous experience with hormones, and concurrent physical or mental health concerns.

Screening for and addressing acute or current mental health concerns is an important part of the informed consent process. This may be done by a mental health professional or by an appropriately trained prescribing provider (see section VII of the SOC). The same provider or another appropriately trained member of the health care team (e.g., a nurse) can address the psychosocial implications of taking hormones when necessary (e.g., the impact of masculinization/feminization on how one is perceived and its potential impact on relationships with family, friends, and coworkers). If indicated, these providers will make referrals for psychotherapy and for the assessment and treatment of coexisting mental health concerns such as anxiety or depression.

The difference between the Informed Consent Model and *SOC, Version 7*, is that the SOC puts greater emphasis on the important role that mental health professionals can play in alleviating gender dysphoria and facilitating changes in gender role and psychosocial adjustment. This may include a comprehensive mental health assessment and psychotherapy, when indicated. In the Informed Consent Model, the focus is on obtaining informed consent as the threshold for the initiation of hormone therapy in a multidisciplinary, harm-reduction environment. Less emphasis is placed on the provision of mental health care until the patient requests it, unless significant mental health concerns are identified that would need to be addressed before hormone prescription.

Physical Effects of Hormone Therapy

Feminizing/masculinizing hormone therapy will induce physical changes that are more congruent with a patient's gender identity.

- In FtM patients, the following physical changes are expected to occur: deepened voice, clitoral enlargement (variable), growth in facial and body hair, cessation of menses, atrophy of breast tissue, and decreased percentage of body fat compared to muscle mass.
- In MtF patients, the following physical changes are expected to occur: breast growth (variable), decreased erectile function, decreased testicular size, and increased percentage of body fat compared to muscle mass.

Most physical changes, whether feminizing or masculinizing, occur over the course of two years. The amount of physical change and the exact timeline of effects can be highly variable. Tables 1a and 1b outline the approximate time course of these physical changes.

TABLE 1A: EFFECTS AND EXPECTED TIME COURSE OF MASCULINIZING HORMONES ^A

Effect	Expected onset ^B	Expected maximum effect ^B
Skin oiliness/acne	1–6 months	1–2 years
Facial/body hair growth	3–6 months	3–5 years
Scalp hair loss	>12 months ^C	Variable
Increased muscle mass/strength	6–12 months	2–5 years ^D
Body fat redistribution	3–6 months	2–5 years
Cessation of menses	2–6 months	n/a
Clitoral enlargement	3–6 months	1–2 years
Vaginal atrophy	3–6 months	1–2 years
Deepened voice	3–12 months	1–2 years

^A Adapted with permission from Hembree et al.(2009). Copyright 2009, The Endocrine Society.^B Estimates represent published and unpublished clinical observations.^C Highly dependent on age and inheritance; may be minimal.^D Significantly dependent on amount of exercise.

TABLE 1B: EFFECTS AND EXPECTED TIME COURSE OF FEMINIZING HORMONES ^A

Effect	Expected onset ^B	Expected maximum effect ^B
Body fat redistribution	3–6 months	2–5 years
Decreased muscle mass/ strength	3–6 months	1–2 years ^C
Softening of skin/decreased oiliness	3–6 months	Unknown
Decreased libido	1–3 months	1–2 years
Decreased spontaneous erections	1–3 months	3–6 months
Male sexual dysfunction	Variable	Variable
Breast growth	3–6 months	2–3 years
Decreased testicular volume	3–6 months	2–3 years
Decreased sperm production	Variable	Variable
Thinning and slowed growth of body and facial hair	6–12 months	> 3 years ^D
Male pattern baldness	No regrowth, loss stops 1–3 months	1–2 years

^A Adapted with permission from Hembree et al. (2009). Copyright 2009, The Endocrine Society.^B Estimates represent published and unpublished clinical observations.^C Significantly dependent on amount of exercise.^D Complete removal of male facial and body hair requires electrolysis, laser treatment, or both.

The degree and rate of physical effects depends in part on the dose, route of administration, and medications used, which are selected in accordance with a patient's specific medical goals (e.g., changes in gender role expression, plans for sex reassignment) and medical risk profile. There is no current evidence that response to hormone therapy—with the possible exception of voice deepening in FtM persons—can be reliably predicted based on age, body habitus, ethnicity, or family appearance. All other factors being equal, there is no evidence to suggest that any medically approved type or method of administering hormones is more effective than any other in producing the desired physical changes.

Risks of Hormone Therapy

All medical interventions carry risks. The likelihood of a serious adverse event is dependent on numerous factors: the medication itself, dose, route of administration, and a patient's clinical characteristics (age, comorbidities, family history, health habits). It is thus impossible to predict whether a given adverse effect will happen in an individual patient.

The risks associated with feminizing/masculinizing hormone therapy for the transsexual, transgender, and gender-nonconforming population as a whole are summarized in Table 2. Based on the level of evidence, risks are categorized as follows: (i) likely increased risk with hormone therapy, (ii) possibly increased risk with hormone therapy, or (iii) inconclusive or no increased risk. Items in the last category include those that may present risk, but for which the evidence is so minimal that no clear conclusion can be reached.

Additional detail about these risks can be found in Appendix B, which is based on two comprehensive, evidence-based literature reviews of masculinizing/feminizing hormone therapy (Feldman & Safer, 2009; Hembree et al., 2009), along with a large cohort study (Asscheman et al., 2011). These reviews can serve as detailed references for providers, along with other widely recognized, published clinical materials (Dahl, Feldman, Goldberg, & Jaber, 2006; Ettner, Monstrey, & Eyler, 2007).

TABLE 2: RISKS ASSOCIATED WITH HORMONE THERAPY. BOLDED ITEMS ARE CLINICALLY SIGNIFICANT

Risk Level	Feminizing hormones	Masculinizing hormones
Likely increased risk	Venous thromboembolic disease^A Gallstones Elevated liver enzymes Weight gain Hypertriglyceridemia	Polycythemia Weight gain Acne Androgenic alopecia (balding) Sleep apnea
Likely increased risk with presence of additional risk factors ^B	Cardiovascular disease	
Possible increased risk	Hypertension Hyperprolactinemia or prolactinoma	Elevated liver enzymes Hyperlipidemia
Possible increased risk with presence of additional risk factors ^B	Type 2 diabetes^A	Destabilization of certain psychiatric disorders^C Cardiovascular disease Hypertension Type 2 diabetes
No increased risk or inconclusive	Breast cancer	Loss of bone density Breast cancer Cervical cancer Ovarian cancer Uterine cancer

* **Note:** Risk is greater with oral estrogen administration than with transdermal estrogen administration.

^A Risk is greater with oral estrogen administration than with transdermal estrogen administration.

^B Additional risk factors include age.

^C Includes bipolar, schizoaffective, and other disorders that may include manic or psychotic symptoms. This adverse event appears to be associated with higher doses or supraphysiologic blood levels of testosterone.

Competency of Hormone-Prescribing Physicians, Relationship with Other Health Professionals

Feminizing/masculinizing hormone therapy is best undertaken in the context of a complete approach to health care that includes comprehensive primary care and a coordinated approach to psychosocial issues (Feldman & Safer, 2009). While psychotherapy or ongoing counseling is not required for the initiation of hormone therapy, if a therapist is involved, then regular communication among health professionals is advised (with the patient's consent) to ensure that the transition process is going well, both physically and psychosocially.

With appropriate training, feminizing/masculinizing hormone therapy can be managed by a variety of providers, including nurse practitioners, physician assistants, and primary care physicians (Dahl et al., 2006). Medical visits relating to hormone maintenance provide an opportunity to deliver broader care to a population that is often medically underserved (Clements, Wilkinson, Kitano, & Marx, 1999; Feldman, 2007; Xavier, 2000). Many of the screening tasks and management of comorbidities associated with long-term hormone use, such as cardiovascular risk factors and cancer screening, fall more uniformly within the scope of primary care rather than specialist care (American Academy of Family Physicians, 2005; Eyler, 2007; World Health Organization, 2008), particularly in locations where dedicated gender teams or specialized physicians are not available.

Given the multidisciplinary needs of transsexual, transgender, and gender-nonconforming people seeking hormone therapy, as well as the difficulties associated with fragmentation of care in general (World Health Organization, 2008), WPATH strongly encourages the increased training and involvement of primary care providers in the area of feminizing/masculinizing hormone therapy. If hormones are prescribed by a specialist, there should be close communication with the patient's primary care provider. Conversely, an experienced hormone provider or endocrinologist should be involved if the primary care physician has no experience with this type of hormone therapy, or if the patient has a pre-existing metabolic or endocrine disorder that could be affected by endocrine therapy.

While formal training programs in transgender medicine do not yet exist, hormone providers have a responsibility to obtain appropriate knowledge and experience in this field. Clinicians can increase their experience and comfort in providing feminizing/masculinizing hormone therapy by co-managing care or consulting with a more experienced provider, or by providing more limited types of hormone therapy before progressing to initiation of hormone therapy. Because this field of medicine is evolving, clinicians should become familiar and keep current with the medical literature, and discuss emerging issues with colleagues. Such discussions might occur through networks established by WPATH and other national/local organizations.

Responsibilities of Hormone-Prescribing Physicians

In general, clinicians who prescribe hormone therapy should engage in the following tasks:

1. Perform an initial evaluation that includes discussion of a patient's physical transition goals, health history, physical examination, risk assessment, and relevant laboratory tests.
2. Discuss with patients the expected effects of feminizing/masculinizing medications and the possible adverse health effects. These effects can include a reduction in fertility (Feldman & Safer, 2009; Hembree et al., 2009). Therefore, reproductive options should be discussed with patients before starting hormone therapy (see section IX).
3. Confirm that patients have the capacity to understand the risks and benefits of treatment and are capable of making an informed decision about medical care.
4. Provide ongoing medical monitoring, including regular physical and laboratory examination to monitor hormone effectiveness and side effects.
5. Communicate as needed with a patient's primary care provider, mental health professional, and surgeon.
6. If needed, provide patients with a brief written statement indicating that they are under medical supervision and care that includes feminizing/masculinizing hormone therapy. Particularly during the early phases of hormone treatment, a patient may wish to carry this statement at all times to help prevent difficulties with the police and other authorities.

Depending on the clinical situation for providing hormones (see below), some of these responsibilities are less relevant. Thus, the degree of counseling, physical examinations, and laboratory evaluations should be individualized to a patient's needs.

Clinical Situations for Hormone Therapy

There are circumstances in which clinicians may be called upon to provide hormones without necessarily initiating or maintaining long-term feminizing/masculinizing hormone therapy. By acknowledging these different clinical situations (see below, from least to highest level of complexity), it may be possible to involve clinicians in feminizing/masculinizing hormone therapy who might not otherwise feel able to offer this treatment.

1. Bridging

Whether prescribed by another clinician or obtained through other means (e.g., purchased over the Internet), patients may present for care already on hormone therapy. Clinicians can provide a limited (1–6 month) prescription for hormones while helping patients find a provider who can prescribe long-term hormone therapy. Providers should assess a patient's current regimen for safety and drug interactions and substitute safer medications or doses when indicated (Dahl et al., 2006; Feldman & Safer, 2009). If hormones were previously prescribed, medical records should be requested (with the patient's permission) to obtain the results of baseline examinations and laboratory tests and any adverse events. Hormone providers should also communicate with any mental health professional who is currently involved in a patient's care. If a patient has never had a psychosocial assessment as recommended by the SOC (see section VII), clinicians should refer the patient to a qualified mental health professional if appropriate and feasible (Feldman & Safer, 2009). Providers who prescribe bridging hormones need to work with patients to establish limits as to the duration of bridging therapy.

2. Hormone Therapy Following Gonad Removal

Hormone replacement with estrogen or testosterone is usually continued lifelong after an oophorectomy or orchiectomy, unless medical contraindications arise. Because hormone doses are often decreased after these surgeries (Basson, 2001; Levy, Crown, & Reid, 2003; Moore, Wisniewski, & Dobs, 2003) and only adjusted for age and comorbid health concerns, hormone management in this situation is quite similar to hormone replacement in any hypogonadal patient.

3. Hormone Maintenance Prior to Gonad Removal

Once patients have achieved maximal feminizing/masculinizing benefits from hormones (typically two or more years), they remain on a maintenance dose. The maintenance dose is then adjusted for changes in health conditions, aging, or other considerations such as lifestyle changes (Dahl et al., 2006). When a patient on maintenance hormones presents for care, the provider should assess the patient's current regimen for safety and drug interactions and substitute safer medications or doses when indicated. The patient should continue to be monitored by physical examinations and laboratory testing on a regular basis, as outlined in the literature (Feldman & Safer, 2009; Hembree et al., 2009). The dose and form of hormones should be revisited regularly with any changes in the patient's health status and available evidence on the potential long-term risks of hormones (See *Hormone Regimens*, below).

4. Initiating Hormonal Feminization/Masculinization

This clinical situation requires the greatest commitment in terms of provider time and expertise. Hormone therapy must be individualized based on a patient's goals, the risk/benefit ratio of medications, the presence of other medical conditions, and consideration of social and economic issues. Although a wide variety of hormone regimens have been published (Dahl et al., 2006; Hembree et al., 2009; Moore et al., 2003), there are no published reports of randomized clinical trials comparing safety and efficacy. Despite this variation, a reasonable framework for initial risk assessment and ongoing monitoring of hormone therapy can be constructed, based on the efficacy and safety evidence presented above.

Risk Assessment and Modification for Initiating Hormone Therapy

The initial evaluation for hormone therapy assesses a patient's clinical goals and risk factors for hormone-related adverse events. During the risk assessment, the patient and clinician should develop a plan for reducing risks wherever possible, either prior to initiating therapy or as part of ongoing harm reduction.

All assessments should include a thorough physical exam, including weight, height, and blood pressure. The need for breast, genital, and rectal exams, which are sensitive issues for most transsexual, transgender, and gender-nonconforming patients, should be based on individual risks and preventive health care needs (Feldman & Goldberg, 2006; Feldman, 2007).

Preventive Care

Hormone providers should address preventive health care with patients, particularly if a patient does not have a primary care provider. Depending on a patient's age and risk profile, there may be appropriate screening tests or exams for conditions affected by hormone therapy. Ideally, these screening tests should be carried out prior to the start of hormone therapy.

Risk Assessment and Modification for Feminizing Hormone Therapy (MtF)

There are no absolute contraindications to feminizing therapy per se, but absolute contraindications exist for the different feminizing agents, particularly estrogen. These include previous venous thrombotic events related to an underlying hypercoagulable condition, history of estrogen-sensitive neoplasm, and end-stage chronic liver disease (Gharib et al., 2005).

Other medical conditions, as noted in Table 2 and Appendix B, can be exacerbated by estrogen or androgen blockade, and therefore should be evaluated and reasonably well controlled prior to starting hormone therapy (Feldman & Safer, 2009; Hembree et al., 2009). Clinicians should particularly attend to tobacco use, as it is associated with increased risk of venous thrombosis, which is further increased with estrogen use. Consultation with a cardiologist may be advisable for patients with known cardio- or cerebrovascular disease.

Baseline laboratory values are important to both assess initial risk and evaluate possible future adverse events. Initial labs should be based on the risks of feminizing hormone therapy outlined in Table 2, as well as individual patient risk factors, including family history. Suggested initial lab panels have been published (Feldman & Safer, 2009; Hembree et al., 2009). These can be modified for patients or health care systems with limited resources, and in otherwise healthy patients.

Risk Assessment and Modification for Masculinizing Hormone Therapy (FtM)

Absolute contraindications to testosterone therapy include pregnancy, unstable coronary artery disease, and untreated polycythemia with a hematocrit of 55% or higher (Carnegie, 2004). Because the aromatization of testosterone to estrogen may increase risk in patients with a history of breast or other estrogen dependent cancers (Moore et al., 2003), consultation with an oncologist may be indicated prior to hormone use. Comorbid conditions likely to be exacerbated by testosterone use should be evaluated and treated, ideally prior to starting hormone therapy (Feldman & Safer, 2009; Hembree et al., 2009). Consultation with a cardiologist may be advisable for patients with known cardio- or cerebrovascular disease. (Dhejne et al., 2011).

An increased prevalence of polycystic ovarian syndrome (PCOS) has been noted among FtM patients even in the absence of testosterone use (Baba et al., 2007; Balen, Schachter, Montgomery, Reid, & Jacobs, 1993; Bosinski et al., 1997). While there is no evidence that PCOS is related to the development of a transsexual, transgender, or gender-nonconforming identity, PCOS is associated with increased risk of diabetes, cardiac disease, high blood pressure, and ovarian and endometrial cancers (Catrall & Healy, 2004). Signs and symptoms of PCOS should be evaluated prior to initiating testosterone therapy, as testosterone may affect many of these conditions. Testosterone can affect the developing fetus (*Physicians' Desk Reference*, 2010), and patients at risk of becoming pregnant require highly effective birth control.

Baseline laboratory values are important to both assess initial risk and evaluate possible future adverse events. Initial labs should be based on the risks of masculinizing hormone therapy outlined in Table 2, as well as individual patient risk factors, including family history. Suggested initial lab panels have been published (Feldman & Safer, 2009; Hembree et al., 2009). These can be modified for patients or health care systems with limited resources, and in otherwise healthy patients.

Clinical Monitoring During Hormone Therapy for Efficacy and Adverse Events

The purpose of clinical monitoring during hormone use is to assess the degree of feminization/masculinization and the possible presence of adverse effects of medication. However, as with the monitoring of any long-term medication, monitoring should take place in the context of comprehensive health care. Suggested clinical monitoring protocols have been published (Feldman & Safer, 2009; Hembree et al., 2009). Patients with comorbid medical conditions may need to be monitored more frequently. Healthy patients in geographically remote or resource-poor areas may be able to use alternative strategies, such as telehealth, or cooperation with local providers such as nurses and physician assistants. In the absence of other indications, health professionals may prioritize monitoring for those risks that are either likely to be increased by hormone therapy or possibly increased by hormone therapy but clinically serious in nature.

Efficacy and Risk Monitoring During Feminizing Hormone Therapy (MtF)

The best assessment of hormone efficacy is clinical response: Is a patient developing a feminized body while minimizing masculine characteristics, consistent with that patient's gender goals? In order to more rapidly predict the hormone dosages that will achieve clinical response, one can measure testosterone levels for suppression below the upper limit of the normal female range and estradiol levels within a premenopausal female range but well below supraphysiologic levels (Feldman & Safer, 2009; Hembree et al., 2009).

Monitoring for adverse events should include both clinical and laboratory evaluation. Follow-up should include careful assessment for signs of cardiovascular impairment and venous thromboembolism (VTE) through measurement of blood pressure, weight, and pulse; heart and lung exams; and examination of the extremities for peripheral edema, localized swelling, or pain (Feldman & Safer, 2009). Laboratory monitoring should be based on the risks of hormone therapy described above, a patient's individual comorbidities and risk factors, and the specific hormone regimen itself. Specific lab-monitoring protocols have been published (Feldman & Safer, 2009; Hembree et al., 2009).

Efficacy and Risk Monitoring During Masculinizing Hormone Therapy (FtM)

The best assessment of hormone efficacy is clinical response: Is a patient developing a masculinized body while minimizing feminine characteristics, consistent with that patient's gender goals? Clinicians can achieve a good clinical response with the least likelihood of adverse events by maintaining testosterone levels within the normal male range while avoiding supraphysiological

levels (Dahl et al., 2006; Hembree et al., 2009). For patients using intramuscular (IM) testosterone cypionate or enanthate, some clinicians check trough levels while others prefer midcycle levels (Dahl et al., 2006; Hembree et al., 2009; Tangpricha, Turner, Malabanan, & Holick, 2001; Tangpricha, Ducharme, Barber, & Chipkin, 2003).

Monitoring for adverse events should include both clinical and laboratory evaluation. Follow-up should include careful assessment for signs and symptoms of excessive weight gain, acne, uterine break-through bleeding, and cardiovascular impairment, as well as psychiatric symptoms in at-risk patients. Physical examinations should include measurement of blood pressure, weight, and pulse; and heart, lung, and skin exams (Feldman & Safer, 2009). Laboratory monitoring should be based on the risks of hormone therapy described above, a patient's individual comorbidities and risk factors, and the specific hormone regimen itself. Specific lab monitoring protocols have been published (Feldman & Safer, 2009; Hembree et al., 2009).

Hormone Regimens

To date, no controlled clinical trials of any feminizing/masculinizing hormone regimen have been conducted to evaluate safety or efficacy in producing physical transition. As a result, wide variation in doses and types of hormones have been published in the medical literature (Moore et al., 2003; Tangpricha et al., 2003; van Kesteren, Asscheman, Megens, & Gooren, 1997). In addition, access to particular medications may be limited by a patient's geographical location and/or social or economic situations. For these reasons, WPATH does not describe or endorse a particular feminizing/masculinizing hormone regimen. Rather, the medication classes and routes of administration used in most published regimens are broadly reviewed.

As outlined above, there are demonstrated safety differences in individual elements of various regimens. The Endocrine Society Guidelines (Hembree et al., 2009) and Feldman and Safer (2009) provide specific guidance regarding the types of hormones and suggested dosing to maintain levels within physiologic ranges for a patient's desired gender expression (based on goals of full feminization/masculinization). It is strongly recommend that hormone providers regularly review the literature for new information and use those medications that safely meet individual patient needs with available local resources.

Regimens for Feminizing Hormone Therapy (MtF)Estrogen

Use of oral estrogen, and specifically ethinyl estradiol, appears to increase the risk of VTE. Because of this safety concern, ethinyl estradiol is not recommended for feminizing hormone therapy. Transdermal estrogen is recommended for those patients with risks factors for VTE. The risk of adverse events increases with higher doses, particular doses resulting in supraphysiologic levels (Hembree et al., 2009). Patients with co-morbid conditions that can be affected by estrogen should avoid oral estrogen if possible and be started at lower levels. Some patients may not be able to safely use the levels of estrogen needed to get the desired results. This possibility needs to be discussed with patients well in advance of starting hormone therapy.

Androgen-reducing medications (“anti-androgens”)

A combination of estrogen and “anti-androgens” is the most commonly studied regimen for feminization. Androgen-reducing medications, from a variety of classes of drugs, have the effect of reducing either endogenous testosterone levels or testosterone activity, and thus diminishing masculine characteristics such as body hair. They minimize the dosage of estrogen needed to suppress testosterone, thereby reducing the risks associated with high-dose exogenous estrogen (Prior, Vigna, Watson, Diewold, & Robinow, 1986; Prior, Vigna, & Watson, 1989).

Common anti-androgens include the following:

- Spironolactone, an antihypertensive agent, directly inhibits testosterone secretion and androgen binding to the androgen receptor. Blood pressure and electrolytes need to be monitored because of the potential for hyperkalemia.
- Cyproterone acetate is a progestational compound with anti-androgenic properties. This medication is not approved in the United States because of concerns over potential hepatotoxicity, but it is widely used elsewhere (De Cuypere et al., 2005).
- GnRH agonists (e.g., goserelin, buserelin, triptorelin) are neurohormones that block the gonadotropin-releasing hormone receptor, thus blocking the release of follicle stimulating hormone and luteinizing hormone. This leads to highly effective gonadal blockade. However, these medications are expensive and only available as injectables or implants.
- 5-alpha reductase inhibitors (finasteride and dutasteride) block the conversion of testosterone to the more active agent, 5-alpha-dihydrotestosterone. These medications have beneficial effects on scalp hair loss, body hair growth, sebaceous glands, and skin consistency.

Cyproterone and spironolactone are the most commonly used anti-androgens and are likely the most cost-effective.

Progestins

With the exception of cyproterone, the inclusion of progestins in feminizing hormone therapy is controversial (Oriel, 2000). Because progestins play a role in mammary development on a cellular level, some clinicians believe that these agents are necessary for full breast development (Basson & Prior, 1998; Oriel, 2000). However, a clinical comparison of feminization regimens with and without progestins found that the addition of progestins neither enhanced breast growth nor lowered serum levels of free testosterone (Meyer et al., 1986). There are concerns regarding potential adverse effects of progestins, including depression, weight gain, and lipid changes (Meyer et al., 1986; Tangpricha et al., 2003). Progestins (especially medroxyprogesterone) are also suspected to increase breast cancer risk and cardiovascular risk in women (Rossouw et al., 2002). Micronized progesterone may be better tolerated and have a more favorable impact on the lipid profile than medroxyprogesterone does (de Lignières, 1999; Fitzpatrick, Pace, & Wiita, 2000).

Regimens for Masculinizing Hormone Therapy (FtM)

Testosterone

Testosterone generally can be given orally, transdermally, or parenterally (IM), although buccal and implantable preparations are also available. Oral testosterone undecanoate, available outside the United States, results in lower serum testosterone levels than nonoral preparations and has limited efficacy in suppressing menses (Feldman, 2005, April; Moore et al., 2003). Because intramuscular testosterone cypionate or enanthate are often administered every 2–4 weeks, some patients may notice cyclic variation in effects (e.g., fatigue and irritability at the end of the injection cycle, aggression or expansive mood at the beginning of the injection cycle), as well as more time outside the normal physiologic levels (Jockenhövel, 2004). This may be mitigated by using a lower but more frequent dosage schedule or by using a daily transdermal preparation (Dobs et al., 1999; Jockenhövel, 2004; Nieschlag et al., 2004). Intramuscular testosterone undecanoate (not currently available in the United States) maintains stable, physiologic testosterone levels over approximately 12 weeks and has been effective in both the setting of hypogonadism and in FtM individuals (Mueller, Kiesewetter, Binder, Beckmann, & Dittrich, 2007; Zitzmann, Saad, & Nieschlag, 2006). There is evidence that transdermal and intramuscular testosterone achieve similar masculinizing results, although the timeframe may be somewhat slower with transdermal preparations (Feldman, 2005, April). Especially as patients age, the goal is to use the lowest dose needed to maintain the desired clinical result, with appropriate precautions being made to maintain bone density.

Other agents

Progestins, most commonly medroxyprogesterone, can be used for a short period of time to assist with menstrual cessation early in hormone therapy. GnRH agonists can be used similarly, as well as for refractory uterine bleeding in patients without an underlying gynecological abnormality.

Bioidentical and Compounded Hormones

As discussion surrounding the use of bioidentical hormones in postmenopausal hormone replacement has heightened, interest has also increased in the use of similar compounds in feminizing/masculinizing hormone therapy. There is no evidence that custom compounded bioidentical hormones are safer or more effective than government agency-approved bioidentical hormones (Sood, Shuster, Smith, Vincent, & Jatoi, 2011). Therefore, it has been advised by the North American Menopause Society (2010) and others to assume that, whether the hormone is from a compounding pharmacy or not, if the active ingredients are similar, it should have a similar side-effect profile. WPATH concurs with this assessment.

IX

Reproductive Health

Many transgender, transsexual, and gender-nonconforming people will want to have children. Because feminizing/masculinizing hormone therapy limits fertility (Darney, 2008; Zhang, Gu, Wang, Cui, & Bremner, 1999), it is desirable for patients to make decisions concerning fertility before starting hormone therapy or undergoing surgery to remove/alter their reproductive organs. Cases are known of people who received hormone therapy and genital surgery and later regretted their inability to parent genetically related children (De Sutter, Kira, Verschoor, & Hotimsky, 2002).

Health care professionals—including mental health professionals recommending hormone therapy or surgery, hormone-prescribing physicians, and surgeons—should discuss reproductive options with patients prior to initiation of these medical treatments for gender dysphoria. These discussions should occur even if patients are not interested in these issues at the time of treatment, which may be more common for younger patients (De Sutter, 2009). Early discussions are desirable, but not always possible. If an individual has not had complete sex reassignment surgery, it may be possible to stop hormones long enough for natal hormones to recover, allowing

the production of mature gametes (Payer, Meyer, & Walker, 1979; Van den Broecke, Van der Elst, Liu, Hovatta, & Dhont, 2001).

Besides debate and opinion papers, very few research papers have been published on the reproductive health issues of individuals receiving different medical treatments for gender dysphoria. Another group who faces the need to preserve reproductive function in light of loss or damage to their gonads are people with malignancies that require removal of reproductive organs or use of damaging radiation or chemotherapy. Lessons learned from that group can be applied to people treated for gender dysphoria.

MtF patients, especially those who have not already reproduced, should be informed about sperm-preservation options and encouraged to consider banking their sperm prior to hormone therapy. In a study examining testes that were exposed to high-dose estrogen (Payer et al., 1979), findings suggest that stopping estrogen may allow the testes to recover. In an article reporting on the opinions of MtF individuals towards sperm freezing (De Sutter et al., 2002), the vast majority of 121 survey respondents felt that the availability of freezing sperm should be discussed and offered by the medical world. Sperm should be collected before hormone therapy or after stopping the therapy until the sperm count rises again. Cryopreservation should be discussed even if there is poor semen quality. In adults with azoospermia, a testicular biopsy with subsequent cryopreservation of biopsied material for sperm is possible, but may not be successful.

Reproductive options for FtM patients might include oocyte (egg) or embryo freezing. The frozen gametes and embryo could later be used with a surrogate woman to carry to pregnancy. Studies of women with polycystic ovarian disease suggest that the ovary can recover in part from the effects of high testosterone levels (Hunter & Sterrett, 2000). Stopping the testosterone briefly might allow for ovaries to recover enough to release eggs; success likely depends on the patient's age and duration of testosterone treatment. While not systematically studied, some FtM individuals are doing exactly that, and some have been able to become pregnant and deliver children (More, 1998).

Patients should be advised that these techniques are not available everywhere and can be very costly. Transsexual, transgender, and gender-nonconforming people should not be refused reproductive options for any reason.

A special group of individuals are prepubertal or pubertal adolescents who will never develop reproductive function in their natal sex due to blockers or cross-gender hormones. At this time there is no technique for preserving function from the gonads of these individuals.



Voice and Communication Therapy

Communication, both verbal and nonverbal, is an important aspect of human behavior and gender expression. Transsexual, transgender, and gender-nonconforming people might seek the assistance of a voice and communication specialist to develop vocal characteristics (e.g., pitch, intonation, resonance, speech rate, phrasing patterns) and non-verbal communication patterns (e.g., gestures, posture/movement, facial expressions) that facilitate comfort with their gender identity. Voice and communication therapy may help to alleviate gender dysphoria and be a positive and motivating step towards achieving one's goals for gender role expression.

Competency of Voice and Communication Specialists Working with Transsexual, Transgender, and Gender-Nonconforming Clients

Specialists may include speech-language pathologists, speech therapists, and speech-voice clinicians. In most countries the professional association for speech-language pathologists requires specific qualifications and credentials for membership. In some countries the government regulates practice through licensing, certification, or registration processes (American Speech-Language-Hearing Association, 2011; Canadian Association of Speech-Language Pathologists and Audiologists; Royal College of Speech Therapists, United Kingdom; Speech Pathology Australia).

The following are recommended minimum credentials for voice and communication specialists working with transsexual, transgender, and gender-nonconforming clients:

1. Specialized training and competence in the assessment and development of communication skills in transsexual, transgender, and gender-nonconforming clients.
2. A basic understanding of transgender health, including hormonal and surgical treatments for feminization/masculinization and trans-specific psychosocial issues as outlined in the SOC; and familiarity with basic sensitivity protocols such as the use of preferred gender pronoun and name (Canadian Association of Speech-Language Pathologists and Audiologists; Royal College of Speech Therapists, United Kingdom; Speech Pathology Australia).

3. Continuing education in the assessment and development of communication skills in transsexual, transgender, and gender-nonconforming clients. This may include attendance at professional meetings, workshops, or seminars; participation in research related to gender identity issues; independent study; or mentoring from an experienced, certified clinician.

Other professionals such as vocal coaches, theatre professionals, singing teachers, and movement experts may play a valuable adjunct role. Such professionals will ideally have experience working with, or be actively collaborating with, speech-language pathologists.

Assessment and Treatment Considerations

The overall purpose of voice and communication therapy is to help clients adapt their voice and communication in a way that is both safe and authentic, resulting in communication patterns that clients feel are congruent with their gender identity and that reflect their sense of self (Adler, Hirsch, & Mordaunt, 2006). It is essential that voice and communication specialists be sensitive to individual communication preferences. Communication—style, voice, choice of language, etc.—is personal. Individuals should not be counseled to adopt behaviors with which they are not comfortable or which do not feel authentic. Specialists can best serve their clients by taking the time to understand a person's gender concerns and goals for gender-role expression (American Speech-Language-Hearing Association, 2011; Canadian Association of Speech-Language Pathologists and Audiologists; Royal College of Speech Therapists, United Kingdom; Speech Pathology Australia).

Individuals may choose the communication behaviors that they wish to acquire in accordance with their gender identity. These decisions are also informed and supported by the knowledge of the voice and communication specialist and by the assessment data for a specific client (Hancock, Krissinger, & Owen, 2010). Assessment includes a client's self-evaluation and a specialist's evaluation of voice, resonance, articulation, spoken language, and non-verbal communication (Adler et al., 2006; Hancock et al., 2010).

Voice-and-communication treatment plans are developed by considering the available research evidence, the clinical knowledge and experience of the specialist, and the client's own goals and values (American Speech-Language-Hearing Association, 2011; Canadian Association of Speech-Language Pathologists and Audiologists; Royal College of Speech Therapists, United Kingdom; Speech Pathology Australia). Targets of treatment typically include pitch, intonation, loudness and stress patterns, voice quality, resonance, articulation, speech rate and phrasing, language, and nonverbal communication (Adler et al., 2006; Davies & Goldberg, 2006; de Bruin, Coerts, & Greven, 2000; Gelfer, 1999; McNeill, 2006; Oates & Dacakis, 1983). Treatment may involve individual and/or group sessions. The frequency and duration of treatment will vary according to a client's needs. Existing protocols for voice-and-communication treatment can be considered in

developing an individualized therapy plan (Carew, Dacakis, & Oates, 2007; Dacakis, 2000; Davies & Goldberg, 2006; Gelfer, 1999; McNeill, Wilson, Clark, & Deakin, 2008; Mount & Salmon, 1988).

Feminizing or masculinizing the voice involves non-habitual use of the voice production mechanism. Prevention measures are necessary to avoid the possibility of vocal misuse and long-term vocal damage. All voice and communication therapy services should therefore include a vocal health component (Adler et al., 2006).

Vocal Health Considerations After Voice Feminization Surgery

As noted in section XI, some transsexual, transgender, and gender-nonconforming people will undergo voice feminization surgery. (Voice deepening can be achieved through masculinizing hormone therapy, but feminizing hormones do not have an impact on the adult MtF voice.) There are varying degrees of satisfaction, safety, and long-term improvement in patients who have had such surgery. It is recommended that individuals undergoing voice feminization surgery also consult a voice and communication specialist to maximize the surgical outcome, help protect vocal health, and learn nonpitch related aspects of communication. Voice surgery procedures should include follow-up sessions with a voice and communication specialist who is licensed and/or credentialed by the board responsible for speech therapists/speech-language pathologists in that country (Kanagalingam et al., 2005; Neumann & Welzel, 2004).

XI

Surgery

Sex Reassignment Surgery Is Effective and Medically Necessary

Surgery – particularly genital surgery – is often the last and the most considered step in the treatment process for gender dysphoria. While many transsexual, transgender, and gender-nonconforming individuals find comfort with their gender identity, role, and expression without surgery, for many others surgery is essential and medically necessary to alleviate their gender dysphoria (Hage & Karim, 2000). For the latter group, relief from gender dysphoria cannot be achieved

without modification of their primary and/or secondary sex characteristics to establish greater congruence with their gender identity. Moreover, surgery can help patients feel more at ease in the presence of sex partners or in venues such as physicians' offices, swimming pools, or health clubs. In some settings, surgery might reduce risk of harm in the event of arrest or search by police or other authorities.

Follow-up studies have shown an undeniable beneficial effect of sex reassignment surgery on postoperative outcomes such as subjective well-being, cosmesis, and sexual function (De Cuypere et al., 2005; Gijs & Brewaeys, 2007; Klein & Gorzalka, 2009; Pfäfflin & Junge, 1998). Additional information on the outcomes of surgical treatments are summarized in Appendix D.

Ethical Questions Regarding Sex Reassignment Surgery

In ordinary surgical practice, pathological tissues are removed to restore disturbed functions, or alterations are made to body features to improve a patient's self image. Some people, including some health professionals, object on ethical grounds to surgery as a treatment for gender dysphoria, because these conditions are thought not to apply.

It is important that health professionals caring for patients with gender dysphoria feel comfortable about altering anatomically normal structures. In order to understand how surgery can alleviate the psychological discomfort and distress of individuals with gender dysphoria, professionals need to listen to these patients discuss their symptoms, dilemmas, and life histories. The resistance against performing surgery on the ethical basis of "above all do no harm" should be respected, discussed, and met with the opportunity to learn from patients themselves about the psychological distress of having gender dysphoria and the potential for harm caused by denying access to appropriate treatments.

Genital and breast/chest surgical treatments for gender dysphoria are not merely another set of elective procedures. Typical elective procedures involve only a private mutually consenting contract between a patient and a surgeon. Genital and breast/chest surgeries as medically necessary treatments for gender dysphoria are to be undertaken only after assessment of the patient by qualified mental health professionals, as outlined in section VII of the SOC. These surgeries may be performed once there is written documentation that this assessment has occurred and that the person has met the criteria for a specific surgical treatment. By following this procedure, mental health professionals, surgeons, and patients share responsibility for the decision to make irreversible changes to the body.

It is unethical to deny availability or eligibility for sex reassignment surgeries solely on the basis of blood seropositivity for blood-borne infections such as HIV or hepatitis C or B.

Relationship of Surgeons with Mental Health Professionals, Hormone-Prescribing Physicians (if Applicable), and Patients (Informed Consent)

The role of a surgeon in the treatment of gender dysphoria is not that of a mere technician. Rather, conscientious surgeons will have insight into each patient's history and the rationale that led to the referral for surgery. To that end, surgeons must talk at length with their patients and have close working relationships with other health professionals who have been actively involved in their clinical care.

Consultation is readily accomplished when a surgeon practices as part of an interdisciplinary health care team. In the absence of this, a surgeon must be confident that the referring mental health professional(s), and if applicable the physician who prescribes hormones, is/are competent in the assessment and treatment of gender dysphoria, because the surgeon is relying heavily on his/her/their expertise.

Once a surgeon is satisfied that the criteria for specific surgeries have been met (as outlined below), surgical treatment should be considered and a preoperative surgical consultation should take place. During this consultation, the procedure and postoperative course should be extensively discussed with the patient. Surgeons are responsible for discussing all of the following with patients seeking surgical treatments for gender dysphoria:

- The different surgical techniques available (with referral to colleagues who provide alternative options);
- The advantages and disadvantages of each technique;
- The limitations of a procedure to achieve “ideal” results; surgeons should provide a full range of before-and-after photographs of their own patients, including both successful and unsuccessful outcomes;
- The inherent risks and possible complications of the various techniques; surgeons should inform patients of their own complication rates with each procedure.

These discussions are the core of the informed consent process, which is both an ethical and legal requirement for any surgical procedure. Ensuring that patients have a realistic expectation of outcomes is important in achieving a result that will alleviate their gender dysphoria.

All of this information should be provided to patients in writing, in a language in which they are fluent, and in graphic illustrations. Patients should receive the information in advance (possibly

via the Internet) and be given ample time to review it carefully. The elements of informed consent should always be discussed face-to-face prior to the surgical intervention. Questions can then be answered and written informed consent can be provided by the patient. Because these surgeries are irreversible, care should be taken to ensure that patients have sufficient time to absorb information fully before they are asked to provide informed consent. A minimum of 24 hours is suggested.

Surgeons should provide immediate aftercare and consultation with other physicians serving the patient in the future. Patients should work with their surgeon to develop an adequate aftercare plan for the surgery.

Overview of Surgical Procedures for the Treatment of Patients with Gender Dysphoria

For the Male-to-Female (MtF) Patient, Surgical Procedures May Include the Following:

1. Breast/chest surgery: augmentation mammoplasty (implants/lipofilling);
2. Genital surgery: penectomy, orchiectomy, vaginoplasty, clitoroplasty, vulvoplasty;
3. Nongenital, nonbreast surgical interventions: facial feminization surgery, liposuction, lipofilling, voice surgery, thyroid cartilage reduction, gluteal augmentation (implants/lipofilling), hair reconstruction, and various aesthetic procedures.

For the Female-to-Male (FtM) Patient, Surgical Procedures May Include the Following:

1. Breast/chest surgery: subcutaneous mastectomy, creation of a male chest;
2. Genital surgery: hysterectomy/salpingo-oophorectomy, reconstruction of the fixed part of the urethra, which can be combined with a metoidioplasty or with a phalloplasty (employing a pedicled or free vascularized flap), vaginectomy, scrotoplasty, and implantation of erection and/or testicular prostheses;
3. Nongenital, nonbreast surgical interventions: voice surgery (rare), liposuction, lipofilling, pectoral implants, and various aesthetic procedures.

Reconstructive Versus Aesthetic Surgery

The question of whether sex reassignment surgery should be considered “aesthetic” surgery or “reconstructive” surgery is pertinent not only from a philosophical point of view, but also from a financial point of view. Aesthetic or cosmetic surgery is mostly regarded as not medically necessary and therefore is typically paid for entirely by the patient. In contrast, reconstructive procedures are considered medically necessary—with unquestionable therapeutic results—and thus paid for partially or entirely by national health systems or insurance companies.

Unfortunately, in the field of plastic and reconstructive surgery (both in general and specifically for gender-related surgeries), there is no clear distinction between what is purely reconstructive and what is purely cosmetic. Most plastic surgery procedures actually are a mixture of both reconstructive and cosmetic components.

While most professionals agree that genital surgery and mastectomy cannot be considered purely cosmetic, opinions diverge as to what degree other surgical procedures (e.g., breast augmentation, facial feminization surgery) can be considered purely reconstructive. Although it may be much easier to see a phalloplasty or a vaginoplasty as an intervention to end lifelong suffering, for certain patients an intervention like a reduction rhinoplasty can have a radical and permanent effect on their quality of life, and therefore is much more medically necessary than for somebody without gender dysphoria.

Criteria for Surgeries

As for all of the *SOC*, the criteria for initiation of surgical treatments for gender dysphoria were developed to promote optimal patient care. While the *SOC* allow for an individualized approach to best meet a patient's health care needs, a criterion for all breast/chest and genital surgeries is documentation of persistent gender dysphoria by a qualified mental health professional. For some surgeries, additional criteria include preparation and treatment consisting of feminizing/masculinizing hormone therapy and one year of continuous living in a gender role that is congruent with one's gender identity.

These criteria are outlined below. Based on the available evidence and expert clinical consensus, different recommendations are made for different surgeries.

The *SOC* do not specify an order in which different surgeries should occur. The number and sequence of surgical procedures may vary from patient to patient, according to their clinical needs.

Criteria for Breast/Chest Surgery (One Referral)

Criteria for mastectomy and creation of a male chest in FtM patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC for children and adolescents);
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Hormone therapy is not a prerequisite.

Criteria for breast augmentation (implants/lipofilling) in MtF patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC for children and adolescents);
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Although not an explicit criterion, it is recommended that MtF patients undergo feminizing hormone therapy (minimum 12 months) prior to breast augmentation surgery. The purpose is to maximize breast growth in order to obtain better surgical (aesthetic) results.

Criteria for Genital Surgery (Two Referrals)

The criteria for genital surgery are specific to the type of surgery being requested.

Criteria for hysterectomy and salpingo-oophorectomy in FtM patients and for orchiectomy in MtF patients:

1. Persistent, well-documented gender dysphoria;

2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country;
4. If significant medical or mental health concerns are present, they must be well controlled.
5. 12 continuous months of hormone therapy as appropriate to the patient's gender goals (unless hormones are not clinically indicated for the individual).

The aim of hormone therapy prior to gonadectomy is primarily to introduce a period of reversible estrogen or testosterone suppression, before the patient undergoes irreversible surgical intervention.

These criteria do not apply to patients who are having these procedures for medical indications other than gender dysphoria.

Criteria for metoidioplasty or phalloplasty in FtM patients and for vaginoplasty in MtF patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country;
4. If significant medical or mental health concerns are present, they must be well controlled;
5. 12 continuous months of hormone therapy as appropriate to the patient's gender goals (unless hormones are not clinically indicated for the individual).
6. 12 continuous months of living in a gender role that is congruent with their gender identity.

Although not an explicit criterion, it is recommended that these patients also have regular visits with a mental health or other medical professional.

Rationale for a preoperative, 12-month experience of living in an identity-congruent gender role:

The criterion noted above for some types of genital surgeries—i.e., that patients engage in 12 continuous months of living in a gender role that is congruent with their gender identity—is based on expert clinical consensus that this experience provides ample opportunity for patients to experience and socially adjust in their desired gender role, before undergoing irreversible surgery. As noted in section VII, the social aspects of changing one's gender role are usually challenging—

often more so than the physical aspects. Changing gender role can have profound personal and social consequences, and the decision to do so should include an awareness of what the familial, interpersonal, educational, vocational, economic, and legal challenges are likely to be, so that people can function successfully in their gender role. Support from a qualified mental health professional and from peers can be invaluable in ensuring a successful gender role adaptation (Bockting, 2008).

The duration of 12 months allows for a range of different life experiences and events that may occur throughout the year (e.g., family events, holidays, vacations, season-specific work or school experiences). During this time, patients should present consistently, on a day-to-day basis and across all settings of life, in their desired gender role. This includes coming out to partners, family, friends, and community members (e.g., at school, work, other settings).

Health professionals should clearly document a patient's experience in the gender role in the medical chart, including the start date of living full time for those who are preparing for genital surgery. In some situations, if needed, health professionals may request verification that this criterion has been fulfilled: They may communicate with individuals who have related to the patient in an identity-congruent gender role, or request documentation of a legal name and/or gender marker change, if applicable.

Surgery for People with Psychotic Conditions and Other Serious Mental Illnesses

When patients with gender dysphoria are also diagnosed with severe psychiatric disorders and impaired reality testing (e.g., psychotic episodes, bipolar disorder, dissociative identity disorder, borderline personality disorder), an effort must be made to improve these conditions with psychotropic medications and/or psychotherapy before surgery is contemplated. (Dhejne et al., 2011). Reevaluation by a mental health professional qualified to assess and manage psychotic conditions should be conducted prior to surgery, describing the patient's mental status and readiness for surgery. It is preferable that this mental health professional be familiar with the patient. No surgery should be performed while a patient is actively psychotic (De Cuypere & Vercruysse, 2009).

Competency of Surgeons Performing Breast/Chest or Genital Surgery

Physicians who perform surgical treatments for gender dysphoria should be urologists, gynecologists, plastic surgeons, or general surgeons, and board-certified as such by the relevant national

and/or regional association. Surgeons should have specialized competence in genital reconstructive techniques as indicated by documented supervised training with a more experienced surgeon. Even experienced surgeons must be willing to have their surgical skills reviewed by their peers. An official audit of surgical outcomes and publication of these results would be greatly reassuring to both referring health professionals and patients. Surgeons should regularly attend professional meetings where new techniques are presented. The internet is often effectively used by patients to share information on their experience with surgeons and their teams.

Ideally, surgeons should be knowledgeable about more than one surgical technique for genital reconstruction so that they, in consultation with patients, can choose the ideal technique for each individual. Alternatively, if a surgeon is skilled in a single technique and this procedure is either not suitable for or desired by a patient, the surgeon should inform the patient about other procedures and offer referral to another appropriately skilled surgeon.

Breast/Chest Surgery Techniques and Complications

Although breast/chest appearance is an important secondary sex characteristic, breast presence or size is not involved in the legal definitions of sex and gender and is not necessary for reproduction. The performance of breast/chest operations for treatment of gender dysphoria should be considered with the same care as beginning hormone therapy, as both produce relatively irreversible changes to the body.

For the MtF patient, a breast augmentation (sometimes called “chest reconstruction”) is not different from the procedure in a natal female patient. It is usually performed through implantation of breast prostheses and occasionally with the lipofilling technique. Infections and capsular fibrosis are rare complications of augmentation mammoplasty in MtF patients (Kanhai, Hage, Karim, & Mulder, 1999).

For the FtM patient, a mastectomy or “male chest contouring” procedure is available. For many FtM patients, this is the only surgery undertaken. When the amount of breast tissue removed requires skin removal, a scar will result and the patient should be so informed. Complications of subcutaneous mastectomy can include nipple necrosis, contour irregularities, and unsightly scarring (Monstrey et al., 2008).

Genital Surgery Techniques and Complications

Genital surgical procedures for the MtF patient may include orchiectomy, penectomy, vaginoplasty, clitoroplasty, and labiaplasty. Techniques include penile skin inversion, pedicled colosigmoid

transplant, and free skin grafts to line the neovagina. Sexual sensation is an important objective in vaginoplasty, along with creation of a functional vagina and acceptable cosmesis.

Surgical complications of MtF genital surgery may include complete or partial necrosis of the vagina and labia, fistulas from the bladder or bowel into the vagina, stenosis of the urethra, and vaginas that are either too short or too small for coitus. While the surgical techniques for creating a neovagina are functionally and aesthetically excellent, anorgasmia following the procedure has been reported, and a second stage labiaplasty may be needed for cosmesis (Klein & Gorzalka, 2009; Lawrence, 2006).

Genital surgical procedures for FtM patients may include hysterectomy, salpingo-oophorectomy, vaginectomy, metoidioplasty, scrotoplasty, urethroplasty, placement of testicular prostheses, and phalloplasty. For patients without former abdominal surgery, the laparoscopic technique for hysterectomy and salpingo-oophorectomy is recommended to avoid a lower-abdominal scar. Vaginal access may be difficult as most patients are nulliparous and have often not experienced penetrative intercourse. Current operative techniques for phalloplasty are varied. The choice of techniques may be restricted by anatomical or surgical considerations and by a client's financial considerations. If the objectives of phalloplasty are a neophallus of good appearance, standing micturition, sexual sensation, and/or coital ability, patients should be clearly informed that there are several separate stages of surgery and frequent technical difficulties, which may require additional operations. Even metoidioplasty, which in theory is a one-stage procedure for construction of a microphallus, often requires more than one operation. The objective of standing micturition with this technique can not always be ensured (Monstrey et al., 2009).

Complications of phalloplasty in FtMs may include frequent urinary tract stenoses and fistulas, and occasionally necrosis of the neophallus. Metoidioplasty results in a micropenis, without the capacity for standing urination. Phalloplasty, using a pedicled or a free vascularized flap, is a lengthy, multi-stage procedure with significant morbidity that includes frequent urinary complications and unavoidable donor site scarring. For this reason, many FtM patients never undergo genital surgery other than hysterectomy and salpingo-oophorectomy (Hage & De Graaf, 1993).

Even patients who develop severe surgical complications seldom regret having undergone surgery. The importance of surgery can be appreciated by the repeated finding that quality of surgical results is one of the best predictors of the overall outcome of sex reassignment (Lawrence, 2006).

Other Surgeries

Other surgeries for assisting in body feminization include reduction thyroid chondroplasty (reduction of the Adam's apple), voice modification surgery, suction-assisted lipoplasty (contour

modeling) of the waist, rhinoplasty (nose correction), facial bone reduction, face-lift, and blepharoplasty (rejuvenation of the eyelid). Other surgeries for assisting in body masculinization include liposuction, lipofilling, and pectoral implants. Voice surgery to obtain a deeper voice is rare but may be recommended in some cases, such as when hormone therapy has been ineffective.

Although these surgeries do not require referral by mental health professionals, such professionals can play an important role in assisting clients in making a fully informed decision about the timing and implications of such procedures in the context of the social transition.

Although most of these procedures are generally labeled “purely aesthetic,” these same operations in an individual with severe gender dysphoria can be considered medically necessary, depending on the unique clinical situation of a given patient’s condition and life situation. This ambiguity reflects reality in clinical situations, and allows for individual decisions as to the need and desirability of these procedures.

XII

Postoperative Care and Follow-Up

Long-term postoperative care and follow-up after surgical treatments for gender dysphoria are associated with good surgical and psychosocial outcomes (Monstrey et al., 2009). Follow-up is important to a patient’s subsequent physical and mental health and to a surgeon’s knowledge about the benefits and limitations of surgery. Surgeons who operate on patients coming from long distances should include personal follow-up in their care plan and attempt to ensure affordable local long-term aftercare in their patients’ geographic region.

Postoperative patients may sometimes exclude themselves from follow-up by specialty providers, including the hormone-prescribing physician (for patients receiving hormones), not recognizing that these providers are often best able to prevent, diagnose, and treat medical conditions that are unique to hormonally and surgically treated patients. The need for follow-up equally extends to mental health professionals, who may have spent a longer period of time with the patient than any other professional and therefore are in an excellent position to assist in any postoperative adjustment difficulties. Health professionals should stress the importance of postoperative follow-up care with their patients and offer continuity of care.

Postoperative patients should undergo regular medical screening according to recommended guidelines for their age. This is discussed more in the next section.

XIII

Lifelong Preventive and Primary Care

Transsexual, transgender, and gender-nonconforming people need health care throughout their lives. For example, to avoid the negative secondary effects of having a gonadectomy at a relatively young age and/or receiving long-term, high-dose hormone therapy, patients need thorough medical care by providers experienced in primary care and transgender health. If one provider is not able to provide all services, ongoing communication among providers is essential.

Primary care and health maintenance issues should be addressed before, during, and after any possible changes in gender role and medical interventions to alleviate gender dysphoria. While hormone providers and surgeons play important roles in preventive care, every transsexual, transgender, and gender-nonconforming person should partner with a primary care provider for overall health care needs (Feldman, 2007).

General Preventive Health Care

Screening guidelines developed for the general population are appropriate for organ systems that are unlikely to be affected by feminizing/masculinizing hormone therapy. However, in areas such as cardiovascular risk factors, osteoporosis, and some cancers (breast, cervical, ovarian, uterine, and prostate), such general guidelines may either over- or underestimate the cost-effectiveness of screening individuals who are receiving hormone therapy.

Several resources provide detailed protocols for the primary care of patients undergoing feminizing/masculinizing hormone therapy, including therapy that is provided after sex reassignment surgeries (Center of Excellence for Transgender Health, UCSF, 2011; Feldman & Goldberg, 2006; Feldman, 2007; Gorton, Buth, & Spade, 2005). Clinicians should consult their national evidence-based guidelines and discuss screening with their patients in light of the effects of hormone therapy on their baseline risk.

Cancer Screening

Cancer screening of organ systems that are associated with sex can present particular medical and psychosocial challenges for transsexual, transgender, and gender-nonconforming patients and their health care providers. In the absence of large-scale prospective studies, providers are unlikely to have enough evidence to determine the appropriate type and frequency of cancer screenings for this population. Over-screening results in higher health care costs, high false positive rates, and often unnecessary exposure to radiation and/or diagnostic interventions such as biopsies. Under-screening results in diagnostic delay for potentially treatable cancers. Patients may find cancer screening gender affirming (such as mammograms for MtF patients) or both physically and emotionally painful (such as Pap smears offer continuity of care for FtM patients).

Urogenital Care

Gynecologic care may be necessary for transsexual, transgender, and gender-nonconforming people of both sexes. For FtM patients, such care is needed predominantly for individuals who have not had genital surgery. For MtF patients, such care is needed after genital surgery. While many surgeons counsel patients regarding postoperative urogenital care, primary care clinicians and gynecologists should also be familiar with the special genital concerns of this population.

All MtF patients should receive counseling regarding genital hygiene, sexuality, and prevention of sexually transmitted infections; those who have had genital surgery should also be counseled on the need for regular vaginal dilation or penetrative intercourse in order to maintain vaginal depth and width (van Trotsenburg, 2009). Due to the anatomy of the male pelvis, the axis and the dimensions of the neovagina differ substantially from those of a biologic vagina. This anatomic difference can affect intercourse if not understood by MtF patients and their partners (van Trotsenburg, 2009).

Lower urinary tract infections occur frequently in MtF patients who have had surgery because of the reconstructive requirements of the shortened urethra. In addition, these patients may suffer from functional disorders of the lower urinary tract; such disorders may be caused by damage of the autonomous nerve supply of the bladder floor during dissection between the rectum and the bladder, and by a change of the position of the bladder itself. A dysfunctional bladder (e.g., overactive bladder, stress or urge urinary incontinence) may occur after sex reassignment surgery (Hoebeker et al., 2005; Kuhn, Hildebrand, & Birkhauser, 2007).

Most FtM patients do not undergo vaginectomy (colpectomy). For patients who take masculinizing hormones, despite considerable conversion of testosterone to estrogens, atrophic changes of the vaginal lining can be observed regularly and may lead to pruritus or burning. Examination can be

both physically and emotionally painful, but lack of treatment can seriously aggravate the situation. Gynecologists treating the genital complaints of FtM patients should be aware of the sensitivity that patients with a male gender identity and masculine gender expression might have around having genitals typically associated with the female sex.

XIV

Applicability of the *Standards of Care* to People Living in Institutional Environments

The SOC in their entirety apply to all transsexual, transgender, and gender-nonconforming people, irrespective of their housing situation. People should not be discriminated against in their access to appropriate health care based on where they live, including institutional environments such as prisons or long-/intermediate-term health care facilities (Brown, 2009). Health care for transsexual, transgender, and gender-nonconforming people living in an institutional environment should mirror that which would be available to them if they were living in a non-institutional setting within the same community.

All elements of assessment and treatment as described in the SOC can be provided to people living in institutions (Brown, 2009). Access to these medically necessary treatments should not be denied on the basis of institutionalization or housing arrangements. If the in-house expertise of health professionals in the direct or indirect employ of the institution does not exist to assess and/or treat people with gender dysphoria, it is appropriate to obtain outside consultation from professionals who are knowledgeable about this specialized area of health care.

People with gender dysphoria in institutions may also have coexisting mental health conditions (Cole et al., 1997). These conditions should be evaluated and treated appropriately.

People who enter an institution on an appropriate regimen of hormone therapy should be continued on the same, or similar, therapies and monitored according to the SOC. A “freeze frame” approach is not considered appropriate care in most situations (*Kosilek v. Massachusetts Department of Corrections/Maloney*, C.A. No. 92–12820-MLW, 2002). People with gender dysphoria who are deemed appropriate for hormone therapy (following the SOC) should be started on such therapy. The consequences of abrupt withdrawal of hormones or lack of initiation of hormone therapy when medically necessary include a high likelihood of negative outcomes such as surgical self-treatment by autocastration, depressed mood, dysphoria, and/or suicidality (Brown, 2010).

Reasonable accommodations to the institutional environment can be made in the delivery of care consistent with the SOC, if such accommodations do not jeopardize the delivery of medically necessary care to people with gender dysphoria. An example of a reasonable accommodation is the use of injectable hormones, if not medically contraindicated, in an environment where diversion of oral preparations is highly likely (Brown, 2009). Denial of needed changes in gender role or access to treatments, including sex reassignment surgery, on the basis of residence in an institution are not reasonable accommodations under the SOC (Brown, 2010).

Housing and shower/bathroom facilities for transsexual, transgender, and gender-nonconforming people living in institutions should take into account their gender identity and role, physical status, dignity, and personal safety. Placement in a single-sex housing unit, ward, or pod on the sole basis of the appearance of the external genitalia may not be appropriate and may place the individual at risk for victimization (Brown, 2009).

Institutions where transsexual, transgender, and gender-nonconforming people reside and receive health care should monitor for a tolerant and positive climate to ensure that residents are not under attack by staff or other residents.

XV

Applicability of the *Standards of Care* to People With Disorders of Sex Development

Terminology

The term *disorder of sex development* (DSD) refers to a somatic condition of atypical development of the reproductive tract (Hughes, Houk, Ahmed, Lee, & LWPES/ESPE Consensus Group, 2006). DSDs include the condition that used to be called *intersexuality*. Although the terminology was changed to DSD during an international consensus conference in 2005 (Hughes et al., 2006), disagreement about language use remains. Some people object strongly to the “disorder” label, preferring instead to view these congenital conditions as a matter of diversity (Diamond, 2009) and to continue using the terms *intersex* or *intersexuality*. In the SOC, WPATH uses the term DSD in an objective and value-free manner, with the goal of ensuring that health professionals recognize this medical term and use it to access relevant literature as the field progresses. WPATH remains

open to new terminology that will further illuminate the experience of members of this diverse population and lead to improvements in health care access and delivery.

Rationale for Addition to the SOC

Previously, individuals with a DSD who also met the *DSM-IV-TR*'s behavioral criteria for Gender Identity Disorder (American Psychiatric Association, 2000) were excluded from that general diagnosis. Instead, they were categorized as having a "Gender Identity Disorder - Not Otherwise Specified." They were also excluded from the WPATH *Standards of Care*.

The current proposal for *DSM-5* (www.dsm5.org) is to replace the term *gender identity disorder* with *gender dysphoria*. Moreover, the proposed changes to the *DSM* consider gender dysphoric people with a DSD to have a subtype of gender dysphoria. This proposed categorization—which explicitly differentiates between gender dysphoric individuals with and without a DSD—is justified: In people with a DSD, gender dysphoria differs in its phenomenological presentation, epidemiology, life trajectories, and etiology (Meyer-Bahlburg, 2009).

Adults with a DSD and gender dysphoria have increasingly come to the attention of health professionals. Accordingly, a brief discussion of their care is included in this version of the SOC.

Health History Considerations

Health professionals assisting patients with both a DSD and gender dysphoria need to be aware that the medical context in which such patients have grown up is typically very different from that of people without a DSD.

Some people are recognized as having a DSD through the observation of gender-atypical genitals at birth. (Increasingly this observation is made during the prenatal period by way of imaging procedures such as ultrasound.) These infants then undergo extensive medical diagnostic procedures. After consultation among the family and health professionals—during which the specific diagnosis, physical and hormonal findings, and feedback from long-term outcome studies (Cohen-Kettenis, 2005; Dessens, Slijper, & Drop, 2005; Jurgensen, Hiort, Holterhus, & Thyen, 2007; Mazur, 2005; Meyer-Bahlburg, 2005; Stikkelbroeck et al., 2003; Wisniewski, Migeon, Malouf, & Gearhart, 2004) are considered—the newborn is assigned a sex, either male or female.

Other individuals with a DSD come to the attention of health professionals around the age of puberty through the observation of atypical development of secondary sex characteristics. This observation also leads to a specific medical evaluation.

The type of DSD and severity of the condition has significant implications for decisions about a patient's initial sex assignment, subsequent genital surgery, and other medical and psychosocial care (Meyer-Bahlburg, 2009). For instance, the degree of prenatal androgen exposure in individuals with a DSD has been correlated with the degree of masculinization of gender-related *behavior* (that is, *gender role and expression*); however, the correlation is only moderate, and considerable behavioral variability remains unaccounted for by prenatal androgen exposure (Jurgensen et al., 2007; Meyer-Bahlburg, Dolezal, Baker, Ehrhardt, & New, 2006). Notably, a similar correlation of prenatal hormone exposure with gender *identity* has not been demonstrated (e.g., Meyer-Bahlburg et al., 2004). This is underlined by the fact that people with the same (core) gender identity can vary widely in the degree of masculinization of their gender-related behavior.

Assessment and Treatment of Gender Dysphoria in People with Disorders of Sex Development

Very rarely are individuals with a DSD identified as having gender dysphoria *before* a DSD diagnosis has been made. Even so, a DSD diagnosis is typically apparent with an appropriate history and basic physical exam—both of which are part of a medical evaluation for the appropriateness of hormone therapy or surgical interventions for gender dysphoria. Mental health professionals should ask their clients presenting with gender dysphoria to have a physical exam, particularly if they are not currently seeing a primary care (or other health care) provider.

Most people with a DSD who are born with genital ambiguity do not develop gender dysphoria (e.g., Meyer-Bahlburg, Dolezal, et al., 2004; Wisniewski et al., 2004). However, some people with a DSD will develop chronic gender dysphoria and even undergo a change in their birth-assigned sex and/or their gender role (Meyer-Bahlburg, 2005; Wilson, 1999; Zucker, 1999). If there are persistent and strong indications that gender dysphoria is present, a comprehensive evaluation by clinicians skilled in the assessment and treatment of gender dysphoria is essential, irrespective of the patient's age. Detailed recommendations have been published for conducting such an assessment and for making treatment decisions to address gender dysphoria in the context of a DSD (Meyer-Bahlburg, 2011). Only after thorough assessment should steps be taken in the direction of changing a patient's birth-assigned sex or gender role.

Clinicians assisting these patients with treatment options to alleviate gender dysphoria may profit from the insights gained from providing care to patients without a DSD (Cohen-Kettenis, 2010).

However, certain criteria for treatment (e.g., age, duration of experience with living in the desired gender role) are usually not routinely applied to people with a DSD; rather, the criteria are interpreted in light of a patient's specific situation (Meyer-Bahlburg, 2011). In the context of a DSD, changes in birth-assigned sex and gender role have been made at any age between early elementary-school age and middle adulthood. Even genital surgery may be performed much earlier in these patients than in gender dysphoric individuals without a DSD if the surgery is well justified by the diagnosis, by the evidence-based gender-identity prognosis for the given syndrome and syndrome severity, and by the patient's wishes.

One reason for these treatment differences is that genital surgery in individuals with a DSD is quite common in infancy and adolescence. Infertility may already be present due to either early gonadal failure or to gonadectomy because of a malignancy risk. Even so, it is advisable for patients with a DSD to undergo a full social transition to another gender role only if there is a long-standing history of gender-atypical behavior, and if gender dysphoria and/or the desire to change one's gender role has been strong and persistent for a considerable period of time. Six months is the time period of full symptom expression required for the application of the gender dysphoria diagnosis proposed for *DSM-5* (Meyer-Bahlburg, 2011).

Additional Resources

The gender-relevant medical histories of people with a DSD are often complex. Their histories may include a great variety of inborn genetic, endocrine, and somatic atypicalities, as well as various hormonal, surgical, and other medical treatments. For this reason, many additional issues need to be considered in the psychosocial and medical care of such patients, regardless of the presence of gender dysphoria. Consideration of these issues is beyond what can be covered in the SOC. The interested reader is referred to existing publications (e.g., Cohen-Kettenis & Pfäfflin, 2003; Meyer-Bahlburg, 2002, 2008). Some families and patients also find it useful to consult or work with community support groups.

There is a very substantial medical literature on the medical management of patients with a DSD. Much of this literature has been produced by high-level specialists in pediatric endocrinology and urology, with input from specialized mental health professionals, especially in the area of gender. Recent international consensus conferences have addressed evidence-based care guidelines (including issues of gender and of genital surgery) for DSD in general (Hughes et al., 2006) and specifically for Congenital Adrenal Hyperplasia (Joint LWPES/ESPE CAH Working Group et al., 2002; Speiser et al., 2010). Others have addressed the research needs for DSD in general (Meyer-Bahlburg & Blizzard, 2004) and for selected syndromes such as 46,XXY (Simpson et al., 2003).



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The Standards of Care
VERSION 7

APPENDIX A

GLOSSARY

Terminology in the area of health care for transsexual, transgender, and gender-nonconforming people is rapidly evolving; new terms are being introduced, and the definitions of existing terms are changing. Thus, there is often misunderstanding, debate, or disagreement about language in this field. Terms that may be unfamiliar or that have specific meanings in the SOC are defined below for the purpose of this document only. Others may adopt these definitions, but WPATH acknowledges that these terms may be defined differently in different cultures, communities, and contexts.

WPATH also acknowledges that many terms used in relation to this population are not ideal. For example, the terms *transsexual* and *transvestite*—and, some would argue, the more recent term *transgender*—have been applied to people in an objectifying fashion. Yet such terms have been more or less adopted by many people who are making their best effort to make themselves understood. By continuing to use these terms, WPATH intends only to ensure that concepts and processes are comprehensible, in order to facilitate the delivery of quality health care to transsexual, transgender, and gender-nonconforming people. WPATH remains open to new terminology that will further illuminate the experience of members of this diverse population and lead to improvements in health care access and delivery.

Bioidentical hormones: Hormones that are *structurally* identical to those found in the human body (ACOG Committee of Gynecologic Practice, 2005). The hormones used in bioidentical hormone therapy (BHT) are generally derived from plant sources and are structurally similar to endogenous human hormones, but they need to be commercially processed to become bioidentical.

Bioidentical compounded hormone therapy (BCHT): Use of hormones that are prepared, mixed, assembled, packaged, or labeled as a drug by a pharmacist and custom-made for a patient according to a physician's specifications. Government drug agency approval is not possible for each compounded product made for an individual consumer.

Cross-dressing (transvestism): Wearing clothing and adopting a gender role presentation that, in a given culture, is more typical of the other sex.

Disorders of sex development (DSD): Congenital conditions in which the development of chromosomal, gonadal, or anatomic sex is atypical. Some people strongly object to the “disorder” label and instead view these conditions as a matter of diversity (Diamond, 2009), preferring the terms *intersex* and *intersexuality*.

Female-to-Male (FtM): Adjective to describe individuals assigned female at birth who are changing or who have changed their body and/or gender role from birth-assigned female to a more masculine body or role.

Gender dysphoria: Distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b).

Gender identity: A person's intrinsic sense of being male (a boy or a man), female (a girl or woman), or an alternative gender (e.g., boygirl, girlboy, transgender, genderqueer, eunuch) (Bockting, 1999; Stoller, 1964).

Gender identity disorder: Formal diagnosis set forth by the *Diagnostic Statistical Manual of Mental Disorders, 4th Edition, Text Rev (DSM IV-TR)* (American Psychiatric Association, 2000). Gender identity disorder is characterized by a strong and persistent cross-gender identification and a persistent discomfort with one's sex or sense of inappropriateness in the gender role of that sex, causing clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Gender-nonconforming: Adjective to describe individuals whose gender identity, role, or expression differs from what is normative for their assigned sex in a given culture and historical period.

Gender role or expression: Characteristics in personality, appearance, and behavior that in a given culture and historical period are designated as masculine or feminine (that is, more typical of the male or female social role) (Ruble, Martin, & Berenbaum, 2006). While most individuals present socially in clearly masculine or feminine gender roles, some people present in an alternative gender role such as genderqueer or specifically transgender. All people tend to incorporate both masculine and feminine characteristics in their gender expression in varying ways and to varying degrees (Bockting, 2008).

Genderqueer: Identity label that may be used by individuals whose gender identity and/or role does not conform to a binary understanding of gender as limited to the categories of man or woman, male or female (Bockting, 2008).

Internalized transphobia: Discomfort with one's own transgender feelings or identity as a result of internalizing society's normative gender expectations.

Male-to-Female (MtF): Adjective to describe individuals assigned male at birth who are changing or who have changed their body and/or gender role from birth-assigned male to a more feminine body or role.

Natural hormones: Hormones that are derived from natural *sources* such as plants or animals. Natural hormones may or may not be bioidentical.

Sex: Sex is assigned at birth as male or female, usually based on the appearance of the external genitalia. When the external genitalia are ambiguous, other components of sex (internal genitalia, chromosomal and hormonal sex) are considered in order to assign sex (Grumbach, Hughes, & Conte, 2003; MacLaughlin & Donahoe, 2004; Money & Ehrhardt, 1972; Vilain, 2000). For most people, gender identity and expression are consistent with their sex assigned at birth; for transsexual, transgender, and gender-nonconforming individuals, gender identity or expression differ from their sex assigned at birth.

Sex reassignment surgery (gender affirmation surgery): Surgery to change primary and/or secondary sex characteristics to affirm a person's gender identity. Sex reassignment surgery can be an important part of medically necessary treatment to alleviate gender dysphoria.

Transgender: Adjective to describe a diverse group of individuals who cross or transcend culturally defined categories of gender. The gender identity of transgender people differs to varying degrees from the sex they were assigned at birth (Bockting, 1999).

Transition: Period of time when individuals change from the gender role associated with their sex assigned at birth to a different gender role. For many people, this involves learning how to live socially in another gender role; for others this means finding a gender role and expression that are most comfortable for them. Transition may or may not include feminization or masculinization of the body through hormones or other medical procedures. The nature and duration of transition are variable and individualized.

Transsexual: Adjective (often applied by the medical profession) to describe individuals who seek to change or who have changed their primary and/or secondary sex characteristics through feminizing or masculinizing medical interventions (hormones and/or surgery), typically accompanied by a permanent change in gender role.

APPENDIX B

OVERVIEW OF MEDICAL RISKS OF HORMONE THERAPY

The risks outlined below are based on two comprehensive, evidence-based literature reviews of masculinizing/feminizing hormone therapy (Feldman & Safer, 2009; Hembree et al., 2009), along with a large cohort study (Asscheman et al., 2011). These reviews can serve as detailed references for providers, along with other widely recognized, published clinical materials (e.g., Dahl et al., 2006; Ettner et al., 2007).

Risks of Feminizing Hormone Therapy (MtF)

Likely Increased Risk:

Venous thromboembolic disease

- Estrogen use increases the risk of venous thromboembolic events (VTE), particularly in patients who are over age 40, smokers, highly sedentary, obese, and who have underlying thrombophilic disorders.
- This risk is increased with the additional use of third generation progestins.
- This risk is decreased with use of the transdermal (versus oral) route of estradiol administration, which is recommended for patients at higher risk of VTE.

Cardiovascular, cerebrovascular disease

- Estrogen use increases the risk of cardiovascular events in patients over age 50 with underlying cardiovascular risk factors. Additional progestin use may increase this risk.

Lipids

- Oral estrogen use may markedly increase triglycerides in patients, increasing the risk of pancreatitis and cardiovascular events.
- Different routes of administration will have different metabolic effects on levels of HDL cholesterol, LDL cholesterol and lipoprotein(a).
- In general, clinical evidence suggests that MtF patients with pre-existing lipid disorders may benefit from the use of transdermal rather than oral estrogen.

Liver/gallbladder

- Estrogen and cyproterone acetate use may be associated with transient liver enzyme elevations and, rarely, clinical hepatotoxicity.
- Estrogen use increases the risk of cholelithiasis (gall stones) and subsequent cholecystectomy.

Possible Increased Risk:Type 2 diabetes mellitus

- Feminizing hormone therapy, particularly estrogen, may increase the risk of type 2 diabetes, particularly among patients with a family history of diabetes or other risk factors for this disease.

Hypertension

- Estrogen use may increase blood pressure, but the effect on incidence of overt hypertension is unknown.
- Spironolactone reduces blood pressure and is recommended for at-risk or hypertensive patients desiring feminization.

Prolactinoma

- Estrogen use increases the risk of hyperprolactinemia among MtF patients in the first year of treatment, but this risk is unlikely thereafter.
- High-dose estrogen use may promote the clinical appearance of preexisting but clinically unapparent prolactinoma.

Inconclusive or No Increased Risk:

Items in this category include those that may present risk, but for which the evidence is so minimal that no clear conclusion can be reached.

Breast cancer

- MtF persons who have taken feminizing hormones do experience breast cancer, but it is unknown how their degree of risk compares to that of persons born with female genitalia.
- Longer duration of feminizing hormone exposure (i.e., number of years taking estrogen preparations), family history of breast cancer, obesity (BMI >35), and the use of progestins likely influence the level of risk.

Other Side Effects of Feminizing Therapy:

The following effects may be considered minor or even desired, depending on the patient, but are clearly associated with feminizing hormone therapy.

Fertility and sexual function

- Feminizing hormone therapy may impair fertility.
- Feminizing hormone therapy may decrease libido.
- Feminizing hormone therapy reduces nocturnal erections, with variable impact on sexually stimulated erections.

Risks of Anti-Androgen Medications:

Feminizing hormone regimens often include a variety of agents that affect testosterone production or action. These include GnRH agonists, progestins (including cyproterone acetate), spironolactone, and 5-alpha reductase inhibitors. An extensive discussion of the specific risks of these agents is beyond the scope of the SOC. However, both spironolactone and cyproterone acetate are widely used and deserve some comment.

Cyproterone acetate is a progestational compound with anti-androgenic properties (Gooren, 2005; Levy et al., 2003). Although widely used in Europe, it is not approved for use in the United States because of concerns about hepatotoxicity (Thole, Manso, Salgueiro, Revuelta, & Hidalgo, 2004). Spironolactone is commonly used as an anti-androgen in feminizing hormone therapy, particularly in regions where cyproterone is not approved for use (Dahl et al., 2006; Moore et al., 2003; Tangpricha et al., 2003). Spironolactone has a long history of use in treating hypertension and congestive heart failure. Its common side effects include hyperkalemia, dizziness, and gastrointestinal symptoms (*Physicians' Desk Reference*, 2007).

Risks of Masculinizing Hormone Therapy (FtM)

Likely Increased Risk:

Polycythemia

- Masculinizing hormone therapy involving testosterone or other androgenic steroids increases the risk of polycythemia (hematocrit > 50%), particularly in patients with other risk factors.
- Transdermal administration and adaptation of dosage may reduce this risk.

Weight gain/visceral fat

- Masculinizing hormone therapy can result in modest weight gain, with an increase in visceral fat.

Possible Increased Risk:

Lipids

- Testosterone therapy decreases HDL, but variably affects LDL and triglycerides.
- Supraphysiologic (beyond normal male range) serum levels of testosterone, often found with extended intramuscular dosing, may worsen lipid profiles, whereas transdermal administration appears to be more lipid neutral.
- Patients with underlying polycystic ovarian syndrome or dyslipidemia may be at increased risk of worsening dyslipidemia with testosterone therapy.

Liver

- Transient elevations in liver enzymes may occur with testosterone therapy.
- Hepatic dysfunction and malignancies have been noted with oral methyltestosterone. However, methyltestosterone is no longer available in most countries and should no longer be used.

Psychiatric

Masculinizing therapy involving testosterone or other androgenic steroids may increase the risk of hypomanic, manic, or psychotic symptoms in patients with underlying psychiatric disorders that include such symptoms. This adverse event appears to be associated with higher doses or supraphysiologic blood levels of testosterone.

Inconclusive or No Increased Risk:

Items in this category include those that may present risk, but for which the evidence is so minimal that no clear conclusion can be reached.

Osteoporosis

- Testosterone therapy maintains or increases bone mineral density among FtM patients prior to oophorectomy, at least in the first three years of treatment.
- There is an increased risk of bone density loss after oophorectomy, particularly if testosterone therapy is interrupted or insufficient. This includes patients utilizing solely oral testosterone.

Cardiovascular

- Masculinizing hormone therapy at normal physiologic doses does not appear to increase the risk of cardiovascular events among healthy patients.
- Masculinizing hormone therapy may increase the risk of cardiovascular disease in patients with underlying risks factors.

Hypertension

- Masculinizing hormone therapy at normal physiologic doses may increase blood pressure but does not appear to increase the risk of hypertension.
- Patients with risk factors for hypertension, such as weight gain, family history, or polycystic ovarian syndrome, may be at increased risk.

Type 2 diabetes mellitus

- Testosterone therapy does not appear to increase the risk of type 2 diabetes among FtM patients overall, unless other risk factors are present.
- Testosterone therapy may further increase the risk of type 2 diabetes in patients with other risk factors, such as significant weight gain, family history, and polycystic ovarian syndrome. There are no data that suggest or show an increase in risk in those with risk factors for dyslipidemia.

Breast cancer

- Testosterone therapy in FtM patients does not increase the risk of breast cancer.

Cervical cancer

- Testosterone therapy in FtM patients does not increase the risk of cervical cancer, although it may increase the risk of minimally abnormal Pap smears due to atrophic changes.

Ovarian cancer

- Analogous to persons born with female genitalia with elevated androgen levels, testosterone therapy in FtM patients may increase the risk of ovarian cancer, although evidence is limited.

Endometrial (uterine) cancer

- Testosterone therapy in FtM patients may increase the risk of endometrial cancer, although evidence is limited.

Other Side Effects of Masculinizing Therapy:

The following effects may be considered minor or even desired, depending on the patient, but are clearly associated with masculinization.

Fertility and sexual function

- Testosterone therapy in FtM patients reduces fertility, although the degree and reversibility are unknown.

- Testosterone therapy can induce permanent anatomic changes in the developing embryo or fetus.
- Testosterone therapy induces clitoral enlargement and increases libido.

Acne, androgenic alopecia

Acne and varying degrees of male pattern hair loss (androgenic alopecia) are common side effects of masculinizing hormone therapy.

APPENDIX C

SUMMARY OF CRITERIA FOR HORMONE THERAPY AND SURGERIES

As for all previous versions of the SOC, the criteria put forth in the SOC for hormone therapy and surgical treatments for gender dysphoria are clinical guidelines; individual health professionals and programs may modify them. Clinical departures from the SOC may come about because of a patient's unique anatomic, social, or psychological situation; an experienced health professional's evolving method of handling a common situation; a research protocol; lack of resources in various parts of the world; or the need for specific harm-reduction strategies. These departures should be recognized as such, explained to the patient, and documented through informed consent for quality patient care and legal protection. This documentation is also valuable to accumulate new data, which can be retrospectively examined to allow for health care—and the SOC—to evolve.

Criteria for Feminizing/Masculinizing Hormone Therapy (One Referral or Chart Documentation of Psychosocial Assessment)

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to give consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC for children and adolescents);
4. If significant medical or mental concerns are present, they must be reasonably well controlled.

Criteria for Breast/Chest Surgery (One Referral)

Mastectomy and Creation of a Male Chest in FtM Patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to give consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC for children and adolescents);
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Hormone therapy is not a prerequisite.

Breast Augmentation (Implants/Lipofilling) in MtF Patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to give consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC for children and adolescents);
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Although not an explicit criterion, it is recommended that MtF patients undergo feminizing hormone therapy (minimum 12 months) prior to breast augmentation surgery. The purpose is to maximize breast growth in order to obtain better surgical (aesthetic) results.

Criteria for Genital Surgery (Two Referrals)

Hysterectomy and Salpingo-Oophorectomy in FtM Patients and Orchiectomy in MtF Patients:

1. Persistent, well documented gender dysphoria;
2. Capacity to make a fully informed decision and to give consent for treatment;

3. Age of majority in a given country;
4. If significant medical or mental health concerns are present, they must be well controlled;
5. 12 continuous months of hormone therapy as appropriate to the patient's gender goals (unless hormones are not clinically indicated for the individual).

The aim of hormone therapy prior to gonadectomy is primarily to introduce a period of reversible estrogen or testosterone suppression, before a patient undergoes irreversible surgical intervention.

These criteria do not apply to patients who are having these surgical procedures for medical indications other than gender dysphoria.

Metoidioplasty or Phalloplasty in FtM Patients and Vaginoplasty in MtF Patients:

1. Persistent, well documented gender dysphoria;
2. Capacity to make a fully informed decision and to give consent for treatment;
3. Age of majority in a given country;
4. If significant medical or mental health concerns are present, they must be well controlled;
5. 12 continuous months of hormone therapy as appropriate to the patient's gender goals (unless hormones are not clinically indicated for the individual);
6. 12 continuous months of living in a gender role that is congruent with their gender identity.

Although not an explicit criterion, it is recommended that these patients also have regular visits with a mental health or other medical professional.

The criterion noted above for some types of genital surgeries—that is, that patients engage in 12 continuous months of living in a gender role that is congruent with their gender identity—is based on expert clinical consensus that this experience provides ample opportunity for patients to experience and socially adjust in their desired gender role, before undergoing irreversible surgery.

APPENDIX D

EVIDENCE FOR CLINICAL OUTCOMES OF THERAPEUTIC APPROACHES

One of the real supports for any new therapy is an outcome analysis. Because of the controversial nature of sex reassignment surgery, this type of analysis has been very important. Almost all of the outcome studies in this area have been retrospective.

One of the first studies to examine the post-treatment psychosocial outcomes of transsexual patients was done in 1979 at Johns Hopkins University School of Medicine and Hospital (USA) (J. K. Meyer & Reter, 1979). This study focused on patients' occupational, educational, marital, and domiciliary stability. The results revealed several significant changes with treatment. These changes were not seen as positive; rather, they showed that many individuals who had entered the treatment program were no better off or were worse off in many measures after participation in the program. These findings resulted in closure of the treatment program at that hospital/medical school (Abramowitz, 1986).

Subsequently, a significant number of health professionals called for a standard for eligibility for sex reassignment surgery. This led to the formulation of the original *Standards of Care* of the Harry Benjamin International Gender Dysphoria Association (now WPATH) in 1979.

In 1981, Pauly published results from a large retrospective study of people who had undergone sex reassignment surgery. Participants in that study had much better outcomes: Among 83 FtM patients, 80.7% had a satisfactory outcome (i.e., patient self report of "improved social and emotional adjustment"), 6.0% unsatisfactory. Among 283 MtF patients, 71.4% had a satisfactory outcome, 8.1% unsatisfactory. This study included patients who were treated before the publication and use of the *Standards of Care*.

Since the *Standards of Care* have been in place, there has been a steady increase in patient satisfaction and decrease in dissatisfaction with the outcome of sex reassignment surgery. Studies conducted after 1996 focused on patients who were treated according to the *Standards of Care*. The findings of Rehman and colleagues (1999) and Krege and colleagues (2001) are typical of this body of work; none of the patients in these studies regretted having had surgery, and most reported being satisfied with the cosmetic and functional results of the surgery. Even patients who develop severe surgical complications seldom regret having undergone surgery. Quality of surgical results is one of the best predictors of the overall outcome of sex reassignment (Lawrence, 2003). The vast majority of follow-up studies have shown an undeniable beneficial effect of sex reassignment surgery on postoperative outcomes such as subjective well being, cosmesis, and sexual function (De Cuypere et al., 2005; Garaffa, Christopher, & Ralph, 2010; Klein & Gorzalka, 2009), although the specific magnitude of benefit is uncertain from

the currently available evidence. One study (Emory, Cole, Avery, Meyer, & Meyer, 2003) even showed improvement in patient income.

One troubling report (Newfield et al., 2006) documented lower scores on quality of life (measured with the SF-36) for FtM patients than for the general population. A weakness of that study is that it recruited its 384 participants by a general email rather than a systematic approach, and the degree and type of treatment were not recorded. Study participants who were taking testosterone had typically been doing so for less than 5 years. Reported quality of life was higher for patients who had undergone breast/chest surgery than for those who had not ($p < .001$). (A similar analysis was not done for genital surgery.) In other work, Kuhn and colleagues (2009) used the King's Health Questionnaire to assess the quality of life of 55 transsexual patients at 15 years after surgery. Scores were compared to those of 20 healthy female control patients who had undergone abdominal/pelvic surgery in the past. Quality of life scores for transsexual patients were the same or better than those of control patients for some subscales (emotions, sleep, incontinence, symptom severity, and role limitation), but worse in other domains (general health, physical limitation, and personal limitation).

Two long-term observational studies, both retrospective, compared the mortality and psychiatric morbidity of transsexual adults to those of general population samples (Asscheman et al., 2011; Dhejne et al., 2011). An analysis of data from the Swedish National Board of Health and Welfare information registry found that individuals who had received sex reassignment surgery (191 MtF and 133 FtM) had significantly higher rates of mortality, suicide, suicidal behavior, and psychiatric morbidity than those for a nontranssexual control group matched on age, immigrant status, prior psychiatric morbidity, and birth sex (Dhejne et al., 2011). Similarly, a study in the Netherlands reported a higher total mortality rate, including incidence of suicide, in both pre- and post-surgery transsexual patients (966 MtF and 365 FtM) than in the general population of that country (Asscheman et al., 2011). Neither of these studies questioned the efficacy of sex reassignment; indeed, both lacked an adequate comparison group of transsexuals who either did not receive treatment or who received treatment other than genital surgery. Moreover, transsexual people in these studies were treated as far back as the 1970s. However, these findings do emphasize the need to have good long-term psychological and psychiatric care available for this population. More studies are needed that focus on the outcomes of current assessment and treatment approaches for gender dysphoria.

It is difficult to determine the effectiveness of hormones alone in the relief of gender dysphoria. Most studies evaluating the effectiveness of masculinizing/feminizing hormone therapy on gender dysphoria have been conducted with patients who have also undergone sex reassignment surgery. Favorable effects of therapies that included both hormones and surgery were reported in a comprehensive review of over 3000 patients in 79 studies (mostly observational) conducted between 1961 and 1991 (Eldh, Berg, & Gustafsson, 1997; Gijs & Brewaeys, 2007; Murad et al., 2010; Pfäfflin & Junge, 1998). Patients operated on after 1986 did better than those before 1986; this reflects significant improvement in surgical complications (Eldh et al., 1997). Most patients have reported improved psychosocial outcomes, ranging between 87% for MtF patients and 97% for FtM patients (Green & Fleming, 1990).

Similar improvements were found in a Swedish study in which “almost all patients were satisfied with sex reassignment at 5 years, and 86% were assessed by clinicians at follow-up as stable or improved in global functioning” (Johansson, Sundbom, Höjerback, & Bodlund, 2010). Weaknesses of these earlier studies are their retrospective design and use of different criteria to evaluate outcomes.

A prospective study conducted in the Netherlands evaluated 325 consecutive adult and adolescent subjects seeking sex reassignment (Smith, Van Goozen, Kuiper, & Cohen-Kettenis, 2005). Patients who underwent sex reassignment therapy (both hormonal and surgical intervention) showed improvements in their mean gender dysphoria scores, measured by the Utrecht Gender Dysphoria Scale. Scores for body dissatisfaction and psychological function also improved in most categories. Fewer than 2% of patients expressed regret after therapy. This is the largest prospective study to affirm the results from retrospective studies that a combination of hormone therapy and surgery improves gender dysphoria and other areas of psychosocial functioning. There is a need for further research on the effects of hormone therapy without surgery, and without the goal of maximum physical feminization or masculinization.

Overall, studies have been reporting a steady improvement in outcomes as the field becomes more advanced. Outcome research has mainly focused on the outcome of sex reassignment surgery. In current practice there is a range of identity, role, and physical adaptations that could use additional follow-up or outcome research (Institute of Medicine, 2011).

APPENDIX E

DEVELOPMENT PROCESS FOR THE STANDARDS OF CARE, VERSION 7

The process of developing *Standards of Care, Version 7* began when an initial SOC “work group” was established in 2006. Members were invited to examine specific sections of SOC, *Version 6*. For each section, they were asked to review the relevant literature, identify where research was lacking and needed, and recommend potential revisions to the SOC as warranted by new evidence. Invited papers were submitted by the following authors: Aaron Devor, Walter Bockting, George Brown, Michael Brownstein, Peggy Cohen-Kettenis, Griet DeCuypere, Petra DeSutter, Jamie Feldman, Lin Fraser, Arlene Istar Lev, Stephen Levine, Walter Meyer, Heino Meyer-Bahlburg, Stan Monstrey, Loren Schechter, Mick van Trotsenburg, Sam Winter, and Ken Zucker. Some of these authors chose to add co-authors to assist them in their task.

Initial drafts of these papers were due June 1, 2007. Most were completed by September 2007, with the rest completed by the end of 2007. These manuscripts were then submitted to the *International*

Journal of Transgenderism (IJT). Each underwent the regular *IJT* peer review process. The final papers were published in Volume 11 (1–4) in 2009, making them available for discussion and debate.

After these articles were published, an SOC Revision Committee was established by the WPATH Board of Directors in 2010. The Revision Committee was first charged with debating and discussing the *IJT* background papers through a Google website. A subgroup of the Revision Committee was appointed by the Board of Directors to serve as the Writing Group. This group was charged with preparing the first draft of SOC, *Version 7* and continuing to work on revisions for consideration by the broader Revision Committee. The Board also appointed an International Advisory Group of transsexual, transgender, and gender-nonconforming individuals to give input on the revision.

A technical writer was hired to (1) review all of the recommendations for revision—both the original recommendations as outlined in the *IJT* articles and additional recommendations that emanated from the online discussion—and (2) create a survey to solicit further input on these potential revisions. From the survey results, the Writing Group was able to discern where these experts stood in terms of areas of agreement and areas in need of more discussion and debate. The technical writer then (3) created a very rough first draft of SOC, *Version 7* for the Writing Group to consider and build on.

The Writing Group met on March 4 and 5, 2011 in a face-to-face expert consultation meeting. They reviewed all recommended changes and debated and came to consensus on various controversial areas. Decisions were made based on the best available science and expert consensus. These decisions were incorporated into the draft, and additional sections were written by the Writing Group with the assistance of the technical writer.

The draft that emerged from the consultation meeting was then circulated among the Writing Group and finalized with the help of the technical writer. Once this initial draft was finalized, it was circulated among the broader SOC Revision Committee and the International Advisory Group. Discussion was opened up on the Google website and a conference call was held to resolve issues. Feedback from these groups was considered by the Writing Group, who then made further revisions. Two additional drafts were created and posted on the Google website for consideration by the broader SOC Revision Committee and the International Advisory Group. Upon completion of these three iterations of review and revision, the final document was presented to the WPATH Board of Directors for approval. The Board of Directors approved this version on September 14, 2011.

Funding

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1. Costs of a professional technical writer;
2. Process of soliciting international input on proposed changes from gender identity professionals and the transgender community;
3. Working meeting of the Writing Group;
4. Process of gathering additional feedback and arriving at final expert consensus from the professional and transgender communities, the *Standards of Care, Version 7*, Revision Committee, and WPATH Board of Directors;
5. Costs of printing and distributing *Standards of Care, Version 7*, and posting a free downloadable copy on the WPATH website;
6. Plenary session to launch the *Standards of Care, Version 7*, at the 2011 WPATH Biennial Symposium in Atlanta, Georgia, USA.

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Review Article

EVIDENCE SUPPORTING THE BIOLOGIC NATURE
OF GENDER IDENTITYAruna Saraswat, MD¹; Jamie D. Weinand, BA, BS²; Joshua D. Safer, MD^{1,3}

ABSTRACT

Objective: To review current literature that supports a biologic basis of gender identity.

Methods: A traditional literature review.

Results: Evidence that there is a biologic basis for gender identity primarily involves (1) data on gender identity in patients with disorders of sex development (DSDs, also known as differences of sex development) along with (2) neuroanatomical differences associated with gender identity.

Conclusions: Although the mechanisms remain to be determined, there is strong support in the literature for a biologic basis of gender identity. (*Endocr Pract.* 2015;21:199-204)

Abbreviations:

BDNF = brain-derived neurotrophic factor; **BSTC** = bed nucleus of the stria terminalis; **CAH** = congenital adrenal hyperplasia; **DES** = diethylstilbestrol; **DSD** = disorder of sex development; **MTF** = male-to-female; **FTM** = female-to-male

INTRODUCTION

Gender identity is a fundamental human attribute that has a profound impact on personal well-being. Transgender individuals are those whose lived and identified gender identity differs from their natal sex. Various etiologies for transgender identity have been proposed, but misconceptions that gender identity can be altered persist. However, clinical experience with treatment of transgender persons has clearly demonstrated that the best outcomes for these individuals are achieved with their requested hormone therapy and surgical sexual transition as opposed to psychiatric intervention alone (1). In this review, we will discuss the data in support of a fixed, biologic basis for gender identity.

METHODS

This traditional literature review was conducted using a search of PubMed and Google Scholar for the following key terms: gender identity, gender dysphoria, transsexual, transgender, transmen, and transwomen.

RESULTS

Disorders (or Differences) of
Sex Development (DSDs)

A seminal study by Meyer-Bahlburg et al involving outcomes of XY individuals raised as females due to severe nonhormonal, anatomic abnormalities of sex development provided the most convincing evidence that gender identity is fixed (2). These congenital abnormalities include penile agenesis, cloacal exstrophy, and penile ablation. For many years, female gender assignment along with surgical feminization was the dominant approach for these patients. In this study, 78% of all female-assigned 46 XY patients were living as females. While the majority of these patients did not initiate a gender change to male, none of the 15 male-raised 46 XY patients initiated a gender change to female. Thus, the risk of questioning gender identity was higher in

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those 46 XY subjects raised as females than in those raised as males. The same group examined the degree of satisfaction with surgical intervention reported by patients with 46 XY genotypes and found that those subjects raised as boys were considerably more comfortable with their gender identity (3).

Another seminal study relevant to this topic was by Reiner and Gearhart (4). In their review of 16 XY genotype subjects with cloacal exstrophy who underwent female gender reassignment surgery, 4 of the 14 individuals raised as girls announced they were male, and 4 later chose to live as boys when they became aware of their genotype. The 2 individuals who were raised as males identified as males throughout life. The sexual behavior and attitudes of all 16 subjects ultimately reflected strong masculine characteristics regardless of gender assignment. Thus, children who were born genetically and hormonally male identified as males despite being raised as females and undergoing feminizing genitoplasty at birth. Although the cohort sizes in these studies were small, the data provide the strongest evidence for the biologic underpinnings of gender identity.

In congenital adrenal hyperplasia (CAH), the adrenal glands produce excessive amounts of androgens, causing genital virilization with a spectrum of different phenotypes in 46 XX neonates. Dessens et al (5) reported that the prevalence of male gender identity in 46 XX female-raised subjects with CAH was higher than the prevalence of female-to-male (FTM) transgender individuals in the general population of chromosomal females. In this study, the large majority (95%) of 250 female-raised patients later maintained a female gender identity. However, 13 (5.2%) had serious problems with their gender identity. Deficiencies of 5 alpha-reductase-2 and 17-beta-hydroxy-steroid dehydrogenase-3 are similar conditions in which the synthesis and conversion of testosterone to dihydrotestosterone is inhibited, preventing the development of external male genitalia and resulting in potential genital ambiguity. As with CAH, affected individuals are often raised as females. In a study of affected subjects, gender role changes were reported in 56 to 63% of cases with 5 alpha-reductase-2 deficiency and 39 to 64% of cases with 17-beta-hydroxy-steroid dehydrogenase-3 deficiency who were raised as girls (6). These data support the concept that gender identity might be attributed to hormone milieu during intrauterine development.

Data from DSDs highlight the potential influence of abnormal hormone exposure on the development of transgender identity in some individuals. However, it is important to note that most transgender individuals develop a gender identity that cannot be explained by atypical sexual differentiation. It is possible for individuals with normal sexual differentiation to develop transgender identity later in life.

Neuroanatomical Differences

Many of the current hypotheses for the biologic origin of transgender identity are based on atypical sexual differentiation of the brain. The perception of one's own gender is linked to sexual differentiation of the brain, which differs from the body phenotype in transgender individuals (7). Swaab et al have proposed that this discrepancy could be due to the fact that sexual differentiation of the brain takes place only after sexual differentiation of the gonads in early fetal life (8). Along these lines, the degree of genital masculinization may not reflect that of the brain.

The notion of transgender-specific cerebral phenotypes is further supported by postmortem brain studies investigating the underlying neuroanatomical correlates of gender identity (9,10,12). The vast majority of these studies have compared particular regions of interest only in male-to-female (MTF) transgender individuals (13-15). These studies support the hypothesis that atypical cerebral networks in transgender individuals have a neuroanatomical basis.

Gray Matter Studies

Studies of cerebral gray matter in transgender individuals have provided the strongest neuroanatomical case for transgender gender identity. Postmortem brain studies suggest that some subcortical structures are feminized in MTF individuals. One of the earliest and most influential studies in this area investigated the bed nucleus of the stria terminalis (BSTc), which was reported to be a sexually dimorphic nucleus in humans with a larger volume in males than in females. In 1995, Zhou et al reported that the size and number of neurons in the BSTc of 6 MTF estrogen-treated transgender individuals was typical for the size and neuron numbers generally found in control females (9). The authors further reported that these findings could not be explained by differences in adult sex hormone levels.

A similar study by Kruijver et al provided further data supporting the role of the BSTc in transgender identity (10). They examined tissue from the same 6 MTF estrogen-treated transgender persons studied by Zhou et al and found that the number of neurons in the BSTc was more similar to genetic XX female controls. BSTc neuron number was also in the male range in the 1 FTM androgen-treated transgender individual studied.

Most transgender individuals experience feelings of gender dysphoria that begin in childhood. However, in a study of BSTc volume in postmortem brains of 50 control subjects, Chung et al reported that sexual dimorphism in the BSTc did not develop until adulthood (11). Yet, the same group remarked that changes in fetal hormone levels could have delayed effects on BSTc volume and neurons in adulthood, thereby suggesting a role for BSTc as a marker for gender identity. Still, delayed development of

sexual dimorphism in the BSTc would not explain childhood development of gender dysphoria or gender identity discrepancy.

In 2008, Garcia-Falgueras and Swaab were the first to report a sex reversal in the uncinate nucleus. They examined the third interstitial nucleus of the anterior hypothalamus (INAH 3), which is a sexually dimorphic component of the uncinate nucleus, in relation to the brains of transgender individuals (12). They reported that the mean INAH3 volume and neuron number in 11 MTF transgender subjects were in the female ranges.

The above studies are limited by the fact that they involved postmortem examinations of a small number of brains from MTF individuals, some of whom had either received hormone treatment or surgery. Therefore, the study findings may represent confounding effects from exogenous hormones in a small group of transgender individuals. Despite their small sample size, these studies provide valuable evidence that gender identity is linked to neuroanatomy.

Studies by Luders et al provided further evidence that transgender identity is associated with distinct cerebral patterns (13,14). In 2009, the group analyzed magnetic resonance imaging (MRI) data of 24 MTF transgender individuals who had not yet begun hormone treatment. These subjects were shown to have a pattern that was more similar to control males. However, they also observed a significantly larger, more “feminized” volume of regional gray matter in the right putamen in these subjects. In 2012, the same group observed thicker cortices in 24 MTF transgender individuals who had not yet received exogenous hormones compared with 24 age-matched control males in a number of regions across the lateral and medial cortical surfaces. The data supported a dichotomy between MTF transgender individuals and gender congruent males with regard to brain structure.

Differences in brain volume and cerebral activation patterns have been proposed as potential explanations for transgender identity. In 2011, Savic et al examined brains of 24 living MTF transgender individuals and found significant volume reductions of the putamen in MTF transgender individuals and significant increases in gray matter volumes compared with male and female controls (15). Although these findings differ from the findings of smaller, “feminized,” putamens in MTF transgender individuals, they still indicate that certain brain areas in the transgender group have characteristic structural features compared with controls.

The same group investigated 12 living MTF transgender individuals who smelled 2 steroidal compounds: the progesterone derivative 4,16-androstadien-3-one (AND) and the estrogen-like compound estra-1,3,5 (10), 16-tetraen-3-ol (EST). These compounds have been reported to activate the hypothalamic networks in a sex-differentiated way. MTF transgender individuals who had not received

hormone treatment were found to respond similarly to female controls, with AND activating the anterior hypothalamus (16). Another study by Gizewski et al showed a similar cerebral activation in MTF transgender individuals relative to female controls while they viewed erotic stimuli (17). While the above studies only involved MTF transgender individuals, they nonetheless provided evidence of neuroanatomical pathway alteration as an explanation for transgender identity.

The following 2 studies were unique from the aforementioned ones because they included both MTF and FTM transgender individuals who had not received hormone treatment. Zubiaurre et al reported that FTM transgender individuals showed evidence of subcortical gray matter masculinization in the right putamen, while MTF transgender individuals had feminized cortical thickness (18). In 2013, Simon et al reported differences in gray matter in 17 living transgender subjects compared with controls (19). Differences were seen in transgender patients in the cerebellum, angular gyrus, and parietal lobe compared with controls, independent of their biologic gender.

White Matter Studies

Although an early study by Emory et al (20) found no difference in the whole corpus callosum or splenium region between MTF and FTM transgender individuals, the following MRI studies of white matter brain characteristics of transgender individuals suggested a strong neuroanatomical explanation for transgender identity. Yokota et al reported that the pattern of corpus callosum shape in both FTM and MTF transgender individuals was closer to subjects with shared gender identities than to subjects who shared the same natal sex (21). Among FTM transgender individuals who had not received hormone treatment, certain white matter fasciculi involved in higher cognitive functions were closer to the pattern of control males than to control females (22). Among MTF transgender individuals who had not received treatment, diffusion tensor imaging revealed an intermediate white matter pattern that was between those of male and female controls (23).

Genetic Factors and Exposures

Although limited in size and scope, the role of genetic factors in transgender identity is supported by small studies of gene abnormalities associated with steroid hormones, twin case studies, neuroproteins, and prenatal exposures.

Steroid Hormone Genetics

Select genes have been associated with transgender identity. Although these studies have been small, they are most convincing findings to date linking atypical genes with transgender identity in both MTF and FTM transgender individuals. The *CYP17* gene encodes the 17-alpha hydroxylase enzyme and is associated with elevated serum levels of estradiol, progesterone, and testosterone. In a

case-control study of 151 transgender individuals, Bentz et al reported a significant association between the *CYP17* gene and FTM transgender individuals but not in MTF transgender individuals (24). Another study by the same group examined a polymorphism in the gene coding for 5-alpha reductase and found no association in a sample of both MTF and FTM transgender individuals (25).

Various groups have investigated steroid hormone receptor gene variants to determine if they confer risk of developing transgender identity. Steroid hormones exert profound influences on fetal sexual development and act via specific receptors. It is therefore plausible that abnormal sex hormone receptor function may predispose to transgender identity. However, the existing studies on this topic have been contradictory and require replication. Henningson et al found an association between MTF transgender individuals and a dinucleotide CA polymorphism in the estrogen receptor beta gene (ERb) (26). However, 2 subsequent studies by separate groups reported different results. Hare et al performed a larger study of MTF transgender individuals and found no relationship with the ERb, but they did find a significant association with an androgen receptor repeat (27). In a similar study of 242 MTF and FTM transgender individuals, Ujike et al examined sex steroid receptor genes and found no association with transgender identity (28).

There have been several small case reports of atypical sex chromosomes in transgender individuals. The most common association reported was with disomy-Y (47, XXY); however, no statistically significant association between particular genes has been described (29). Two recent studies of MTF and FTM transgender individuals reported that aneuploidies are slightly more common in transgender individuals than in the general population, but neither was controlled. In the first, karyotype abnormalities were found in 2.5% of the 368 transgender individuals studied (30). A second study of 302 transgender individuals also showed a low overall incidence (1.5%) of chromosomal abnormalities (31).

Twin Studies

Twin literature supports the potential contribution of genetic factors to the development of transgender identity. In 2 separate retrospective studies of twin pairs, Bailey et al and Coolidge et al demonstrated a strong heritable component among twins with transgender identity (32,33). Hylens et al performed a similar study of 23 monozygotic twin pairs and showed that 9 were concordant for transgender identity compared to no concordance among dizygotic twin pairs (34). Two small studies (35,36) also demonstrated a higher concordance for transgender identity among monozygotic twins versus dizygotic twins. Nevertheless, the overall prevalence of monozygotic twins

discordant for transgender identity still outnumbers those who are concordant.

Neuroproteins

Brain-derived neurotrophic factor (BDNF) is a member of the growth factor family involved in synaptic plasticity and neuronal development. Altered BDNF signaling is thought to be a contributor to psychiatric conditions. Fontanari et al (37) reported that serum BDNF levels were 15% lower in an uncontrolled study of 45 MTF transgender individuals. However, all study subjects were treated with hormones, and no female subjects were included.

Neurokinin B (NKB) is a potent regulator of gonadotropin-releasing hormone secretion, which is essential for reproductive function. A postmortem brain study of 4 MTF transgender individuals by Taziaux et al (38) showed a mean infundibular NKB volume similar to control females. The observed feminization may have been explained either by medical estrogen therapy or lack of androgens due to orchiectomy.

Prenatal Exposures

Dessens et al (39) reported that 3 prenatally anticonvulsant-exposed subjects were transgender individuals. For many years, researchers have been assessing the impact of prenatal exposure to the estrogenic antimiscarriage drug DES (diethylstilbestrol) on the development of gender dysphoria in affected offspring. While the vast majority of DES-exposed children have not developed transgender identity, a 5-year online study of DES-exposed sons by Kerlin et al reported at least 150 cases of moderate-to-severe gender dysphoria among 500 sons with confirmed or suspected prenatal DES exposure (40).

Although no studies to date demonstrate mechanism, multiple studies have reported associations with gender identity that support it being a biologic phenomenon. Table 1 organizes areas studied by study type and lists the associations that have been made.

CONCLUSION

Current data suggest a biologic etiology for transgender identity. Studies of DSD patients and neuroanatomical studies provide the strongest evidence for the organic basis of transgender identity. Because the sample sizes of most studies on this subject were small, the conclusions must be interpreted with caution. Further research is required to assign specific biologic mechanisms for gender identity.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

Table 1
Evidence for a Biologic Basis of Gender Identity

Studies showing rigid gender identity in patients with disorders (or differences) of sexual development (DSD)

- Congenital, nonhormonal conditions Penile ablation/agenesis, cloacal exstrophy

Studies showing that gender identity may be associated with prenatal hormone exposure in some (perhaps otherwise predisposed) individuals

- Congenital adrenal hyperplasia
- Hormone deficiencies 5 alpha-reductase-2,
17-beta-hydroxy-steroid dehydrogenase-3

Studies with gender identity associated with neuroanatomical differences

- Gray matter studies BSTc
Uncinate nucleus
Putamen volumes
Cortical thickness
Hypothalamic response to odorous steroids
- White matter studies Corpus callosum
Microstructure differences

Studies with gender identity associated with genetic factors and exposures

- Steroid hormone genetics Genes: CYP17, SRD5A2, ERb, androgen receptor
- Sex chromosome aneuploidy Disomy-Y
- Twin case studies
- Neuropoteins BDNF, NKB
- Prenatal exposures Anticonvulsants, DES

Abbreviations: BDNF = brain-derived neurotrophic factor; BSTc = bed nucleus of stria terminalis; CYP17 = cytochrome P-450 17 alpha gene; DES = diethylstilbestrol; ERb = estrogen receptor beta gene; NKB = neurokinin B; SRD5A2 = steroid-5-alpha reductase, alpha polypeptide 2 gene.

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