UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF INDIANA
INDIANAPOLIS DIVISION

K.C., et al., Plaintiffs, v. THE INDIVIDUAL MEMBERS OF THE MEDICAL LICENSING BOARD OF INDIANA, in their official capacities, et al., Defendants.	)	Case No. 1:23-cv-00595-JPH-KMB

DEFENDANTS' SUBMISSION OF EVIDENTIARY MATERIAL

Defendants submit the attached evidentiary material upon which they will be relying in their forthcoming Motion to Exclude Opinions of Plaintiffs' Experts.

Exhibit 1	National Health Service (NHS), *Gender Dysphoria: Treatment*, https://www.nhs.uk/conditions/gender-dysphoria/.
Exhibit 2	*Search Methodology for Research Analysis on the Effect of Gender Transition on Transgender Well-being*, What We Know Project, https://whatweknow.inequality.cornell.edu/about/selection-methodology/
Exhibit 3	de Vries, A. L. C.; McGuire, J. K.; Steensma, T. D.; et al. (2014). Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics*, 134, 1–9.
Exhibit 4	D'Angelo, R.; Syrulnik, E.; Ayad, S.; et al. (2020). One size does not fit all: In support of psychotherapy for gender dysphoria. *Archives of Sexual Behavior*, 50:7–16.
Exhibit 5	Rametti, G.; Carrillo, B.; Gómez-Gil, E.; et al. (2011). White matter microstructure in female to male transsexuals before cross-sex hormonal treatment. A diffusion tensor imaging study. *J. of Psychiatric Research*, 45(2):199–204.
Exhibit 6	Jack Turban, Tweet from May 13, 2023 at 4:36 PM, twitter.com.

Exhibit 7	Chung, W. C., De Vries, G. J., & Swaab, D. F. (2002). Sexual differentiation of the bed nucleus of the stria terminalis in humans may extend into adulthood. *The J. of Neuroscience* 22(3):1027–1033.
Exhibit 8	Baker, K. E.; Wilson, L. M.; Sharma, R.; et al. (2021). Hormone therapy, mental health, and quality of life among transgender people. *J. of the Endocrine Soc'y*, 2021, 5.
Exhibit 9	Zucker, K.J.; Bradley, S.J.; Owen-Anderson, A.; et al. (2010). Puberty-Blocking Hormonal Therapy for Adolescents with Gender Identity Disorder: A Descriptive Clinical Study, *J. of Gay & Lesbian Mental Health*, 15(1):58–82
Exhibit 10	Owen-Smith, A.A.; Gerth, J.; Sineath, R.C.; et al, (2018). Association Between Gender Confirmation Treatments and Perceived Gender Congruence, Body Image Satisfaction, and Mental Health in a Cohort of Transgender Individuals. *The J. of Sexual Medicine*, 15(4), 591–600.

Office of the Indiana Attorney General
IGC-South, Fifth Floor
302 West Washington Street
Indianapolis, Indiana 46204-2770
Telephone: (317) 232-6255
Fax: (317) 232-7979
Email: Tom.Fisher@atg.in.gov

Respectfully submitted,

Theodore E. Rokita
Indiana Attorney General

By: /s/ Thomas M. Fisher
Thomas M. Fisher
Solicitor General

James A. Barta
Deputy Solicitor General

Corrine Youngs
Policy Director and Legislative Counsel

Melinda R. Holmes
Razi S. Lane
Deputy Attorneys General

Counsel for Defendants

Exhibit 1

Treatment

Gender dysphoria

Overview (Link: www.nhs.uk/conditions/gender-dysphoria/)

- Signs (Link: www.nhs.uk/conditions/gender-dysphoria/symptoms/)
- How to get help and support (Link: www.nhs.uk/conditions/gender-dysphoria/how-get-help-and-support/)
- **Treatment**

Treatment for gender dysphoria aims to help people live the way they want to, in their preferred gender identity or as non-binary.

What this means will vary from person to person, and is different for children, young people and adults. Waiting times for referral and treatment are currently long.

Treatment for children and young people

If your child is under 18 and may have gender dysphoria, they'll usually be referred to the Gender Identity Development Service (GIDS) (Link: https://gids.nhs.uk/) at the Tavistock and Portman NHS Foundation Trust.

GIDS has 2 main clinics in London and Leeds.

Your child or teenager will be seen by a multidisciplinary team at GIDS including a:

- clinical psychologist
- child psychotherapist
- child and adolescent psychiatrist
- family therapist
- social worker

The team will carry out a detailed assessment, usually over 3 to 6 appointments over a period of several months.

Depending on the results of the assessment, options for children and teenagers include:

- family therapy
- individual child psychotherapy
- parental support or counselling
- group work for young people and their parents
- regular reviews to monitor gender identity development
- referral to a local Children and Young People's Mental Health Service (CYPMHS) for more serious emotional issues
- a referral to a specialist hormone (endocrine) clinic for hormone blockers for children who meet strict criteria (at puberty)

Most treatments offered at this stage are psychological rather than medical. This is because in many cases gender variant behaviour or feelings disappear as children reach puberty.

Hormone therapy in children and young people

Some young people with lasting signs of gender dysphoria who meet strict criteria may be referred to a hormone specialist (consultant endocrinologist) to see if they can take hormone blockers as they reach puberty. This is in addition to psychological support.

Puberty blockers and cross-sex hormones

Puberty blockers (gonadotrophin-releasing hormone analogues) pause the physical changes of puberty, such as breast development or facial hair.

Little is known about the long-term side effects of hormone or puberty blockers in children with gender dysphoria.

Although GIDS advises this is a physically reversible treatment if stopped, it is not known what the psychological effects may be.

It's also not known whether hormone blockers affect the development of the teenage brain or children's bones. Side effects may also include hot flushes, fatigue and mood alterations.

From the age of 16, teenagers who've been on hormone blockers for at least 12 months may be given cross-sex hormones, also known as gender-affirming hormones.

These hormones cause some irreversible changes, such as:

- breast development (caused by taking oestrogen)
- breaking or deepening of the voice (caused by taking testosterone)

Long-term cross-sex hormone treatment may cause temporary or even permanent infertility.

However, as cross-sex hormones affect people differently, they should not be considered a reliable form of contraception.

There is some uncertainty about the risks of long-term cross-sex hormone treatment.

Transition to adult gender identity services

Young people aged 17 or older may be seen in an adult gender identity clinic or be referred to one from GIDS.

By this age, a teenager and the clinic team may be more confident about confirming a diagnosis of gender dysphoria. If desired, steps can be taken to more permanent treatments that fit with the chosen gender identity or as non-binary.

Treatment for adults

Adults who think they may have gender dysphoria should be referred to a gender dysphoria clinic (GDC).

Find an NHS gender dysphoria clinic in England (Link: www.nhs.uk/nhs-services/how-to-find-an-nhs-gender-identity-clinic/).

GDCs have a multidisciplinary team of healthcare professionals, who offer ongoing assessments, treatments, support and advice, including:

- psychological support, such as counselling
- cross-sex hormone therapy
- speech and language therapy (voice therapy) to help you sound more typical of your gender identity

For some people, support and advice from the clinic are all they need to feel comfortable with their gender identity. Others will need more extensive treatment.

Hormone therapy for adults

The aim of hormone therapy is to make you more comfortable with yourself, both in terms of physical appearance and how you feel. The hormones usually need to be taken for the rest of your life, even if you have gender surgery.

It's important to remember that hormone therapy is only one of the treatments for gender dysphoria. Others include voice therapy and psychological support. The decision to have hormone therapy will be taken after a discussion between you and your clinic team.

In general, people wanting masculinisation usually take testosterone and people after feminisation usually take oestrogen.

Both usually have the additional effect of suppressing the release of "unwanted" hormones from the testes or ovaries.

Whatever hormone therapy is used, it can take several months for hormone therapy to be effective, which can be frustrating.

It's also important to remember what it cannot change, such as your height or how wide or narrow your shoulders are.

The effectiveness of hormone therapy is also limited by factors unique to the individual (such as genetic factors) that cannot be overcome simply by adjusting the dose.

Find out how to save money on prescriptions for hormone therapy medicines with a prescription prepayment certificate (Link: www.nhs.uk/nhs-services/prescriptions-and-pharmacies/save-money-with-a-prescription-prepayment-certificate-ppc/).

Risks of hormone therapy

There is some uncertainty about the risks of long-term cross-sex hormone treatment. The clinic will discuss these with you and the importance of regular monitoring blood tests with your GP.

The most common risks or side effects include:

- blood clots (Link: www.nhs.uk/conditions/blood-clots/)
- gallstones (Link: www.nhs.uk/conditions/gallstones/)
- weight gain
- acne (Link: www.nhs.uk/conditions/acne/)
- dyslipidaemia (abnormal levels of fat in the blood)
- elevated liver enzymes
- polycythaemia (Link: www.nhs.uk/conditions/erythrocytosis/) (high concentration of red blood cells)

- hair loss or balding (androgenic alopecia)

There are other risks if you're taking hormones bought over the internet or from unregulated sources. It's strongly recommended you avoid these.

Long-term cross-sex hormone treatment may also lead, eventually, to infertility, even if treatment is stopped.

The GP can help you with advice about gamete storage. This is the harvesting and storing of eggs or sperm for your future use.

Gamete storage is sometimes available on the NHS. It cannot be provided by the gender dysphoria clinic.

Read more about fertility preservation (Link: https://www.hfea.gov.uk/treatments/fertility-preservation/information-for-trans-and-non-binary-people-seeking-fertility-treatment/) on the HFEA website.

Surgery for adults

Some people may decide to have surgery to permanently alter body parts associated with their biological sex.

Based on the recommendations of doctors at the gender dysphoria clinic, you will be referred to a surgeon outside the clinic who is an expert in this type of surgery.

In addition to you having socially transitioned to your preferred gender identity for at least a year before a referral is made for gender surgery, it is also advisable to:

- not smoke
- lose weight if you are overweight (BMI of 25 or over)
- have taken cross-sex hormones for some surgical procedures

It's also important that any long-term conditions, such as diabetes or high blood pressure, are well controlled.

Surgery for trans men

Common chest procedures for trans men (trans-masculine people) include:

- removal of both breasts (bilateral mastectomy) and associated chest reconstruction
- nipple repositioning
- dermal implant and tattoo

Gender surgery for trans men includes:

- construction of a penis (phalloplasty or metoidioplasty)
- construction of a scrotum (scrotoplasty) and testicular implants
- a penile implant

Removal of the womb (hysterectomy) and the ovaries and fallopian tubes (salpingo-oophorectomy) may also be considered.

Surgery for trans women

Gender surgery for trans women includes:

- removal of the testes (orchidectomy)
- removal of the penis (penectomy)
- construction of a vagina (vaginoplasty)
- construction of a vulva (vulvoplasty)
- construction of a clitoris (clitoroplasty)

Breast implants for trans women (trans-feminine people) are not routinely available on the NHS.

Facial feminisation surgery and hair transplants are not routinely available on the NHS.

As with all surgical procedures there can be complications. Your surgeon should discuss the risks and limitations of surgery with you before you consent to the procedure.

Life after transition

Whether you've had hormone therapy alone or combined with surgery, the aim is that you no longer have gender dysphoria and feel at ease with your identity.

Your health needs are the same as anyone else's with a few exceptions:

- you'll need lifelong monitoring of your hormone levels by your GP
- you'll still need contraception if you are sexually active and have not yet had any gender surgery
- you'll need to let your optician and dentist know if you're on hormone therapy as this may affect your treatment

- you may not be called for screening tests as you've changed your name on medical records – ask your GP to notify you for cervical and breast screening if you're a trans man with a cervix or breast tissue
- trans-feminine people with breast tissue (and registered with a GP as female) are routinely invited for breast screening from the ages of 50 up to 71

Find out more about screening for trans and non-binary people (Link: https://www.gov.uk/government/publications/nhs-population-screening-information-for-transgender-people) on GOV.UK.

NHS guidelines for gender dysphoria

NHS England has published what are known as service specifications that describe how clinical and medical care is offered to people with gender dysphoria:

- Non-surgical interventions for adults (Link: https://www.england.nhs.uk/publication/service-specification-gender-identity-services-for-adults-non-surgical-interventions/)
- Surgical interventions for adults (Link: https://www.england.nhs.uk/publication/service-specification-gender-identity-services-for-adults-surgical-interventions/)
- Services for children and young people (PDF, 1.15Mb) (Link: https://www.england.nhs.uk/wp-content/uploads/2017/04/gender-development-service-children-adolescents.pdf)
- Amendments to services for children and young people (PDF, 16kb) (Link: https://www.england.nhs.uk/wp-content/uploads/2020/12/Amendment-to-Gender-Identity-Development-Service-Specification-for-Children-and-Adolescents.pdf)

Review of gender identity services

NHS England has commissioned an independent review of gender identity services for children and young people. The review will advise on any changes needed to the service specifications for children and young people.

Page last reviewed: 28 May 2020
Next review due: 28 May 2023

Exhibit 2

Cornell University

Search Methodology

Search Methodology for Research Analysis on the Effect of Gender Transition on Transgender Well-being:

We conducted a comprehensive literature review of all scholarly articles published in English between 1991 and June 2017 that addressed the following question: *What does the scholarly research say about the effect of gender transition on transgender well-being?*

Our research protocol was developed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Guidelines. We used the PICOS (Participants, Interventions, Comparisons, Outcomes, and Study Design) criteria to organize our approach to this research question:

- **Participants:** Adults who have been diagnosed with gender dysphoria, who have transitioned gender, or who self-identify as transgender
- **Interventions:** Any medical service that affirms the individual's self-identified gender identity; a relevant medical service was any service, treatment, or procedure indicated for the treatment of gender dysphoria in the accepted expert *Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming Individuals* maintained by the World Professional Association for Transgender Health (version 7, 2011)
- **Comparisons:** No specific comparison design was required so long as the study investigated the effect of gender transition on transgender well-being
- **Outcomes:** Assessment of a transgender individual's mental or social well-being, such as successful functioning, mental status, quality of life, or life or relationship satisfaction
- **Study Design:** Any peer-reviewed study that undertook an evaluative (quantitative or qualitative) assessment of relevant outcomes for the population of interest; we did not impose requirements regarding minimum length of follow-up or other aspects of the study design

To identify eligible studies, we began by searching PubMed using the Medical Subject Headings (MeSH) "transgender persons," "transsexualism," "sex reassignment procedures," "sex reassignment surgery," and "health services for transgender persons" in conjunction with text words such as "transgender men," "transgender women," "male to female," "female to male," "quality of life," and "outcomes."

This search returned 4347 non-duplicate articles. We then performed a hand-search of journals known to address transgender issues as well as existing literature reviews on the topic of gender transition and transgender well-being. From this search, we selected additional studies that appeared to address our research question. On the basis of title reviews, we narrowed our list to 589 studies that appeared to address our research question. We then read the abstracts of those studies and further narrowed our list based on whether the studies directly assessed well-being in the context of gender transition. This process yielded 124 studies.

The final step of our search was for two reviewers to independently read the full text of each article to determine if it directly addressed our research question. We eliminated studies, for instance, that did not assess the outcomes of gender transition, that investigated minors instead of adults, and that evaluated physical rather than mental health outcomes (because we did not want to conflate assessments of specific surgical techniques, for example, with the broader question of whether gender transition improves well-being).

We identified 56 peer-reviewed studies consisting of primary research that met all the above criteria. We then classified them according to whether they found improved well-being, had mixed or null findings, or found that gender transition causes harm, and reported both the number of studies in each category, as well as eight findings that emerged from our review of the literature.

Separately from the 56 studies we evaluated, we included in our portal 16 additional articles that consist of literature reviews and practitioner guidelines that we did not count in our tally. We provide these as an added resource for researchers, practitioners, journalists, policymakers and the public with an interest in transgender care issues.

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Exhibit 3

Young Adult Psychological Outcome After Puberty Suppression and Gender Reassignment

WHAT'S KNOWN ON THIS SUBJECT: Puberty suppression has rapidly become part of the standard clinical management protocols for transgender adolescents. To date, there is only limited evidence for the long-term effectiveness of this approach after gender reassignment (cross-sex hormones and surgery).

WHAT THIS STUDY ADDS: In young adulthood, gender dysphoria had resolved, psychological functioning had steadily improved, and well-being was comparable to same-age peers. The clinical protocol including puberty suppression had provided these formerly gender-dysphoric youth the opportunity to develop into well-functioning young adults.

abstract

BACKGROUND: In recent years, puberty suppression by means of gonadotropin releasing hormone analogs has become accepted in clinical management of adolescents who have gender dysphoria (GD). The current study is the first longer term longitudinal evaluation of the effectiveness of this approach.

METHODS: A total of 55 young transgender adults (22 transwomen and 33 transmen) who had received puberty suppression during adolescence were assessed 3 times: before the start of puberty suppression (mean age, 13.6 years), when cross sex hormones were introduced (mean age, 16.7 years), and at least 1 year after gender reassignment surgery (mean age, 20.7 years). Psychological functioning (GD, body image, global functioning, depression, anxiety, emotional and behavioral problems) and objective (social and educational/professional functioning) and subjective (quality of life, satisfaction with life and happiness) well being were investigated.

RESULTS: After gender reassignment, in young adulthood, the GD was alleviated and psychological functioning had steadily improved. Well being was similar to or better than same age young adults from the general population. Improvements in psychological functioning were positively correlated with postsurgical subjective well being.

CONCLUSIONS: A clinical protocol of a multidisciplinary team with mental health professionals, physicians, and surgeons, including puberty suppression, followed by cross sex hormones and gender reassignment surgery, provides gender dysphoric youth who seek gender reassignment from early puberty on, the opportunity to develop into well functioning young adults. *Pediatrics* 2014;134:696 704

AUTHORS: Annelou L.C. de Vries, MD, PhD,[a] Jenifer K. McGuire, PhD, MPH,[b] Thomas D. Steensma, PhD,[a] Eva C.F. Wagenaar, MD,[a] Theo A.H. Doreleijers, MD, PhD,[a] and Peggy T. Cohen-Kettenis, PhD[a]

[a]Center of Expertise on Gender Dysphoria, VU University Medical Center, Amsterdam, Netherlands; and [b]Department of Human Development, Washington State University, Pullman, Washington

KEY WORDS

gender dysphoria, transgenderism, adolescents, psychological functioning, puberty suppression, longitudinal outcomes

ABBREVIATIONS

ABCL Adult Behavior Checklist
ASR Adult Self Report
BDI Beck Depression Inventory
BIS Body Image Scale
CBCL Child Behavior Checklist
CGAS Children's Global Assessment Scale
CSH cross sex hormones
GD gender dysphoria
GnRHa gonadotropin releasing hormone analogs
GRS gender reassignment surgery
SHS Subjective Happiness Scale
STAI Spielberger's Trait Anxiety Scale
SWLS Satisfaction With Life Scale
TPI Spielberger's Trait Anger Scale
UGDS Utrecht Gender Dysphoria Scale
YSR Youth Self Report

Dr de Vries conceptualized the study, clinically assessed the participants, drafted the initial manuscript, and reviewed and revised the manuscript; Dr McGuire conceptualized the study, planned and carried out the analyses, assisted in drafting the initial manuscript, and reviewed and revised the manuscript; Dr Steensma conceptualized the study, coordinated and supervised data collection, and reviewed and revised the manuscript; Dr Wagenaar coordinated and invited participants for assessments and reviewed and revised the manuscript; Drs Doreleijers and Cohen Kettenis conceptualized the study and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

Dr McGuire's current affiliation is Department of Family Social Science, College of Education and Human Development, St Paul, Minnesota.

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Address correspondence to Annelou L.C. de Vries, MD, PhD, Child and Adolescent Psychiatrist, Center of Expertise on Gender Dysphoria, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, Netherlands. E mail: alc.devries@vumc.nl

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Transgender adolescents experience an incongruence between their assigned gender and their experienced gender and may meet the Diagnostic and Statistical Manual of Mental Disorders 5 criteria for gender dysphoria (GD).[1] Fifteen years ago, pubertal delay was introduced as an aid in the treatment of a gender dysphoric adolescent.[2] Although not without debate, blocking pubertal development has rapidly become more widely available[3 7] and is now part of the clinical management guidelines for GD.[8 12]

Gonadotropin releasing hormone analogs (GnRHa) are a putatively fully reversible[13] medical intervention intended to relieve distress that gender dysphoric adolescents experience when their secondary sex characteristics develop. A protocol designed by Cohen Kettenis and Delemarre van de Waal[14] (sometimes referred to as "the Dutch model")[4,7] considers adolescents, after a comprehensive psychological evaluation with many sessions over a longer period of time, eligible for puberty suppression, cross sex hormones (CSH), and gender reassignment surgery (GRS) at the respective ages of 12, 16, and 18 years when there is a history of GD; no psychosocial problems interfering with assessment or treatment, for example, treatment might be postponed because of continuous moving from 1 institution to another or repeated psychiatric crises; adequate family or other support; and good comprehension of the impact of medical interventions.[12] Puberty suppression is only started after the adolescent actually enters the first stages of puberty (Tanner stages 2 3), because although in most prepubertal children GD will desist, onset of puberty serves as a critical diagnostic stage, because the likelihood that GD will persist into adulthood is much higher in adolescence than in the case of childhood GD.[15,16]

Despite the apparent usefulness of puberty suppression, there is only limited evidence available about the effectiveness of this approach. In the first cohort of adolescents who received GnRHa, we demonstrated an improvement in several domains of psychological functioning after, on average, 2 years of puberty suppression while GD remained unchanged.[16] The current study is a longer term evaluation of the same cohort, on average, 6 years after their initial presentation at the gender identity clinic. This time, we were not only interested in psychological functioning and GD, but added as important outcome measures objective and subjective well being (often referred to as "quality of life"), that is, the individuals' social life circumstances and their perceptions of satisfaction with life and happiness.[17 19] After all, treatment cannot be considered a success if GD resolves without young adults reporting they are healthy, content with their lives, and in a position to make a good start with their adult professional and personal lives.[20] Because various studies show that transgender youth may present with psychosocial problems,[21,22] a clinical approach that includes both medical (puberty suppression) and mental health support (regular sessions, treatment when necessary, see Cohen Kettenis et al[12]) aims to improve long term well being in all respects.

In the present longitudinal study, 3 primary research questions are addressed. Do gender dysphoric youth improve over time with medical intervention consisting of GnRHa, CSH, and GRS? After gender reassignment, how satisfied are young adults with their treatment and how do they evaluate their objective and subjective well being? Finally, do young people who report relatively greater gains in psychological functioning also report a higher subjective well being after gender reassignment?

METHODS

Participants and Procedure

Participants included 55 young adults (22 transwomen [natal males who have a female gender identity] and 33 transmen [natal females who have a male gender identity]) of the first cohort of 70 adolescents who had GD who were prescribed puberty suppression at the Center of Expertise on Gender Dysphoria of the VU University Medical Center and continued with GRS between 2004 and 2011. These adolescents belonged to a group of 196 consecutively referred adolescents between 2000 and 2008, of whom 140 had been considered eligible for medical intervention and 111 were prescribed puberty suppression (see de Vries et al[16]). The young adults were invited between 2008 and 2012, when they were at least 1 year past their GRS (vaginoplasty for transwomen, mastectomy and hysterectomy with ovariectomy for transmen; many transmen chose not to undergo a phalloplasty or were on a long waiting list). Nonparticipation (n = 15, 11 transwomen and 4 transmen) was attributable to not being 1 year postsurgical yet (n = 6), refusal (n = 2), failure to return questionnaires (n = 2), being medically not eligible (eg, uncontrolled diabetes, morbid obesity) for surgery (n = 3), dropping out of care (n = 1), and 1 transfemale died after her vaginoplasty owing to a postsurgical necrotizing fasciitis. Between the 55 participants and the 15 nonparticipating individuals, Student's t tests revealed no significant differences on any of the pretreatment variables. A similar lack of differences was found between the 40 participants who had complete data and the 15 who were missing some data.

Participants were assessed 3 times: pretreatment (T0, at intake), during treatment (T1, at initiation of CSH), and post treatment (T2, 1 year after GRS). See Table 1 for age at the different time points. The VU University Medical Center medical ethics committee approved the study, and all participants gave informed consent.

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TABLE 1 Age at Different Treatment Milestones and Intelligence by Gender

Variable	All Participants[a] (*N* = 55)		Transwomen (Natal Males) (*N* = 22)	Transmen (Natal Females) (*N* = 33)
Age, y	Mean (SD)	Range	Mean (SD)	Mean (SD)
At assessment PreT	13.6 (1.9)	11.1 17.0	13.6 (1.8)	13.7 (2.0)
At start of GnRHa	14.8 (1.8)	11.5 18.5	14.8 (2.0)	14.9 (1.9)
At start of CSH	16.7 (1.1)	13.9 19.0	16.5 (1.3)	16.8 (1.0)
At GRS	19.2 (0.9)	18.0 21.3	19.6 (0.9)	19.0 (0.8)
At assessment PostT	20.7 (1.0)	19.5 22.8	21.0 (1.1)	20.5 (0.8)
Full scale intelligence[b]	99.0 (14.3)	70 128	97.8 (14.2)	100.4 (14.3)

PostT, post treatment; PreT, pre treatment

[a] Comparisons between those who had complete data (*n* 40) and those who had missing data on the CBCL/ABCL (*n* 15) reveal no significant differences between the groups in age at any point in the study or in natal sex

[b] WISC R, the WISC III, or the WAIS III at first assessment, depending on age and time [45 47]

Measures

Time was the predominate independent variable. Other demographic characteristics were incorporated in some models, including, age, natal sex, Full Scale Intelligence, and parent marital status; where significantly different they are reported.

Gender Dysphoria/Body Image

There was 1 indicator measuring GD (Utrecht Gender Dysphoria Scale [UGDS]) and 3 indicators measuring body image (Body Image Scale [BIS] with primary, secondary, and neutral subscales). Higher UGDS (12 items, 1 5 range, total score ranging from 12 60) total scores indicate higher levels of GD, for example, "I feel a continuous desire to be treated as a man/woman."[23] There are separate versions of the UGDS for males and females with mostly different items, permitting no gender difference analyses. BIS (30 items, 1 5 range) higher scores indicate more dissatisfaction with primary sex characteristics (important gender defining body characteristics, eg, genitals, breasts), secondary sex characteristics (less obvious gender defining features, eg, hips, body hair), and neutral (hormonally unresponsive) body characteristics (eg, face, height).[24] The male and the female BIS are identical except for the sexual body parts. The UGDS and the BIS of the natal gender were administered at T0 and T1. At T1, we chose the UGDS of the assigned gender, because no physical changes had occurred yet and some were still treated as their assigned gender. This way, however, decreased GD caused by social transitioning was not measured. At T2 young adults filled out the versions of their affirmed gender.

Psychological Functioning

There were 10 indicators assessing psychological functioning. To assess global functioning, the Children's Global Assessment Scale (CGAS) was used.[25] The Beck Depression Inventory (BDI; 21 items, 0 3 range) indicates presence and severity of depressive symptoms.[26] Spielberger's Trait Anger (TPI) and Spielberger's Trait Anxiety (STAI; 10 and 20 items, respectively, 1 4 range) scales of the State Trait Personality Inventory were administered to assess the tendency to respond with anxiety or anger, respectively, to a threatening or annoying situation.[27,28]

Behavioral and emotional problems were assessed by the total, internalizing, and externalizing T scores as well as clinical range scores for these 3 indices (T score >63) of the Child/Adult Behavior Checklist (CBCL at T0 and T1, ABCL at T2), the Youth/Adult Self Report (YSR at T0 and T1, ASR at T2).[29 31] Items referring to GD in the CBCL/YSR and ABCL/ASR were scored as 0 (for more explanation, see Cohen Kettenis et al[32]).

Objective and Subjective Well Being (T2 Only)

A self constructed questionnaire was used to ask the young adults about their current life circumstances, such as living conditions, school and employment, and social support (objective well being), and satisfaction with treatment (subjective well being). Three instruments further assessed subjective well being. To measure quality of life, the WHOQOL BREF (quality of life measure developed by the World Health Organization) was administered (24 items, 4 domains: Physical Health, Psychological Health, Social Relationships, and Environment, 1 5 range with higher scores indicating better quality of life).[17] The Satisfaction With Life Scale (SWLS, 5 items, 5 35 range, 20 being neutral) was used to assess life satisfaction.[18] Higher scores on the Subjective Happiness Scale (SHS, 4 items, 7 point Likert scale, average score 1 7) reflect greater happiness.[19]

Data Analyses

General Linear Models examined the repeated measures with an analysis of variance based model, incorporating continuous and categorical predictors, and correcting for the unbalanced cell sizes. Linear and quadratic effects of the 14 indicators across 3 time points, with time as the within subjects factor, and sex as a between subjects factor in a second set of analyses are reported in Tables 2 and 3 and Fig 1. A linear effect signifies an overall change across T0 to T2. A quadratic effect signifies that the change was not continuous, such as when an indicator does not improve from T0 to T1 but improves from T1 to T2. It is possible to have both a significant linear and quadratic effect on the same

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TABLE 2 Gender Dysphoria and Body Image of Adolescents at Intake (T0), While on Puberty Suppression (T1), and After Gender Reassignment (T2)

	N[a]	T0	T1	T2	T0 T2	Time	Time × Sex
					t test	Linear Effect Quadratic Effect	Linear Effect Quadratic Effect
		Mean (SD)	Mean (SD)	Mean (SD)	*P*	*P*	*P*
UGDS	33	53.51 (8.29)	54.39 (7.70)	15.81 (2.78)	<.001		
MtF	11	47.07 (11.05)	48.95 (10.80)	17.27 (2.57)	<.001	<.001	n/a
						<.001	
FtM	22	56.74 (3.74)	57.11 (3.40)	15.08 (2.64)	<.001	<.001	n/a
						<.001	
Body Image (BIS)							
Primary sex characteristics	45	4.13 (0.59)	4.05 (0.60)	2.59 (0.82)	<.001	<.001	.01
						<.001	.45
MtF	17	4.03 (0.68)	3.82 (0.56)	2.07 (0.74)	<.001		
FtM	28	4.18 (0.53)	4.13 (0.60)	2.89 (0.71)	<.001		
Secondary sex characteristics	45	2.73 (0.72)	2.86 (0.67)	2.27 (0.56)	<.001	<.001	.10
						<.001	<.001
MtF	17	2.63 (0.60)	2.34 (0.68)	1.93 (0.63)	<.001		
FtM	28	2.80 (0.72)	3.18 (0.43)	2.48 (0.40)	.05		
Neutral body characteristics	45	2.35 (0.68)	2.49 (0.53)	2.23 (0.49)	.29	.29	.007
						.01	.01
MtF	17	2.57 (0.70)	2.29 (0.50)	2.09 (0.56)	.014		
FtM	28	2.21 (0.64)	2.61 (0.52)	2.32 (0.44)	.40		

FtM, female to male transgender; MtF, male to female transgender; n/a, not applicable

[a] Participants who had complete data at all 3 waves were included Some assessments were added to the study later, yielding fewer total participants for those scales

indicator. Other potential between subjects factors (age, total IQ, parental marital status) were examined but excluded owing to a lack of relationship with the 14 indicators at T0. The 1 exception, age predicting secondary sex characteristics, is described below in the findings. We compared T2 sample means to population norms for subjective well being using 1 sample *t* tests from previously published validation studies. Finally, we examined T2 subjective well being correlations with residual change scores from T0 to T2 on the 14 indicators (an indicator of who improved relatively more or less over time).

All measures used were self reported, except the CGAS (attending clinician) and the CBCL/ASR (parents). Each participant was given all measures at each of 3 assessments. Numbers varied across indicators owing to the later inclusion of the YSR, CGAS, BDI, TPI, and STAI, yielding 8 persons who had missing data at T0 and a clinician error yielding missing data at T1 for 10 participants on the UGDS. Dutch versions were used (see de Vries et al[16]).

RESULTS

Gender Dysphoria and Body Satisfaction

Figure 1 and Table 2 show that GD and body image difficulties persisted through puberty suppression (at T0 and T1) and remitted after the administration of CSH and GRS (at T2) (significant linear effects in 3 of 4 indicators, and significant quadratic effects in all indicators). Time by sex interactions revealed that transwomen reported more satisfaction over time with primary sex characteristics than transmen and a continuous improvement in satisfaction with secondary and neutral sex characteristics. Transmen reported more dissatisfaction with secondary and neutral sex characteristics at T1 than T0, but improvement in both from T1 to T2. Age was a significant covariate with secondary sex characteristics (the only significant demographic covariate with any outcome indicator in the study), indicating that older individuals were more dissatisfied at T0, but the age gap in body satisfaction narrowed over time ($F(1, 42) = 8.18$; $P < .01$).

Psychological Functioning

As presented in Table 3, significant linear effects showed improvement over time in global functioning (CGAS), CBCL/ABCL total, internalizing and externalizing *T* scores, and YSR/ASR total and internalizing *T* scores. Quadratic effects revealed decreases from T0 to T1 followed by increases from T1 to T2 in depression and YSR/ASR internalizing *T* scores. Quadratic trends revealed decreases from T0 to T1, followed by increases from T1 to T2 in depression and YSR/ASR internalizing *T* scores. For all CBCL/ABCL and YSR/ASR indicators except YSR/ASR externalizing, the percentage in the clinical range dropped significantly (McNemar's test, *P* value <0.05) from T0 to T1, from T0 to T2, or from T1 to T2.

Over time, transmen showed reduced anger, anxiety, and CBCL/ABCL externalizing *T* scores, whereas transwomen showed stable or slightly more symptomatology on these measures. Transwomen improved in CBCL/ABCL total *T* scores in a quadratic fashion (all the improvement between T1 and T2),

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TABLE 3 Psychological Functioning of Adolescents at Intake (T0), While on Puberty Suppression (T1), and After Gender Reassignment (T2)

	N[a]	T0	T1	T2	T0 T2	Time	Time × Sex
					t test	Linear Effect Quadratic Effect	Linear Effect Quadratic Effect
		Mean (SD)	Mean (SD)	Mean (SD)	*P*	*P*	*P*
Global functioning (CGAS)	32	71.13 (10.46)	74.81 (9.86)	79.94 (11.56)	<.001	<.001	.89
						.61	.68
MtF	15	74.33 (7.53)	78.20 (9.56)	82.40 (8.28)	<.001		
FtM	17	67.65 (11.87)	70.65 (9.89)	76.29 (14.48)	.02		
Depression (BDI)	32	7.89 (7.52)	4.10 (6.17)	5.44 (8.40)	.21	.23	.66
						.04	.49
MtF	12	4.73 (4.20)	2.25 (3.54)	3.38 (4.40)	.12		
FtM	20	10.09 (8.34)	5.05 (7.08)	6.95 (9.83)	.32		
Anger (TPI)	32	17.55 (5.72)	17.22 (5.61)	16.01 (5.28)	.20	.15	.04
						.52	.12
MtF	12	14.17 (3.01)	14.00 (3.36)	5.58 (3.92)	.18		
FtM	20	19.55 (5.96)	19.25 (5.69)	16.56 (6.06)	.05		
Anxiety (STAI)	32	39.57 (10.53)	37.52 (9.87)	37.61 (10.39)	.45	.42	.05
						.47	.52
MtF	12	31.87 (7.42)	31.71 (8.36)	35.83 (10.22)	.14		
FtM	20	44.41 (9.06)	41.59 (9.03)	39.20 (10.53)	.12		
CBCL ABCL							
Total *T* score	40	60.20 (12.66)	54.70 (11.58)	48.10 (9.30)	<.001	<.001	.25
% Clinical		38_x	20_y	5_y		.68	.03
MtF	15	57.40 (12.76)	49.67 (12.29)	48.13 (12.58)	.002		
FtM	25	61.88 (12.56)	57.72 (10.23)	48.08 (6.95)	<.001		
Int *T* score	40	60.83 (12.36)	54.42 (10.58)	50.45 (10.04)	<.001	<.001	.91
% Clinical		30_x	12.5_y	10_y		.42	.33
MtF	15	59.40 (10.03)	50.93 (11.15)	48.73 (12.61)	<.001		
FtM	25	61.68 (13.70)	56.52 (9.86)	51.48 (8.25)	<.001		
Ext *T* score	40	57.85 (13.73)	53.85 (12.77)	47.85 (8.59)	<.001	<.001	.19
% Clinical		40_x	25_x	2.5_y		.43	.12
MtF	15	52.53 (14.11)	47.87 (12.07)	46.33 (10.95)	.10		
FtM	25	61.04 (12.71)	57.44 (12.01)	48.76 (6.89)	<.001		
YSR ASR							
Total *T* score	43	54.72 (12.08)	49.16 (11.16)	48.53 (9.46)	.005	.005	.28
% Clinical		30_x	14_{xy}	7_y		.07	.75
MtF	17	50.65 (12.19)	45.94 (12.24)	47.24 (12.28)	.28		
FtM	26	57.38 (11.47)	51.27 (10.08)	49.38 (7.21)	.01		
Int *T* score	43	55.47 (13.08)	48.65 (12.33)	50.07 (11.15)	.03	.03	.87
% Clinical		30_x	9.3_y	11.6_{xy}		.008	.73
MtF	17	54.00 (12.31)	47.59 (14.26)	48.12 (12.54)	.04		
FtM	26	56.42 (13.86)	49.35 (11.13)	51.35 (10.19)	.17		
Ext *T* score	43	52.77 (12.47)	49.44 (9.59)	49.44 (9.37)	.14	.14	.005
% Clinical		21_x	11.6_x	7_x		.09	.14
MtF	17	46.00 (11.58)	44.71 (9.53)	50.24 (11.18)	.17		
FtM	26	57.16 (11.14)	52.54 (8.43)	48.92 (8.18)	.006		

FtM, female to male transgender; MtF, male to female transgender

$_{xy}$ Percent clinical range, shared subscripts indicate no significant difference in values In no case was an increase in percent in the clinical range significant from 1 time point to any other time point, indicating an overall decline or stability of clinical symptoms over time

[a] Participants who had complete data at all 3 waves were included Some assessments were added to the study later, yielding fewer total participants for those scales

whereas transmen improved steadily across the 3 time points (linear effect only).

Objective Well Being

At T2, the participants were vocationally similar to the Dutch population except they were slightly more likely to live with parents (67% vs 63%), and more likely, when studying, to be pursuing higher education (58% vs 31%).[33]

Families were supportive of the transitioning process: 95% of mothers, 80% of fathers, and 87% of siblings. Most (79%) young adults reported having 3 or more friends, were satisfied with their male (82%) and female peers (88%), and almost all (95%) had received support from friends regarding their gender reassignment. After their GRS, many participants (89%) reported having been never or seldom called names or harassed. The majority (71%) had experienced social transitioning as easy.

Subjective Well Being

None of the participants reported regret during puberty suppression, GSH

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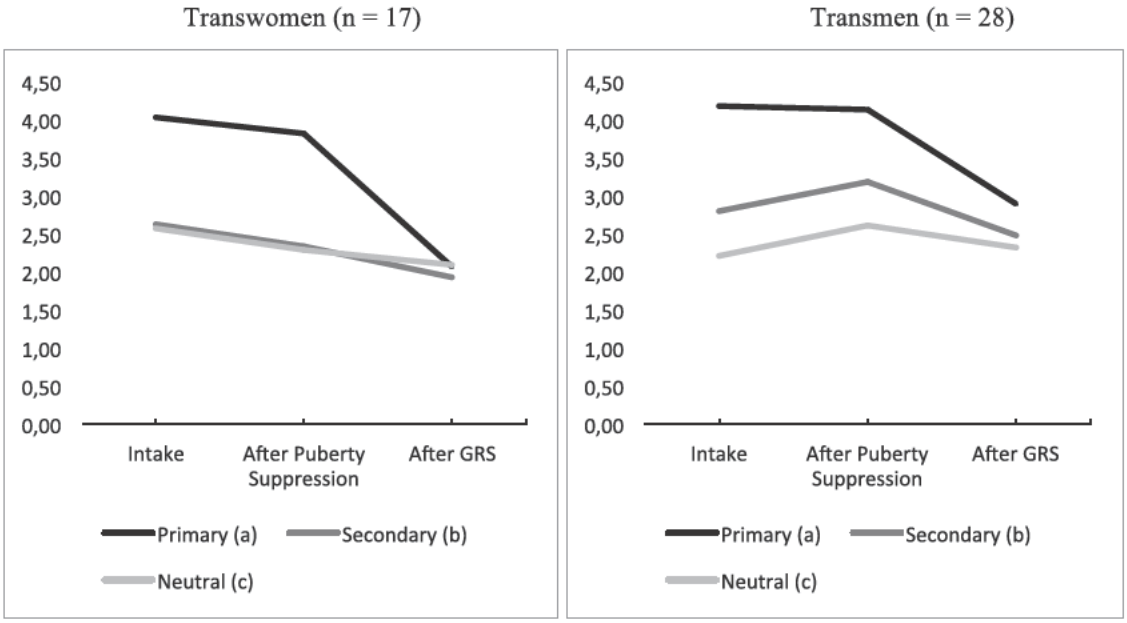

Eta Squared for Linear and Quadratic Effects

(a) Primary sex characteristics
Time: .79 ($P < .001$), .66 ($P < .001$),
Time × sex: .14 ($P = .01$), .01 ($P = .45$),

(b) Secondary sex characteristics
Time: .31($P < .001$), .30 ($P < .001$),
Time × sex: .06 ($P = .10$), .22 ($P < .001$)

(c) Neutral body characteristics
Time: .07($P < .001$), .09 ($P = .29$)
Time × sex: .16 ($P = .007$), .15 ($P = .01$)

FIGURE 1
BIS[23] for transwomen and transmen at T0 (pretreatment, at intake), T1 (during treatment, at initiation of cross gender hormones), and T2 (post treatment, 1 year after GRS).

treatment, or after GRS. Satisfaction with appearance in the new gender was high, and at T2 no one reported being treated by others as someone of their assigned gender. All young adults reported they were very or fairly satisfied with their surgeries.

Mean scores on WHOQOL BREF, the SWLS, and the SHS are presented in Table 4, together with scores from large validation and reliability studies of these measures,[17,19,34] revealing similar scores in all areas except WHOQOL Environment subdomain, which was higher for the participants than the norm. There were some differences across gender; transwomen scored higher than transmen on the SWLS (mean = 27.7; SD = 5.0 vs mean = 23.2; SD = 6.0; t (52) = 2.82; $P < .01$) and on the psychological subdomain of the WHOQOL (mean = 15.77; SD = 2.0 vs mean = 13.92; SD = 2.5; t (53) = 2.95; $P < .01$).

Correlations With Residual Change Scores

The residual change scores of secondary sex characteristics, global functioning, depression, anger, anxiety, and YSR total, internalizing and externalizing from T0 to T2, were significantly correlated with the 6 T2 quality of life indicators. Most correlation coefficients were within the moderate to large magnitude (eg, 0.30 0.60), except depression, which was highly correlated (0.60 0.80) (see Table 5).

DISCUSSION

Results of this first long term evaluation of puberty suppression among transgender adolescents after CSH treatment and GRS indicate that not only was GD resolved, but well being was in many respects comparable to peers.

The effectiveness of CSH and GRS for the treatment of GD in adolescents is in line with findings in adult transsexuals.[35,36] Whereas some studies show that poor surgical results are a determinant of postoperative psychopathology and of dissatisfaction and regret,[37,38] all young adults in this study were generally satisfied with their physical appearance and none regretted treatment. Puberty suppression had caused their bodies to

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TABLE 4 Subjective Well Being: Quality of Life, Satisfaction With Life, and Subjective Happiness Mean Scores With Scores From Validation Studies

	N	Mean (SD)	Range	Validation Studies Scores Mean (SD)	Comparison *P*
WHOQOL[a] Physical	55	15.22 (2.49)	8.6 20.0	15.0 (2.9)[b]	.56
WHOQOL Psychological	55	14.66 (2.44)	6.67 20.0	14.3 (2.8)[b]	.24
WHOQOL Social Relations	55	14.91 (2.35)	9.3 20.00	14.5 (3.4)[b]	.18
WHOQOL Environment	55	15.47 (2.06)	10.5 20.00	13.7 (2.6)[b]	<.001
SWLS	54	24.98 (6.0)	9.0 35.0	26.18 (5.7)[c]	.16
SHS	54	4.73 (0.77)	2.75 6.0	4.89 (1.1)[d]	.17

[a] WHOQOL, Bref, Skevington et al [16]
[b] International field trial, ages 21 to 30 years, Skevington et al [16]
[c] Dutch young adults, Arindell et al [33]
[d] US Public College Students, Lyubomirsky [18]

not (further) develop contrary to their experienced gender.

Psychological functioning improved steadily over time, resulting in rates of clinical problems that are indistinguishable from general population samples (eg, percent in the clinical range dropped from 30% to 7% on the YSR/ASR[30]) and quality of life, satisfaction with life, and subjective happiness comparable to same age peers.[17,19,34] Apparently the clinical protocol of a multidisciplinary team with mental health professionals, physicians, and surgeons gave these formerly gender dysphoric youth the opportunity to develop into well functioning young adults. These individuals, of whom an even higher percentage than the general population were pursuing higher education, seem different from the transgender youth in community samples with high rates of mental health disorders, suicidality and self harming behavior, and poor access to health services.[21,22,39,40]

In this study, young adults who experienced relatively greater improvements in psychological functioning were more likely to also report higher levels of subjective postsurgical well being. This finding suggests value to the protocol that involves monitoring the adolescents' functioning, physically and psychologically, over many years, and providing more support whenever necessary.

This clinic referred sample perceived the Environmental subdomain (with items like "access to health and social care" and "physical safety and security") of the WHOQOL BREF as even better than the Dutch standardization sample.[17] Whereas in some other contexts transgender youth may experience gender related abuse and victimization,[22,41,42] the positive results may also be attributable to supportive parents, open minded peers, and the social and financial support (treatment is covered by health insurance) that gender dysphoric individuals can receive in the Netherlands.

Both genders benefitted from the clinical approach, although transwomen showed more improvement in body image satisfaction (secondary sex characteristics) and in psychological functioning (anger and anxiety). None of the transmen in this study had yet had a phalloplasty because of waiting lists or

TABLE 5 Correlations Between Residual Change in Psychological Functioning Over Time and Young Adult Subjective Well Being

	WHOQOL BREF					
	Physical	Psychological	Social	Environment	SWLS	SHS
Gender dysphoria (UGDS)	0.01 (.97)	0.05 (.75)	−0.09 (.57)	−0.02 (.89)	0.06 (.71)	0.30 (.04)
Body image subscales (BIS)						
Primary sex characteristics	−0.22 (.14)	−0.25 (.09)	−0.35 (.02)	−0.04 (.78)	−0.22 (.14)	−0.21 (.17)
Secondary sex characteristics	−0.39 (.006)	−0.45 (<.001)	−0.47 (<.001)	−0.34 (.02)	−0.35 (.02)	−0.26 (.08)
Neutral body characteristics	−0.21 (.16)	−0.27 (.07)	−0.15 (.32)	−0.28 (.06)	−0.26 (.08)	−0.16 (.28)
Psychological functioning						
Global functioning (CGAS)	0.60 (<.001)	0.52 (.002)	0.52 (.002)	0.27 (.14)	0.58 (<.001)	0.50 (.004)
Depression (BDI)	−0.76 (<.001)	−0.72 (<.001)	−0.51 (.002)	−0.49 (.003)	−0.61 (<.001)	−0.77 (<.001)
Trait anger (TPI)	−0.37 (.03)	−0.18 (.31)	−0.22 (.20)	−0.29 (.09)	−0.33 (.07)	−0.35 (.05)
Trait anxiety (STAI)	−0.58 (<.001)	−0.64 (<.001)	−0.38 (.03)	−0.44 (.01)	−0.49 (.004)	−0.57 (<.001)
CBCL ABCL						
Total *T* score	−0.20 (.20)	−0.12 (.45)	−0.07 (.65)	−0.14 (.35)	−0.32 (.03)	−0.16 (.29)
Internalizing *T* score	−0.29 (.06)	−0.29 (.06)	−0.23 (.14)	−0.12 (.44)	−0.48 (<.001)	−0.36 (.02)
Externalizing *T* score	−0.13 (.40)	−0.05 (.75)	0.16 (.29)	−0.20 (.19)	−0.15 (.36)	0.00 (.99)
Youth Self Report (YSR ASR)						
Total *T* score	−0.53 (<.001)	−0.45 (.002)	−0.33 (.03)	−0.42 (.005)	−0.52 (<.001)	−0.55 (<.001)
Internalizing *T* score	−0.62 (<.001)	−0.61 (<.001)	−0.47 (<.001)	−0.40 (.007)	−0.66 (<.001)	−0.60 (<.001)
Externalizing *T* score	−0.23 (.13)	−0.10 (.53)	−0.07 (.67)	−0.37 (.02)	−0.22 (.15)	−0.35 (.02)

P values are in parentheses

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a desire for improved surgery techni ques. This finding warrants further study of the specific concerns of young transmen.

Despite promising findings, there were various limitations. First, the study sample was small and came from only 1 clinic. Second, this study did not focus on physical side effects of treatment. Pub lications on physical parameters of the same cohort of adolescents are sub mitted or in preparation. A concurring finding exists in the 22 year follow up of the well functioning first case now at age 35 years who has no clinical signs of a negative impact of earlier puberty suppression on brain development, met abolic and endocrine parameters, or bone mineral density.[43] Third, despite the absence of pretreatment differences on measured indicators, a selection bias could exist between adolescents of the original cohort that participated in this study compared with nonparticipants.

Age criteria for puberty suppression and CSH are under debate, although they worked well for adolescents in the current study. Especially in natal fe males, puberty will often start before the age of 12 years. Despite the fact that developing evidence suggests that cog nitive and affective cross gender iden tification, social role transition, and age at assessment are related to persistence of childhood GD into adolescence, pre dicting individual persistence at a young age will always remain difficult.[44] The age criterion of 16 years for the start of CSH may be problematic especially for transwomen, as growth in height con tinues as long as cross sex steroids are not provided (causing the growth plates to close). Therefore, psychological ma turity and the capacity to give full in formed consent may surface as the required criteria for puberty suppres sion and CSH[45] in cases that meet other eligibility criteria.

CONCLUSIONS

Results of this study provide first ev idence that, after CSH and GRS, a treatment protocol including puberty suppression leads to improved psy chological functioning of transgender adolescents. While enabling them to make important age appropriate de velopmental transitions, it contrib utes to a satisfactory objective and subjective well being in young adult hood. Clinicians should realize that it is not only early medical inter vention that determines this success, but also a comprehensive multidis ciplinary approach that attends to the adolescents' GD as well as their fur ther well being and a supportive en vironment.

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Exhibit 4

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LETTER TO THE EDITOR

One Size Does Not Fit All: In Support of Psychotherapy for Gender Dysphoria

Roberto D'Angelo[1,2] · Ema Syrulnik[2] · Sasha Ayad[2] · Lisa Marchiano[2] · Dianna Theadora Kenny[2] · Patrick Clarke[2]

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Turban, Beckwith, Reisner, and Keuroghlian (2020) published a study in which they set out to examine the effects of gender identity conversion on the mental health of transgender-identifying individuals. Using the data from the 2015 U.S. Transgender Survey (USTS) (James et al., 2016), they found that survey participants who responded affirmatively to the survey question, "Did any professional (such as a psychologist, counselor, religious advisor) try to make you identify only with your sex assigned at birth (in other words, try to stop you being trans)?" reported poorer mental health than those who responded negatively to the question. From this, Turban et al. concluded that gender identity conversion efforts (GICE) are detrimental to mental health and should be avoided in children, adolescents, and adults. The study's conclusions were widely publicized by mass media outlets to advocate for legislative bans on GICE, with the study authors endorsing these calls (Bever, 2019; Fitzsimons, 2019; Turban & Keuroghlian, 2019).

We agree with Turban et al.'s (2020) position that therapies using coercive tactics to force a change in gender identity have no place in health care. We do, however, take issue with their problematic analysis and their flawed conclusions, which they use to justify the misguided notion that anything other than "affirmative" psychotherapy for gender dysphoria (GD) is harmful and should be banned. Their analysis is compromised by serious methodological flaws, including the use of a biased data sample, reliance on survey questions with poor validity, and the omission of a key control variable, namely subjects' baseline mental health status. Further, their conclusions are not supported by their own analysis. While they claim to have found evidence that GICE is associated with psychological distress, what they actually found was that those recalling GICE were more likely to be suffering from serious mental illness. Further, Turban et al.'s choice to interpret the said association as evidence of harms of GICE disregards the fact that neither the presence nor the direction of causation can be discerned from this study due to its cross-sectional design. In fact, an alternative explanation for the found association—that individuals with poor underlying mental health were less likely to be affirmed by their therapist as transgender—is just as likely, based on the data presented.

Arguably, even more problematic than the flawed analysis itself is the simplistic "affirmation" versus "conversion" binary, which permeates Turban et al.'s (2020) narrative and establishes the foundation for their analysis and conclusions. The notion that all therapy interventions for GD can be categorically classified into this simplistic binary betrays a misunderstanding of the complexity of psychotherapy. At best, this blunt classification overlooks a wide range of ethical and essential forms of agenda-free psychotherapy that do not fit into such a binary; at worst, it effectively mis-categorizes ethical psychotherapies that do not fit the "affirmation" descriptor as conversion therapies. Stigmatizing non-"affirmative" psychotherapy for GD as "conversion" will reduce access to treatment alternatives for patients seeking non-biomedical solutions to their distress.

We originally raised our concerns about the quality of Turban et al.'s (2020) study and the validity of their conclusions in a Letter to the Editor of *JAMA Psychiatry*, where the study had been published. However, our letter was rejected, apparently due to space limitations. In the ensuing months, as we observed Turban et al.'s unsupported claims of the harms of psychotherapy for GD taking root globally (United Nations, 2020), we felt compelled to write a more detailed critique of the study, which we present here. Our aim is to put the spotlight on the more problematic areas of Turban et al.'s analysis and to illustrate how heeding their recommendations will limit access to ethical psychotherapy for

✉ Roberto D'Angelo
roberto@robertodangelo.com

[1] Institute of Contemporary Psychoanalysis, Los Angeles, CA 90064, USA

[2] Society for Evidence-Based Gender Medicine, Twin Falls, ID, USA

individuals suffering from GD, further disadvantaging this already highly vulnerable population.

Biased Sample

Turban et al.'s (2020) analysis used data from the 2015 USTS survey of transgender-identifying individuals (James et al., 2016). This survey used convenience sampling, a methodology which generates low-quality data (Bornstein, Jager, & Putnick, 2013). Specifically, the participants were recruited through transgender advocacy organizations and subjects were asked to "pledge" to promote the survey among friends and family. This recruiting method yielded a large but highly skewed sample. While Turban et al. acknowledged that the USTS may not be representative of the U.S. transgender population, they treat it as a valid source of data for major policy recommendations, disregarding the significant bias in the underlying data.

To demonstrate this apparent bias, we have constructed Table 1, which compares the demographic characteristics of the USTS participants to those of transgender participants from a high-quality probability sample collected by the Centers for Disease Control Behavioral Risk Factors Surveillance System (BRFSS) (Baker, 2019; CDC, 2014–2017). As Table 1 illustrates, even after applying weighting to correct for known survey biases, the USTS participants were far more likely to be young (42% vs. 22% were 18–24 years old) and educated (47% vs. 14% had completed post-secondary education) than BRFSS participants. They were far less likely to own a home (16% vs. 55%) or to be married or coupled (18% vs. 46%). They were also much more likely to have a non-binary identity (38% vs. 22%) and a markedly different self-reported sexual orientation: Only 15% of the USTS participants reported a heterosexual orientation, compared to 69% of the BRFSS participants. (It is not clear if sexuality in either case was reported relative to one's sex or gender identity.)

A number of additional data irregularities in the USTS raise further questions about the quality of data captured by the survey. A very high number of the survey participants (nearly 40%) had not transitioned medically or socially at the time of the survey, and a significant number reported no intention to transition in the future. The information about treatments received does not appear to be accurate, as a number of respondents reported the initiation of puberty blockers after the age of 18 years, which is highly improbable (Biggs, 2020). Further, the survey had to develop special weighting due to the unexpectedly high proportion of respondents who reported that they were exactly 18 years old. These irregularities raise serious questions about the reliability of the USTS data.

In addition to these demonstrable data problems, there are a number of other biases in the USTS data that likely skewed the responses. By targeting transgender advocacy groups, the survey underrepresented the experiences of transgender individuals who are not politically engaged. The emphasis on the survey's goals to highlight the injustices suffered by transgender people during the recruitment stage and in the introduction of the survey instrument itself made it vulnerable to overreporting of adverse experiences due to "demand bias" (also known as the "good subject effect"). This form of bias occurs when the researchers reveal their hypothesis and aims, which encourages participants to support the investigator's aims with their answers (Nichols & Maner, 2008; Orne, 1962; Weber & Cook, 1972). Finally, the experiences of detransitioners and desisters were not included, as they were disqualified from completing the survey. Failure to include detransitioned and desisted individuals in research regarding psychological interventions for GD is a serious oversight. These individuals, whose transgender identification was transient, may have been hurt by therapies that affirmed them as transgender, and may have benefitted from therapies that helped them successfully ameliorate their GD (D'Angelo, 2020b).

These serious limitations of the USTS survey greatly undermine the validity of the findings it produced. It is imperative that any analysis based on this low-quality biased sample is validated using a high-quality probability sample before any recommendations stemming from the analysis of these data can be used to shape clinical or policy decisions.

Invalid Measure of Gender Conversion Therapy

Turban et al.'s (2020) conclusions rest on the assumption that they have a valid way of determining whether or not a respondent was exposed to the unethical practice of conversion therapy. Yet, the USTS question they relied on (Question 13.2) is too non-specific to serve as a valid measure of gender conversion therapy. Firstly, the question conflates mental health encounters with interactions with other types of professionals. Secondly, there is no information about whether the recalled encounter was self-initiated or coerced. Thirdly, it does not differentiate between diagnostic evaluations or a specific therapeutic intervention. There is also no information about whether the focus of the encounter was gender dysphoria or another condition. And finally, it does not determine whether shaming, threats, or other unethical tactics were utilized during the encounter. This lack of context and detail renders the question incapable of differentiating between ethical non-affirmative (neutral) encounters and unethical conversion therapy.

Consider a common situation where the patient is seeking approval for medical treatment for GD, where the role of the therapist is to assess the individual's mental health to

Table 1 Comparison of demographic characteristics of transgender-identifying individuals in the 2015 US Transgender Survey (USTS) and the Behavioral Risk Factor Surveillance System Survey (BRFSS) 2014–2017

	USTS, 2015[a] Transgender ($n = 27{,}715$)	BRFSS, 2014–2017[b] Transgender ($n = 3075$)
Characteristic		
Gender identity		
Transgender women (male to female)	33%	48%[e]
Transgender men (female to male)	29%	30%[e]
Non-binary/gender-non-conforming	38%	22%[e]
Sexual orientation[c]		
Heterosexual	15%	69%
Lesbian or gay	16%	10%
Bisexual	14%	15%
Other[d]	55%	7%
Age		
18–24	42%	22%
25–44	42%	30%
45–64	14%	32%
65 +	2%	17%
Race/ethnicity		
White, non-Hispanic	62%	55%
Black, non-Hispanic	13%	16%
Asian, Native Hawaiian, or Pacific Islander	5%	5%
Other, non-Hispanic	3%	5%
Hispanic	17%	19%
Education level		
Did not graduate high school	2%	21%
Graduated high school	11%	33%
Some college or technical school	40%	32%
Graduated college or technical school	47%	14%
Annual household income		
< 25,000	38%	39%
25,000–49,999	24%	24%
50,000 +	38%	37%
Home ownership		
Own	16%	55%
Rent	44%	35%
Other arrangement	40%	10%
Marital status		
Married or coupled	18%	46%
Divorced, separated, or widowed	10%	21%
Never married	72%	33%

[a]US Transgender Survey, 2015 (James et al., 2016). Weighted data

[b]CDC BRFSS Survey, 2014–2017 (Baker, 2019). Weighted data

[c]Sexual orientation reported based on the respondent self-identification

[d]Combines all the response options other than "homosexual," "lesbian/gay," or "bisexual."

[e]Calculated using 2014–2017 BRFSS data (CDC, 2014–2017). Weighted data

ensure that GD is not secondary to another condition. Such encounters can be experienced by patients as an attempt to withhold the treatment they so desperately want (Chiland, 1997). Further, patients with psychiatric diagnoses, highly prevalent in transgender-identifying populations (Gijs, van der Putten-Bierman, & De Cuypere, 2013; Goodman & Nash, 2018; Wanta, Niforatos, Durbak, Viguera, & Altinay, 2019), can potentially experience or misinterpret neutral

interpersonal interactions as invalidating or rejecting (Barnow et al., 2009; Beck & Bredemeier, 2016; Gotlib, 1983). Not only does the survey question provide no detail to help discriminate between these essential therapy encounters and unethical conversion therapy, but it arguably biases the recall of neutral encounters toward recall of conversion by using emotionally charged language (e.g., "stop you being trans") and by conflating recall of religiously motivated encounters with clinical ones.

Turban et al. (2020) ignored these issues and instead created a veneer of certainty by referring to USTS question 13.2 as GICE and used it throughout the paper as though it were a valid equivalent of conversion therapy. Not only it the term itself novel (the lead author referred to the same USTS question by yet another term, "PACGI," in a publication just weeks earlier [Turban, King, Reisner, & Keuroghlian, 2019]), but its equivalency to conversion therapy is highly debatable, in part due to the fact that the term itself has not been defined, other than through a circular reference to USTS question 13.2 itself.[1] Accounting for the many gray areas in the question wording, we propose that GICE is "any professional encounter which the subject recalls as non-affirmative of their transgender identity." As we have demonstrated, it is not uncommon for agenda-free, neutral therapy interventions to be experienced by the subjects as non-affirmative. However, non-affirmative is not the same as "conversion," as the latter implies a therapist agenda and an aim for a fixed outcome (American Psychological Association, 2015). In fact, it is the utter inability of USTS question 13.2, and consequently, GICE, to differentiate between agenda-free ethical psychotherapy and coercive, agenda-driven therapy, that is the Achilles heel of Turban et al.'s entire argument.

Misinterpretation of a Key Scale

A key finding of Turban et al.'s (2020) analysis is that the USTS participants who recalled exposure to GICE were more likely to report severe psychological distress, as evidenced by their score of ≥ 13 on the K-6 scale. From this, Turban et al. concluded that GICE has adverse effects on mental health. We will address the unsupported claim of causation in a subsequent section. Here, we would like to further explore the use of the K-6 scale to make these claims, and its implications.

The K-6 scale, and its cutoff score of ≥ 13, was specifically developed by Kessler et al. (2003) in order to discriminate between cases of non-specific psychological distress and cases of serious mental illness (SMI). Scoring ≥ 13 is predictive of having a DSM diagnosis of schizophrenia, bipolar disorder, and a range of other major mental health conditions that cause serious functional impairment (Substance Abuse and Mental Health Services Administration, 2020). Thus, Turban et al.'s (2020) finding of an association between the recall of GICE and scoring ≥ 13 actually suggests that the USTS participants recalling GICE were more likely to have a severe mental illnesses diagnosis than those not recalling GICE. Further, any claim of causation, which Turban et al. continue to suggest throughout the paper (however unsupported by the study design), would imply that exposure to GICE caused serious mental illness, in previously mentally well populations. This is a highly speculative and implausible hypothesis, which further challenges their claims.

Omission of a Key Control Variable

Turban et al.'s (2020) hypothesis, namely, that GICE exposure (during lifetime, as well as in childhood) causes poor mental health and contributes to suicide attempts, is further weakened by a significant flaw in their data analysis: failure to control for the individuals' pre-GICE-exposure mental health status. Not only does this critical omission confound the association between exposure to GICE and present mental health, but it may mask reverse causation, namely, that it was the individual's underlying poor mental health that led to their experience of GICE in the first place.

Let us revisit the example of a common clinical encounter in which a person with GD and one or more comorbid psychiatric conditions presents for assessment with the goal of obtaining approval for cross-sex hormones. An assessment of such a complex presentation generally requires multiple sessions and involves ascertaining whether the GD is secondary to another condition. It is also likely that the clinician might focus on treating the comorbid condition(s) first, before pursuing "gender-affirming" interventions. While such a contact would be recalled by the respondent as non-affirmative and thus likely classified as GICE, it is the patient's poor mental health status that led to the non-affirming content of the encounter, rather than vice versa. If the said individual had attempted suicide in the past or continued to struggle with mental illness more recently, Turban et al.'s (2020) analysis would erroneously conclude that GICE was likely responsible for those difficulties, when, in fact, no such causation occurred.

In fact, failure to control for the subjects' baseline mental health makes it impossible to determine whether the mental health or the suicidality of subjects worsened, stayed the same, or potentially even improved after the non-affirming encounter. Given the high rate of co-occurring mental illness in transgender-identifying patients (Gijs et al., 2013; Goodman & Nash, 2018; Wanta et al., 2019), failure to control for prior mental health status is a serious methodological flaw.

[1] Psychological Attempts to Change Gender Identity.

Internal Inconsistencies in Mental Health Measures

Turban et al.'s (2020) finding that mental health outcomes of persons exposed to GICE are worse than those whose encounters were "gender-affirming" is weakened by internal inconsistencies in the mental health outcome measures. We have already discussed the fact that the threshold chosen by Turban et al. on the K-6 scale detects serious mental illness, rather than distress. Another measure of psychological distress chosen by Turban et al.—substance misuse—was not significantly different between GICE and the non-GICE group. More importantly, there is a lack of consistency in the suicide measures. While lifetime suicide attempts were elevated among the GICE group, total suicide attempts in the prior 12 months, as well as suicide attempts requiring hospitalization, which generally indicate more serious attempts rather than non-suicidal self-injury, were not significantly different between the two groups. Turban et al. did not address this inconsistency. Nor did they explore the relationship between suicidality and the higher levels of serious mental illness among the GICE group, despite the well-documented link between serious mental illness and suicide (Bertolote, Fleischmann, De Leo, & Wasserman, 2004). Turban et al. did not heed their own warning not to attribute the increased lifetime suicidality entirely to GICE since "other factors are also likely to be associated with suicidality among gender-diverse people." Instead, they treat the inconsistent and unclear association between GICE and suicidality as causative and infuse it with an air of certainty by elevating it into title of their paper.

Claim of Causation When Only an Association Has Been Found

Although a causative relationship between recalled GICE and adverse mental health status is possible (even if direction of the causality is unclear), the cross-sectional design of the USTS is not capable of determining causation. While Turban et al. (2020) acknowledged this limitation and correctly referred to the relationship they found as an association, they strongly implied causation throughout their discussion, as well as in their "Conclusions and Relevance" section, which states, "These results support policy statements from several professional organizations that have discouraged this [GICE] practice." Presenting a highly confounded association as causation is a serious error, given its potential to dangerously misinform and mislead clinicians, policymakers, and the public at large about this important issue.

Discussion

The fact that coercive techniques to force unwanted changes in individuals are unethical and have no place is modern psychotherapy is self-evident and needs no additional justification. However, as we have demonstrated, Turban et al. (2020) failed to prove that GICE, as defined by affirmative answers to the USTS question, caused poor mental health or suicide attempts in study subjects. Further, since Turban et al. failed to establish equivalence between GICE, which likely subsumes a range of ethical non-affirmative interventions, and "gender conversion therapy," which implies unethical and coercive attempts to force a change in one's identity, their use of the study findings in support of a ban on "gender conversion therapy" is without any foundation.

Rather than appropriately acknowledging the significant study limitations and calling for more research, Turban et al. (2020) used their flawed findings to engage in a media campaign promoting legislative bans of GICE. Two of the study authors penned an op-ed in which they state, "It's time for conversion efforts to be illegal in every state, before more people die" (Turban & Keuroghlian, 2019). Turban, the lead author, repeated these sweeping, emotive claims on several highly visible national media platforms (Bever, 2019; Fitzsimons, 2019). In contrast, the debate regarding this study in the scientific arena was not allowed to occur. To the best of our knowledge, all of the letters written to the Editor of *JAMA Psychiatry*, many by respected academics and clinicians who outlined the serious problems in the study, have been rejected (some of them were later submitted as non-indexed comments in the online publication). The omission of these important arguments from the scientific discourse stifles scientific debate and perpetuates the current politicization of transgender health care, where treatment decisions are increasingly legislated by politicians.

While the poor study methodology is unfortunate, arguably, the most problematic aspect of Turban et al.'s (2020) work is the choice to view psychotherapy through a binary of "affirmation" versus "conversion," resulting in a conflation of ethical non-affirmative psychotherapy with conversion therapy. The self-evident crudeness of the GICE versus "affirmation" binary, promoted by Turban et al., and the potential harms of such a simplistic view of psychotherapy are illustrated by the following examples.

Consider a female victim of sexual assault, who subsequently develops an intense discomfort with her female anatomy and expresses a desire to undergo biomedical interventions to change her body. It would be unethical for the

clinician to overlook the contribution of sexual victimization to this nascent GD. A therapist enthusiastically supporting this patient's new male identity would be failing to provide appropriate treatment for what amounts to a post-traumatic condition, instead providing an inappropriate treatment with the potential to harm. Similarly, a boy who has been traumatized by relentless bullying due to his gender "non-conformity" (e.g., interest in classical music or fashion and avoidance of sports) may conclude that if he were a girl then he would "fit in" and the humiliation would stop. In this case too, gender-affirming interventions miss the mark when what this traumatized young person requires is psychotherapy.

Another obvious difficulty arises when same-sex attracted adolescents report cross-sex identifications. Research shows that a high number of homosexual adults have experienced periods of "cross-sex" behaviors and cross-gender identification in childhood and adolescence, often to a degree that is severe enough to warrant the diagnosis of GD, or gender identity disorder, as it was previously known (Bailey & Zucker, 1995; Bell, Weinberg, & Hammersmith, 1981; Hiestand & Levitt, 2005; Li, Kung, & Hines, 2017). When a dysphoric same-sex attracted young person in the midst of this developmental process presents for mental health care, a clinician overtly affirming the patient's cross-sex gender identity would be failing this patient by not addressing the patient's struggle with same-sex attraction and/or internalized homophobia. In fact, some homophobic societies and indeed families that reject homosexuality among their children have embraced the "affirmative" biomedical pathway (Bannerman, 2020; Hamedani, 2014), which poses a question as to whether "affirmative" care in some instances serves the role of gay conversion therapy.

Further, GD can present as a transient symptom that resolves spontaneously or in the context of developmentally informed psychotherapeutic treatment. Some common examples of transient gender-dysphoric states include adolescents girls, often on the autism spectrum, experiencing distress around the physical and social changes of puberty or gender-non-conforming young women struggling with shame about being seen as "butch." These individuals, searching for ways to understand and remedy their distress, can incorrectly attribute their discomfort to being transgender. Several case reports (Churcher Clarke & Spiliadis, 2019; Lemma, 2018; Spiliadis, 2019) indicate that the distress of young people with GD can lessen or resolve with appropriate psychotherapeutic interventions that address the central issues.

If anything other than "affirmation" is viewed as GICE, it follows that the provision of psychotherapy in these clinical scenarios would be seen as harmful conversion efforts. Yet these therapeutic interventions do not aim to convert or consolidate an identity, but instead aim to help individuals gain a deeper understanding of their discomfort with themselves, the factors that have contributed to their distress, and their motivations for seeking transition (Bonfatto & Crasnow, 2018; D'Angelo 2020a). These exploratory questions are consistent with the principle of therapeutic neutrality—a cornerstone of ethical psychotherapy (Simon, 1992). In fact, both "conversion" and "affirmation" therapy efforts carry the risk of undue influence, potentially compromising patient autonomy. In contrast, the provision of a neutral, unbiased psychotherapeutic process that allows these patients to clarify their feelings and assess the various treatment options, which range from non-invasive to highly invasive, irreversible procedures, is arguably the only way that meaningful informed consent for the latter can be obtained (Levine, 2018).

Turban et al.'s (2020) unproven assertion that non-affirming therapies are dangerous stands in contrast to the documented risks and uncertainties associated with hormonal and surgical interventions that are a core part of the "affirmation" treatment path. Until recently, puberty blockers were considered safe and fully reversible, but there is now emerging evidence of their adverse effects on the bone and brain health (Klink, Caris, Heijboer, van Trotsenburg, & Rotteveel, 2015; Joseph, Ting, & Butler, 2019; Schneider et al., 2017). Additionally, since almost all of the children treated with puberty blockers proceed to cross-sex hormones (de Vries et al., 2014), concerns have been raised that puberty blockers may consolidate gender dysphoria in young people, putting them on a lifelong path of biomedical interventions.

Cross-sex hormones are associated with cardiovascular complications, including a fourfold increased risk of heart attacks in biological females, and a threefold increase in the incidence of venous thromboembolism in biological males (Alzahrani et al., 2019; Nota et al., 2019). "Gender-affirming" surgeries can cause urethral stricture, neo-vaginal stenosis and prolapse, and long-term post-mastectomy pain (Larsson, Ahm Sørensen, & Bille, 2017; Manrique et al., 2018; Rashid and Tamimy, 2013; Santucci, 2018). The effects of "gender-affirmative" care on fertility have not been adequately studied, but infertility is a likely outcome, depending on the specific treatments pursued. It remains unclear whether fertility concerns will be important to this group of patients as they mature, but increasingly, gender centers are recommending fertility preservation procedures prior to undergoing hormonal interventions.

Given the absence of robust long-term evidence that the benefits of biomedical interventions outweigh the potential for harm, especially among young people (Heneghan & Jefferson, 2019), it is self-evident that the least-invasive treatment options should be pursued before progressing to more risky and irreversible interventions. To the extent that psychological treatments can help an individual obtain relief from GD without undergoing body-altering interventions, ensuring access to these interventions is not only ethical and prudent but also essential.

The importance of continued access to non-affirmation–non-conversion, agenda-free evaluation, and treatment is further underscored by the increasing numbers of detransitioning patients speaking out in social media forums following gender transitions they have come to regret (Entwistle, 2020). The rate of regret, detransition, and desistance from transgender identification is largely unknown (Butler & Hutchinson, 2020). The majority of patients with classical, childhood-onset gender dysphoria (61%-98%) desist from transgender identification some time in adolescence or young adulthood (Korte et al., 2008; Steensma, McGuire, Kreukels, Beekman, & Cohen-Kettenis, 2013; Zucker, 2018). The minority who persist with their transgender identification into adulthood and undergo "gender-affirmative" surgeries have been reported to have low rates of regret (van de Grift, Elaut, Cerwenka, Cohen-Kettenis, & Kreukels, 2018) and detransition (Dhejne, Öberg, Arver, & Landén, 2014). However, these studies may understate true regret rates due to overly stringent definitions of regret (i.e., requiring an official application for reversal of the legal gender status), very high rates of participant loss to follow-up (22%-63%) (D'Angelo, 2018), and an unexplored relationship between regret and high rates of post-transition suicide (Dhejne et al., 2011).

The novel cohort of young GD patients increasingly presenting for help is poorly understood. It is overrepresented by adolescent females with recent-onset GD and with comorbid mental health and neurocognitive issues (Bewley, Clifford, McCartney, & Byng, 2019; de Graaf, Giovanardi, Zitz, & Carmichael, 2018; Kaltiala-Heino, Bergman, Työläjärvi, & Frisen, 2018; Littman, 2018; Zucker, 2019). The trajectory of GD among these young patients, including the rates of desistance and detransition, remains unknown. However, many of us, along with our colleagues, are seeing increasing numbers of detransitioners with adolescent-onset GD who regret not having received exploratory psychotherapy to help them understand their distress and the desire to transition before they underwent irreversible medical and surgical treatments. Equally concerning, a number report that when doubts about their own transgender status arose, their therapists continued to affirm them as transgender, attributing their doubts to internalized transphobia, and encouraging them to continue medical interventions, which, in turn, unnecessarily exacerbated the psychological and physical harms.

Advocates of "affirmative care" tend to downplay the risks of iatrogenic harms resulting from inappropriate transitions and minimize the seriousness of the resulting harms by describing them as merely "cosmetic" (Turban & Keuroghlian, 2018). In stark contrast to these assertions, we are seeing increasing numbers of patients who feel deeply traumatized by inappropriate transitions. They suffer from irreversible physical changes, including alterations to their genitals and sexual function, sterility, painful vaginal atrophy, chest/breast alteration and scarring, deepening of the voice, unwanted permanent changes to facial hair growth, male-pattern baldness, urinary incontinence, and other lasting effects. Apart from the distress that these changes cause, they also negatively impact many areas of their lives, including their ability to form a stable gender identity (many feel trapped in a "gender no-man's land"), to find romantic partners and supportive social networks, to bear children, or to secure employment. The process of coming to terms with these consequences of their transition is psychologically difficult and can be profoundly painful.

Given the risky and irreversible nature of "gender-affirming" treatments, it is concerning that for many years now, there has been a lack of systematic research into the role that developmentally informed psychotherapy can play in the amelioration of GD, especially among young people. The need for the continued development and evaluation of non-invasive psychological treatment alternatives for GD has never been more urgent, given the fact that over 3% of young people report transgender identification or ideation (Johns et al., 2019). Given the sheer magnitude of this change, and the potential for exponential growth in the number of individuals who are medically harmed, it is time to raise the bar on science and to heed the first and most fundamental tenet of medicine: "First, do no harm."

Conclusions

Turban et al.'s (2020) singular endorsement of "affirmative" therapies, which their data failed to substantiate, contributes to the alarming trend to frame any non-"affirming" approaches as harmful. We are deeply concerned that this false dichotomy, reinforced by Turban et al.'s unproven claims of the harms of GICE, will have a chilling effect on the ethical psychotherapists' willingness to take on complex GD patients, which will make it much harder for GD individuals to access quality mental health care. We maintain that availability of a broad range of non-coercive, ethical psychotherapies for individuals with GD is essential to meaningful informed consent, which requires consideration of the full range of treatment options, from highly invasive to non-invasive. Further, given the potential of agenda-free psychotherapy to ameliorate GD non-invasively among young people with GD, withholding this type of intervention, while promoting "affirmation" approaches that pave the way to medical transition, is ethically questionable.

We believe that exploratory psychotherapy that is neither "affirmation" nor "conversion" should be the first-line treatment for all young people with GD, potentially reducing the need for invasive and irreversible medical procedures. This is especially critical now, when we are witnessing an exponential rise in the incidence of young people with GD who

have diverse and complex mental health presentations and require careful assessment and treatment planning.

We are concerned about the deficit in our knowledge base about psychological interventions for GD, beyond a few successful but small case studies, and we fear that the erroneous conclusions presented by Turban et al. (2020) will make it less likely that such research will be carried out in the future. We call on the scientific community to resist the stigmatization of psychotherapy for GD and to support rigorous outcome research investigating the effectiveness of various psychological treatments aimed at ameliorating or resolving GD. The outcomes of psychotherapeutic treatments must be compared to those of biomedical interventions, so that evidence-based standards of care that allow patients and clinicians to make fully informed decisions about how best to alleviate GD can be developed and put into practice.

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Review

The microstructure of white matter in male to female transsexuals before cross-sex hormonal treatment. A DTI study

Giuseppina Rametti [d,f], Beatriz Carrillo [b], Esther Gómez-Gil [c], Carme Junque [b,f], Leire Zubiarre-Elorza [b], Santiago Segovia [a], Ángel Gomez [e], Antonio Guillamon [a,*]

[a] Departamento de Psicobiología, UNED, C/ Juan del Rosal 10, 28040 Madrid, Spain
[b] Departamento de Psiquiatría y Psicobiología Clínica, Universidad de Barcelona, Spain
[c] Unidad de Identidad de Género, Hospital Clínic, Universidad de Barcelona, Barcelona, Spain
[d] Clinical Institute of Neuroscience, Hospital Clínic, Barcelona, Spain
[e] Departamento de Psicología Social y de las Organizaciones, UNED, Madrid, Spain
[f] Institute of Biomedical Research August Pi i Sunyer (IDIBAPS), Barcelona, Spain

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ABSTRACT

Background: Diffusion tensor imaging (DTI) has been shown to be sensitive in detecting white matter differences between sexes. Before cross sex hormone treatment female to male transsexuals (FtM) differ from females but not from males in several brain fibers. The purpose of this paper is to investigate whether white matter patterns in male to female (MtF) transsexuals before commencing cross sex hormone treatment are also more similar to those of their biological sex or whether they are more similar to those of their gender identity.
Method: DTI was performed in 18 MtF transsexuals and 19 male and 19 female controls scanned with a 3 T Trio Tim Magneton. Fractional anisotropy (FA) was performed on white matter of the whole brain, which was spatially analyzed using Tract Based Spatial Statistics.
Results: MtF transsexuals differed from both male and female controls bilaterally in the superior longi tudinal fasciculus, the right anterior cingulum, the right forceps minor, and the right corticospinal tract.
Conclusions: Our results show that the white matter microstructure pattern in untreated MtF trans sexuals falls halfway between the pattern of male and female controls. The nature of these differences suggests that some fasciculi do not complete the masculinization process in MtF transsexuals during brain development.

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1. Introduction

Transsexualism is an extreme form of gender identity disorder (American Psychiatric Association, 2000). Male to female (MtF) transsexuals are characterized by persistent cross gender identifi cation, discomfort with their assigned gender, cross dressing and a search for hormonal and surgical sex reassignment to the desired anatomical sex to become females. The etiology of transsexualism is unknown but biological variables could play a role in its development (Cohen Kettenis and Gooren, 1999; Gooren, 2006; Swaab, 2004).

Postmortem anatomical studies have shown that some subcor tical structures are feminized in MtF transsexuals. The volume and the number of neurons of the central part of the bed nucleus of the stria terminalis (BSTc) and the third interstitial nucleus of the anterior hypothalamus (INAH3), which present sex differences in control subjects, are feminized in MtF transsexuals (Garcia Falgueras and Swaab, 2008; Kruijver et al., 2000; Zhou et al., 1995). These studies all suggest that the feminization of the BSTc and the INAH3 in MtF transsexuals is related to neither their sexual orientation nor their cross hormonal treatment.

Only a few structural and functional MRI studies focus on MtF transsexuals. Luders et al. (2009) found that, before cross sex hormone administration, the regional structure of the gray matter in MtF transsexuals was more similar to the pattern found in males than in females. Nevertheless, the transsexuals did show a signifi cantly larger volume of gray matter in the right putamen than did control males.

MRI functional studies of transsexuals analyze the brain while performing tasks, such as mental rotation, in which males and females consistently differ (Kimura, 1999). There are only three fMRI studies of mental rotation in transsexuals. Sommer et al. (2008), using a longitudinal design, found that activation during mental

* Corresponding author. Tel.: +34 91 398 62 72; fax: +34 91 398 6287.
E-mail address: aguillamon@psi.uned.es (A. Guillamon).

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rotation did not increase during cross sex hormone treatments, probably because of their small sample size. However, in a sample of treated and untreated MtF transsexuals and control males, it was reported that both transsexual groups had increased activation in the temporo occipital regions and decreased activation in the left parietal lobe, suggesting *a priori* differences between control males and MtF transsexuals (Schöning et al., 2010). In addition, comparing chronically hormone treated MtF and FtM transsexuals to male and female controls, we found a parietal hypoactivation in the MtF transsexuals, but no significant differences for FtM transsexuals (Carrillo et al., 2010).

There are two additional functional neuroimaging works that addressed the cerebral patterns of MtF transsexuals. Gizewski et al. (2009) studied the cerebral activation produced by visual erotic stimuli in MtF transsexuals before treatment and found an activation pattern in MtF transsexuals similar to that observed in females. They suggested that MtF transsexuals show a tendency toward female like cerebral processing. Moreover, Berglund et al. (2008), using positron emission tomography (PET), studied brain activation in MtF transsexuals when smelling 4, 16 androstendien 3 one (AND) and estra 1,3,5(10),16 tetraen 3 ol (EST). These steroids activate the hypothalamus in a sex differentiated manner (Savic et al., 2001). Smelling AND and EST, MtF transsexuals showed a pattern of acti vation that was different from their biological sex and was situated in an intermediate position with predominantly female like features (Berglund et al., 2008).

There are two structural MRI studies focused on white matter in transsexuals. The earliest (Emory et al., 1991) found no differences for the whole corpus callosum (CC) or the splenium region between transsexuals and controls. A more recent work, measuring CC shape, concluded that the pattern of CC shape in transsexuals is closer to that in individuals with the same gender identity than to that in individuals with the same biological sex (Yokota et al., 2005).

Diffusion Tensor Imaging (DTI) is the most suitable technique for detecting subtle changes in the white matter of patients with psychiatric disorders (Nucifora et al., 2007). DTI has been used to investigate sex differences in adults (Huster et al., 2009; Westerhausen et al., 2003) and in developmental studies (Schmithorst et al., 2008). Recently, we used DTI to investigate whether white matter patterns of female to male (FtM) transsexuals, who had not begun cross sex hormone treatment, were more similar to that of their biological sex or to that of their gender identity (Rametti et al., in press). We found sex differences in the white matter microstructure of some brain fasciculi. Compared to control females, FtM transsexuals showed higher frac tional anisotropy (FA) values in the anterior and posterior parts of the right superior longitudinal fasciculus and the forceps minor. However, in the corticospinal tract, FA values in FtM transsexuals are signifi cantly less than in males and significantly greater than in females. Thus, we suggested that, for some fasciculi involved in higher cogni tive functions, the white matter microstructure pattern in FtM transsexuals is closer to the pattern of subjects who share their gender identity (males) than to those who share their biological sex (females).

Mammalian brain sex differences, even in humans, occur in complex networks (Garcia Falgueras et al., 2006; Segovia and Guillamon, 1993). If FtM transsexuals show a tendency to have masculinized FA values in some brain fasciculi it could be expected that the opposite would be true for MtF transsexuals. Therefore, the purpose of the present study was to test if the pattern of the white matter microstructure in MtF transsexuals shows a trend toward feminization. We measured FA, which is related to the ordered arrangement of myelinated fibers (Beaulieu, 2002), as an indicator of white matter coherence and axonal organization (Lebel et al., 2008). To the best of our knowledge there are no previous studies in the litera ture describing white matter microstructure in MtF transsexuals.

2. Materials and methods

2.1. Subjects

We recruited 18 untreated MtF transsexuals, 19 female and 19 male controls for this study. Two mental health professionals from the Gender Identity Unit (GIU) at the Hospital Clínic of Barcelona performed several semi structured clinical interviews (Bobes et al., 1997; Gómez Gil et al., 2009a). The estimated prevalence rate of transsexualism in Catalonia (Spain) is 1:21,031 males and 1:48,096 females and the sex ratio is 2.6 (Gómez Gil et al., 2005, 2009b).

Psychological criteria for the diagnosis and treatment followed the guidelines provided by the Harry Benjamin International Gender Dysphoria Association (Meyer et al., 2002). The diagnosis of transsexualism was confirmed following the revised fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000) and the tenth revision of the International Classification of Diseases (World Health Organization, 1993). For study inclusion, transsexual subjects needed to self identify as an MtF transsexual, deny any history of hormonal treatment and declare their intention of undergoing cross sex hormonal therapy. The hormonal levels of the untreated MtF transsexual group were obtained before the study (Table 1). All MtF transsexuals selected had early onset gender nonconformity (before puberty), were erotically attracted to males, and affirmed that they aspired to sex reassignment. Sexual orientation of transsexual subjects was determined by asking what partner (a man, a woman, both or neither) the subjects would prefer or feel sexual attraction to if their body did not interfere.

The control subjects were recruited through responses to advertisements. They were free of any neurological, systemic, or psychiatric disease, as verified by a detailed interview. An inclusion criterion for all participants was to be free of psychotropic medi cation and/or illegal drug use. The study only included heterosexual controls. Informed consent was obtained from all participants, and

Table 1
Characteristics of the sample and group comparisons.

	MtF Transsexuals[a] (*n* 18)	Control Females (*n* 19)	Control Males (*n* 19)	F	*p* values
Age (years)	24.71 ± 8.15[b]	33.00 ± 8.23	31.94 ± 6.11	5.51	0.007
Hormonal levels[c]					
Testosterone (ng/dl)	559.06 ± 163.91				
Free testosterone index (%)	70.50 ± 22.87				
Sex steroid binding globulin (nmol/L)	29.99 ± 9.17				
17-b-estradiol (pg/ml)	19.06 ± 16.57				

[a] Male to Female transsexuals (MtF). Results are expressed as mean ± standard deviation.
[b] At least $p < 0.01$ with respect to male and female controls.
[c] Normal testosterone levels: adult males (275 850 ng/dL) and females (10 80 ng/dL). Normal free testosterone index: adult males (38 123%) and females (1 7%). Normal levels of sex steroid binding globulin: adult males (10 60 nmol/L) and females (35 135 nmol/L). Normal estradiol levels: males (10 41 pg/mL); females: follicular phase (22 55 pg/mL), luteal phase (68 196 pg/mL).

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Table 2
Gray matter, white matter and cerebrospinal fluid volumes.

	MtF[a]		Female controls		Male controls		F	*p*
	Mean	SD	Mean	SD	Mean	SD		
Gray matter (cm^3)	675.40[c]	135.19	580.49[b]	43.98	662.48	52.40	6.66	0.003
White matter (cm^3)	591.21[c]	92.32	520.44[b]	39.65	602.20	54.01	8.73	0.001
Cerebrospinal fluid (cm^3)	305.34[c]	66.71	275.43[b]	28.03	309.43	24.08	3.44	0.04
Intracranial volume (cm^3)	1571.96[c]	283.67	1376.37[b]	82.42	1574.12	123.31	7.29	0.002

[a] MtF: Male to Female transsexuals.
[b] Differences between female and male controls are at least $p < 0.001$.
[c] Differences between MtF and female controls are at least $p < 0.008$.

the study was conducted according to the principles of the Declaration of Helsinki and approved by the Ethical Committee of the Hospital Clínic of Barcelona.

2.2. Imaging protocol

MRI scans were performed using a 3 T magnet (SIEMENS Trio Tim Magneton, Erlangen, Germany). Diffusion tensor images were acquired with singleshot diffusion weighted echo planar imaging (EPI) in the axial plane with diffusion sensitization gradients applied in 64 noncolinear directions with a b value of 1000 mm^2/s (TE 94 ms, TR 9300 ms, flip angle 90, slice thickness 2 mm, providing 1.97 mm in plane resolution). The approximate scanning time for the DTI acquisition was 10 min.

In addition, we acquired a high resolution T1 weighted magnetization prepared rapid gradient echo (MP RAGE) 3D MRI sequence in sagittal plane to use as a reference image for signal attenuation measurement. The echo time was 2.98 ms, the repetition time was 2300 ms, and the inversion time was 900. A set of slices covering the whole brain, including the cerebellum, was acquired with matrix size 256 × 256, field of view (FOV) 25 × 25 cm and voxel size 1 × 1 × 1 mm^3.

2.3. Tract based spatial statistics (TBSS)

Following image acquisition, the diffusion images were transferred to a Linux based workstation and further processed. Image data processing was performed with FSL v4.1.2 (http://www.fmrib.ox.ac.uk/fsl/) (Smith et al., 2004). First, we used SIENAX (Smith, 2002) to estimate gray matter (GM), white matter (WM), cerebrospinal fluid (CSF) and intracranial (ICV) volumes.

For the TBSS analysis, the entire image sets were visually inspected and corrected for motion and eddy currents. The next step involved extraction of the brain matter on the B0 image, using the Brain Extraction Tool (BET) available with the FSL software; a fractional intensity threshold of 0.2 was used for this step. Using the brain extracted B0 image, we then extracted the brain for the FA images. The brain extracted FA images of all participants were used as the input images for TBSS processing (Smith et al., 2006).

The initial step of TBSS analysis consisted of voxelwise nonlinear registration of all subjects' FA data into a common space using the FNIRT registration tool (Andersson et al., 2007a,b). The transformed FA images of all participants were averaged to create a mean FA image. This mean FA image was then used to create a skeleton image, which represents the centers of all the white matter tracts the groups have in common. An FA threshold of 0.2 was used to differentiate between gray and white matter. Each subject's aligned FA data were then projected onto this skeleton.

2.4. Statistical analysis

Using TBSS, voxelwise statistical analysis of individual skeleton images of the three groups was performed using a non parametric permutation test (randomized) and a standard GLM design. We applied a two sample *t* test with a *p* value of <0.05 FWE, after correcting for multiple comparisons. We used the Threshold Free Cluster Enhancement (TFCE) method to define the clusters (Smith et al., 2006). To identify the fasciculi involved in each significant cluster we used the JHU White Matter Tractography Atlas for the MNI 152 brain. We selected the clusters that achieved statistical significance between male and females to obtain a mask for each fasciculus involved. By means of these masks we extracted the FA values of each subject. These tract FA values were analyzed using age and intracranial volume across groups as covariates. Statistical analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago, Illinois). For group comparisons of FA values we used ANCOVA followed by Bonferroni post hoc contrasts. The level of significance was set at $p < 0.05$.

3. Results

As expected, male controls have greater gray and white matter as well as CSF volumes than female controls. MtF have similar global volumes to male controls and these volumes differed significantly from those of the females (Table 2).

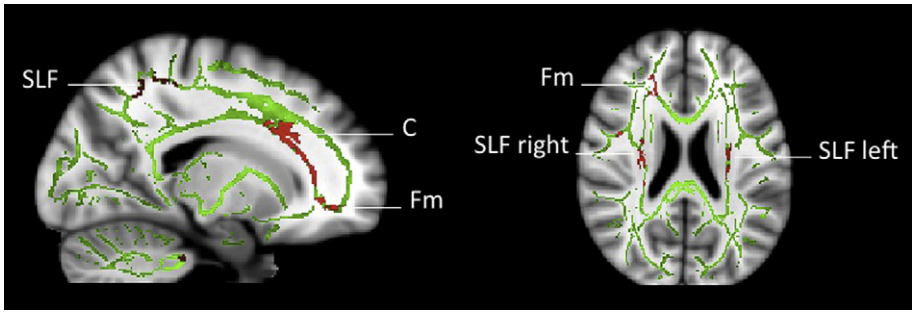

Fig. 1. Sagittal and axial maps of fractional anisotropy (FA) showing sex differences. FA is bilaterally lower in female than in male controls in the superior longitudinal fasciculus (SLF). Control females also show lower than control male FA values in the forceps minor (Fm) and the cingulum (C). The group skeleton used for the between group contrast study is green. The red color shows the clusters of significantly decreased FA in female compared to male controls. The threshold for significance was set at $p < 0.05$ corrected for multiple comparisons. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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Table 3
Coordinates of the clusters showing significant differences between male and female controls.

Locations	MNI coordinates					Cluster size
	x	y	z	t	p	
Control males > Control females						
Superior longitudinal fasciculus (right)	18	−53	50	4.6	<0.004	1227
Forceps minor (right)	18	46	−6	4.89	<0.005	1115
Inferior frontooccipital fasciculus (right)	33	9	2	5.14	<0.01	859
Superior longitudinal fasciculus (left)	−28	−8	22	4.49	<0.02	628
Corticospinal tract (right)	6	−28	−31	4.08	<0.04	466
Cingulum (right)	18	25	28	4.83	<0.04	456

Location x, y and z coordinates are based on the atlas of the Montreal Neurological Institute (MNI).

The whole TBSS analysis showed that control males have significantly higher FA values than control females in the left and the right superior longitudinal fasciculus, in the right inferior front occipital fasciculus, the left cingulum, the forceps minor, and the corticospinal tract (Fig. 1 and Table 3). The contrast analysis testing for females being greater than males did not show any significant differences.

We performed ANCOVA analyses of the FA mean values for each cluster that showed sexual differences, taking as covariates age and intracranial volume. MtF transsexuals showed a constant pattern of differences for all the fasciculi. As can be seen in Fig. 2, the FA values of MtF transsexuals fall between those of male and female controls. Except for the inferior frontooccipital fasciculus (right), the FA values of MtF transsexuals for all the fasciculi were significantly different from those male and female controls (see Table 4).

4. Discussion

4.1. General discussion

From the analysis of FA, which indicates white matter coherence and axonal organization (Lebel et al., 2008), the main result of our study is that MtF transsexuals differ from both male and female controls in almost all the fascicles that showed sex differences. Interestingly the FA values of these fasciculi in MtF transsexuals fall halfway between those of the fasciculi in the male and female controls and are significantly different from either of the control FA values.

MtF transsexuals differed from male and female controls in the right and the left superior longitudinal fasciculus. The SLF connects complex cortical regions that subserve higher cognitive functions and that are sexually dimorphic. Sex differences in cognition are consistently found in spatial abilities and verbal fluency (Kimura, 1999); males outshine females in the former but the females outshine males in the latter. It has been reported that the performance of untreated MtF transsexuals in mental rotation tasks is consistent with that of their biological sex (Haraldsen et al., 2003; Slabbekoorn et al., 1999). Schöning et al. (2010) studied spatial cognition using fMRI and found that untreated and treated MtF transsexuals had increased activation in the temporo occipital regions and decreased activation in the left parietal lobe compared to control men. We have investigated brain activation during mental rotation in chronically hormone treated MtF transsexuals. These MtF transsexuals present less activation than male controls in the superior parietal lobe (Brodman's area 7) and higher activation than females in the superior part of the gyrus frontalis (Brodman's area 9) (Carrillo et al., 2010). Interestingly, these two cerebral regions are connected by the SLF (Makris et al., 2005; Hua et al., 2009).

We found significant differences between MtF transsexuals and male and female controls in the forceps minor and the anterior region of the cingulum, both in the right hemisphere. The forceps minor connects orbitofrontal regions (Park et al., 2008) and the cingulum is an associative bundle that runs from the anterior temporal gyrus to the orbitofrontal cortex (Catani and Thiebaut de Schotten, 2008) and both form part of the emotional networks (Kober et al., 2008). There is evidence that the orbitofrontal cortex and anterior cingulate cortices are involved in reinforcement processing and the reward value of reinforcers and punishers (Cohen, 2008; Kringelbach and Rolls, 2004). Moreover, it has been suggested that the anterior cingulated cortex relates current information with an extended history of reward (Walton et al., 2007).

The FA values of the corticospinal tract in MtF transsexuals also differed from male and female controls. Studies performed in non human primates (Lemon, 2008) have shown that this tract is

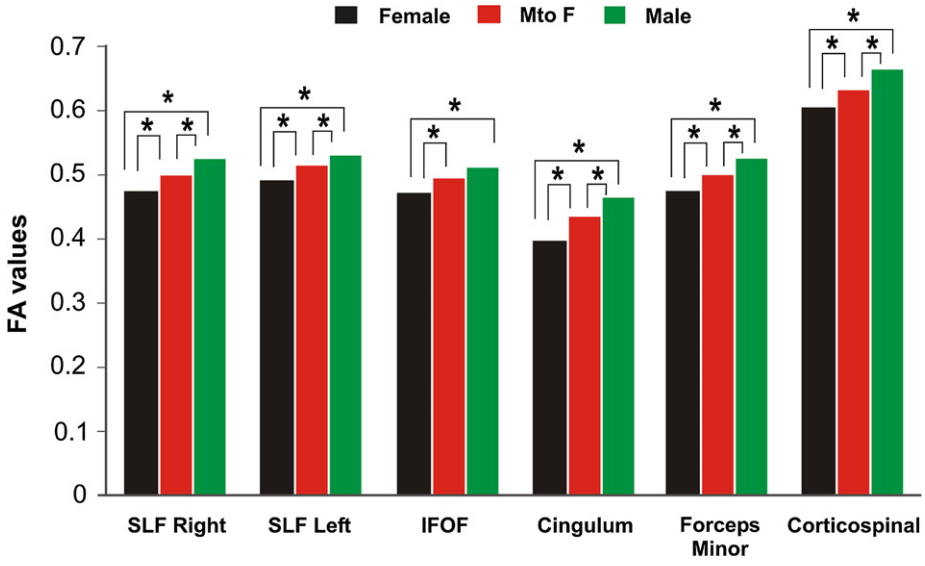

Fig. 2. Histograms showing the FA means between control females (black), male to female transsexuals (MtF) (red) and control males (green). MtF transsexuals significantly differed from female and male controls in almost of all the fascicles in which control males differed from control females. SLF: superior longitudinal fasciculus; IFOF: infero frontooccipital fasciculus. *At least $p < 0.01$. For SD see Table 4. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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Table 4
Group comparisons of the fractional anisotropy in the clusters of the fasciculi presenting sex differences.

	MtF[a]		Female		Male		F	P
	Mean	SD	Mean	SD	Mean	SD		
Superior longitudinal fasciculus (right)	0.504[b,c]	0.022	0.478	0.019	0.526	0.023	22.21	0.001
Forceps minor (right)	0.501[b,c]	0.024	0.473	0.020	0.527	0.023	21.05	0.001
Inferior frontooccipital fasciculus (right)	0.496[b]	0.027	0.476	0.015	0.514	0.023	13.14	0.001
Superior longitudinal fasciculus (left)	0.520[b,c]	0.020	0.497	0.019	0.536	0.020	13.51	0.001
Corticospinal tract (right)	0.639[b,c]	0.031	0.611	0.029	0.668	0.035	13.43	0.001
Cingulum (right)	0.439[b,c]	0.021	0.403	0.025	0.468	0.021	33.66	0.001

At least $p < 0.01$ with respect to female (b) and males (c) controls.
[a] MtF: Male to Female transsexuals.

a descending motor pathway originated from several cortical regions (primary motor cortex, premotor cortices, supplementary motor area and cingulate motor area, primary somatosensory cortex, posterior parietal cortex and the parietal operculum). Limb movements that require a high degree of skill and flexibility are controlled by these motor fibers. Lesions of this tract affect fine sensoriomotor function of the hand (Lemon and Griffith, 2005). The maturation of the corticospinal tract depends on motor experience and genetic factors (Cheeran et al., 2009; Martin et al., 2007).

In a previous work we found that FA values of the corticospinal tract in FtM transsexuals also differed from male and female controls in the same way that we have found for the MtF transsexuals in the current work, but in the former case the FA value was higher than in control females. In contrast, the FA values of SLF and the forceps minor in the FtM differed from control females but not from control males (Rametti et al., in press).

In so far as masculinization and feminization processes, it seems that before cross sex treatment in FtM transsexuals, the SLF and the forceps minor are masculinized, while the corticospinal tract seems to be incompletely feminized (Rametti et al., in press). However, in MtF transsexuals the SLF, the forceps minor, the cingulum and the corticospinal tract seem to present an incomplete masculinization because the FA values were halfway between those of these structures in the male and female controls and the difference with each of the latter was significant.

Considering the present work and the data available in the literature, what can we say of the brain of MtF transsexuals? Most importantly, we would suggest that MtF transsexuals do not show a simple feminization of their brain —rather, they present a complex picture in which feminization and incomplete masculinization are present depending on the brain region studied and the kind of measurements taken.

The histological measurements of the BSTc and the INH3, which are located in regions related to sexual behavior in mammals (Claro et al., 1995; De Jonge et al., 1989), are feminized in MtF transsexuals (Garcia Falgueras and Swaab, 2008; Kruijver et al., 2000; Zhou et al., 1995) and an MRI study also showed a feminization of the putamen (Luders et al., 2009).

Focusing our attention on the white matter, MtF transsexuals show a feminization of the shape of the corpus callosum (Yokota et al., 2005). In addition, we have shown the existence of incomplete masculinization FA values in forceps minor, superior longitudinal fasciculus, cingulum and corticospinal tract.

An fMRI study of the effects of erotic stimuli on cerebral activation, shows that MtF transsexuals, prior to treatment, present a feminized activation pattern in thalamus, amygdala and orbitofrontal and insular cortices (Gizewski et al., 2009). Besides, when smelling odorous steroids, MtF transsexuals present a pattern of hypothalamic activation that differs from their biological sex (Berglund et al., 2008).

A complex picture of the brain of the MtF transsexuals emerges from the above data. Prior to their cross sex hormonal treatment MtF transsexuals do not present a simple feminization of the brain; rather they present a mixture of feminized and incompletely masculinized structures in those regions in which male and female controls differ.

4.2. Strengths and limitations

The current study has several strengths. It is the first to study the white matter microstructure in MtF transsexuals. Second, the subjects had never received cross sex hormone treatment. Third, the hormone assays show that the gonadal hormone levels of the MtF transsexuals reflected no endocrine pathology. Finally, for the FA analyses we used the application of automatic masks that were extracted from the significant clusters obtained in the male female contrast. This procedure avoids the methodological problems associated with classic ROI analyses, such as the variability in the localization of the ROI in several brain structures, and the difficulty for repeatability of DTI measurements (see Brander et al., 2010).

Although we can conclude that there are *a priori* structural brain differences in untreated MtF transsexuals that seem to have occurred during brain maturation, these differences are not seen in the entire brain, but in specific regions of four fascicles. Moreover, we cannot exclude the possibility that future hormonal treatment and surgical treatments could affect brain white matter microstructure in these individuals after the treatment. To solve this question pre and post treatment studies or, at least, comparisons with cross sex hormone treated groups are needed.

5. Conclusion

In conclusion, our results show that the white matter microstructure pattern in untreated MtF transsexuals is intermediate between male and female controls. The direction of the differences suggests that some fasciculi do not complete the masculinization process during brain development before the individual seeks treatments.

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Contributors

None.

Conflict of interest

None.

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Exhibit 6

[illegible] MD @[illegible] · May 12

You couldn't even spell this tweet correctly, let alone properly research your bill

Every major medical organization has labeled bills like this dangerous & unethical

Uneducated and lazy politicians, who don't bother to research the bills they're writing, are unacceptable

> **Senator Bryan Hughes** @SenBryanHughes · May 12 ·
> Honored to co-author SB 14 that passed the Texas House tonight.
>
> Child multination or sterilization is never the answer and this bill will protect Texas children from these awful procedures.
>
> Thankful to Senator @DonnaCampbellTX and Representative @TomOliverson for their bold... Show more

Exhibit 7

The Journal of Neuroscience, February 1, 2002, 22(3):1027–1033

Sexual Differentiation of the Bed Nucleus of the Stria Terminalis in Humans May Extend into Adulthood

Wilson C. J. Chung,[1,2] **Geert J. De Vries,**[2] **and Dick F. Swaab**[1]

[1]*Netherlands Institute for Brain Research, 1105 AZ Amsterdam, The Netherlands, and* [2]*Center for Neuroendocrine Studies and Department of Psychology, University of Massachusetts, Amherst, Massachusetts 01003*

Gonadal steroids have remarkable developmental effects on sex-dependent brain organization and behavior in animals. Presumably, fetal or neonatal gonadal steroids are also responsible for sexual differentiation of the human brain. A limbic structure of special interest in this regard is the sexually dimorphic central subdivision of the bed nucleus of the stria terminalis (BSTc), because its size has been related to the gender identity disorder transsexuality. To determine at what age the BSTc becomes sexually dimorphic, the BSTc volume in males and females was studied from midgestation into adulthood. Using vasoactive intestinal polypeptide and somatostatin immunocytochemical staining as markers, we found that the BSTc was larger and contains more neurons in men than in women. However, this difference became significant only in adulthood, showing that sexual differentiation of the human brain may extend into the adulthood. The unexpectedly late sexual differentiation of the BSTc is discussed in relation to sex differences in developmental, adolescent, and adult gonadal steroid levels.

Key words: bed nucleus of stria terminalis; sexual differentiation; plasticity; brain; adulthood; human

Several regions in the human brain differ in organization between men and women. For example, distinct cell groups in the preoptic and anterior hypothalamic area are larger, and the suprachiasmatic nucleus contains more vasoactive intestinal polypeptide-immunoreactive (VIP-IR) cells in young men than in young women (Swaab and Fliers, 1985; Allen et al., 1989; LeVay, 1991; Swaab et al., 1994; Byne et al., 2000). Clear anatomical sex differences have also been described in the human bed nucleus of the stria terminalis (BST). The darkly staining posteromedial component of the BST (BST-dspm) and the central subdivision of the BST (BSTc) are both larger in men than in women (Allen and Gorski, 1990; Zhou et al., 1995; Kruijver et al., 2000). Differences in the size of the human BSTc have been related to the gender identity disorder transsexuality, in which subjects voice the strong feeling of being born in the wrong sex. In male-to-female transsexuals, the BSTc was similar in size to that of control women, whereas in the only female-to-male transsexual studied so far, the BSTc was similar in size to that of control men (Swaab and Hofman, 1995; Zhou et al., 1995; Kruijver et al., 2000)

In general, perinatal sex differences in gonadal steroid levels are responsible for organizing the vertebrate brain in a sex-dependent manner (Döhler, 1991; Cooke et al., 1998). Studies showed that this was also the case for the sexual differentiation of the BST in the rat brain. For instance, perinatal sex differences in testosterone are required for the principal nucleus of the BST in the rat brain to become larger and contain more cells in males than in females (Del Abril et al., 1987; Guillamon et al., 1988; Chung et al., 2000). Moreover, these sex-dependent morphological changes occur within the first week of postnatal life (Chung et al., 2000). Therefore, gonadal steroids are presumed to play a role in the sexual differentiation of the human BSTc, which was predicted to be apparent early on during fetal or infant development. This idea is further supported by observations in humans, which indicate that dramatic changes in circulating gonadal steroid levels do not seem to alter the size of the BSTc in adult control subjects. For instance, high testosterone and androstenedione levels caused by an adrenal cortex tumor in a female control subject did not result in a larger BSTc, whereas gonadectomy in male control subjects with prostate cancer did not result in a smaller BSTc (Zhou et al., 1995; Kruijver et al., 2000).

In the present study, we used postmortem human brain tissue to determine at what stage of development the volume of the human BSTc diverges between men and women. Moreover, we assessed whether sex differences in total number of Nissl-stained BSTc neurons contributed to the sexual differentiation of the BSTc size.

MATERIALS AND METHODS

Human brain tissue. Brains of 50 control subjects (Table 1) were obtained through autopsies by the Netherlands Brain Bank following the required permissions for brain autopsy and use of tissue and medical information for research purposes. Brain tissue was fixed in formalin and embedded in paraffin. Serial coronal sections (6 μm) were made using a Leitz (Wetzlar, Germany) microtome and mounted on aminoalkylsilane-coated glass slides. Paraffin-embedded sections were processed for immunocytochemistry as described in previous studies (Zhou et al., 1995; Kruijver et al., 2000).

Immunocytochemistry. After deparaffinization and rehydration using xylene and decreasing grades of ethanol, sections were placed in 0.05 M citrate buffer, pH 4.0, microwave treated (for antigen retrieval) at 90°C for 10 min, cooled at room temperature (RT) for 30 min, rinsed three times for 5 min each in 0.05 M Tris-buffered saline (TBS), pH 7.6, and placed into 0.3% Triton X-100 (Sigma, St. Louis, MO) and 5% milk powder (Elk; Campina Melkunie, Eindhoven, The Netherlands) diluted with TBS (TBS-XM) for 30 min to reduce nonspecific staining. Sections were then incubated overnight at 4°C with rabbit anti-VIP polyclonal (VIPER; 1:600) or rabbit anti-somatostatin polyclonal (SOMAAR;

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Correspondence should be addressed to Wilson C. J. Chung, Netherlands Institute for Brain Research, Meibergdreef 33, 1105 AZ Amsterdam, The Netherlands. E-mail: w.chung@nih.knaw.nl.

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Table 1. Control human brain material

	NBB number	Sex	Age	Brain weight (gm)	Postmortem delay (hr)	Fixation (d)	VIP (mm^3)	SOM (mm^3)	Clinicopathological diagnosis
Males (n = 25)	Fetal/neonatal period								
	81024	m	26 4/7 weeks	110	1:52	51	0.216	0.376	Pulmonary failure
	84032	m	27 weeks	142	21:45	45	0.241	0.462	Cardiac failure
	97154	m	33 6/7 weeks	186	7:55	32	0.729	1.136	Respiratory insufficiency
	82002	m	35 1/7 weeks	322	<41:00	32	0.766	1.088	Pericardial rupture
	94054	m	36 2/7 weeks	357	<24:00	118	0.703	1.238	Pulmonalis atresia, cardiac insufficiency
	90095	m	38 1/7 weeks	320	14:05	26	0.624	1.018	Respiratory insufficiency
	88120	m	40 weeks	440	<17:00	31	1.284	2.125	Asphyxia
	Infant/pubertal period								
	88053	m	3 months	485	<41:00	35	1.445	2.520	Pulmonal insufficiency, Fallot's tetralogy
	85036	m	3 months	635	<17:00	73	1.583	2.582	Cardiac failure, aortic stenosis, cerebral ischemia
	84019	m	3 months	710	<11:00	792	1.034	2.318	Sudden infant death syndrome
	86041	m	6 months	800	<6:30	14	1.515	2.663	Sudden infant death syndrome
	88092	m	1 year	920	<41:00	31	2.587	4.536	Penthotal intoxication, hypoxia
	88058	m	1 year	1070	<35:35	28	2.597	3.843	Bacterial meningitis, sepsis
	84016	m	5 years	1565	23:55	100	2.083	3.074	Sepsis
	87057	m	6 years	1550	3:30	41	3.836	5.637	Peritonitis
	98116	m	8 years	nd	<17:10	103	2.826	5.595	Cardiomyopathy
	87036	m	14 years	1640	<41:00	32	4.968	8.059	Lymphadenopathy
	Adult period								
	97083	m	22 years	1334	<16:29	26	4.067	5.897	Cardiomyopathy
	97173	m	24 years	1364	<33:30	31	3.969	6.708	Accidental death
	86042	m	28 years	1450	<17:00	46	3.618	5.254	Guillain-Barré syndrome
	96406	m	35 years	1430	13:30	1214	3.288	6.598	Pulmonary aspergillosis
	99071	m	39 years	1400	<16:30	130	3.362	6.919	Cardiac failure
	88011	m	41 years	1500	20:30	33	4.464	6.745	Suicide
	92011	m	47 years	1500	<89:00	77	4.258	4.915	Sepsis
	97159	m	48 years	1500	5:30	42	3.757	5.948	Diabetes mellitus type I, euthanasia
Females (n = 25)	Fetal/neonatal period								
	89056	f	25 6/7 weeks	100	<65:00	31	0.362	0.579	Idiopathic (infant) respiratory distress syndrome
	96401	f	27 2/7 weeks	77	<41:00	1301	0.217	0.460	Congenital infection
	98193	f	30 6/7 weeks	116	3:00	82	0.579	1.023	Sepsis
	86030	f	31 2/7 weeks	200	<41:00	33	1.011	1.545	Hypoxia
	87024	f	34 5/7 weeks	180	<3:15	38	0.368	0.770	Idiopathic (infant) respiratory distress syndrome
	96403	f	34 4/7 weeks	197	<57:19	1288	0.385	0.951	Developmental syndrome

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Table 1. Continued

NBB number	Sex	Age	Brain weight (gm)	Postmortem delay (hr)	Fixation (d)	VIP (mm^3)	SOM (mm^3)	Clinicopathological diagnosis
88123	f	37 6/7 weeks	350	<41:00	30	1.067	2.544	Cardiac failure
89092	f	40 1/7 weeks	380	30:45	28	0.696	1.066	Asphyxia
88077	f	40 2/7 weeks	350	<65:00	56	0.782	1.378	Asphyxia
87028	f	41 4/7 weeks	350	<41:00	33	0.880	2.444	Aspiration of maternal blood
Infant/pubertal period								
86027	f	5 months	735	10:00	40	1.028	1.890	Sudden infant death syndrome
89027	f	6 months	780	<17:00	28	1.033	2.890	Cardiomyopathy
89036	f	1 year	820	nd	31	2.366	3.956	Hypoglycaemia
85031	f	2 years	nd	<65:00	48	1.028	4.699	Kidney dysplasia, sepsis
87077	f	7 years	1320	<9:45	33	1.033	5.287	Astrocytoma
87035	f	13 years	1250	<13:00	48	2.366	7.243	Histiocystic lymphoma, cardiac failure
99060	f	16 years	1364	<43:00	238	3.251	6.662	Diabetes mellitus, acidosis
Adult period								
85041	f	28 years	nd	5:25	44	3.218	6.384	Cardiac failure
85027	f	29 years	1150	13:10	60	4.318	3.131	Coma, liver cirrhosis
92037	f	32 years	1280	30:00	45	3.518	3.334	Bronchitis, pneumonia
86032	f	33 years	1035	<41:00	20	2.411	4.179	Adenocarcinoma
84002	f	36 years	1420	85:40	51	1.893	3.688	Suicide, multiple fractures, aortic rupture
97131	f	43 years	1345	<92:00	63	2.293	3.647	Cardiac failure, liver cirrhosis
89104	f	49 years	1260	<41:00	32	3.877	6.512	Lung carcinoma, septic shock
96423	f	49 years	1253	<17:00	806	3.183	5.316	Adenocarcinoma, thromboembolism

M, Male; F, female; nd, not determined; NBB, Netherlands Brain Bank; SOM, somatostatin.

1:800) diluted in TBS-XM. Afterward, sections were rinsed one time for 5 min in TBS-XM and two times for 5 min each in TBS and incubated with biotinylated goat anti-rabbit (1:300; Vector Laboratories, Burlingame, CA) diluted in TBS-XM for 60 min at RT. Sections were rinsed three times for 5 min each in TBS and incubated with ABC Elite kit (1:600; Vector Laboratories) diluted in TBS for 60 min and, after an additional three rinses for 5 min each in TBS, reacted with 0.25% nickel–ammonium sulfate-enhanced 3,3′ diaminobenzidine tetrahydrochloride (0.5 mg/ml) and 0.01% H_2O_2 in TBS. The reaction was stopped after 10–20 min, dehydrated with increasing grades of ethanol, cleared with xylene, and coverslipped using entellan (Merck, Darmstadt, Germany).

Volume measurements. The volume of the human BSTc in control subjects (males, $n = 25$; females, $n = 25$) was assessed both by using VIP and somatostatin immunocytochemical staining as markers (Walter et al., 1991; Zhou et al., 1995; Kruijver et al., 2000). Both markers have been shown previously to delineate clearly the borders of the BSTc in adult males and females (Zhou et al., 1995; Kruijver et al., 2000). The present study showed that the same markers delineate the BSTc from 25 weeks of pregnancy onward (Table 1). The volume of the BSTc was estimated by measuring the cross-sectional area delineated by VIP or somatostatin immunoreactivity in approximately every 25th section (fetal/neonatal and infant/pubertal subjects) or every 50th section (adult subjects) using a 2.5× objective (Plan-Neofluar) on a Zeiss (Oberkochen, Germany) Axioskop microscope mounted with a Sony (Tokyo, Japan) B/W CCD camera (model XC77CE) connected to an IBAS imaging analysis system (Kontron Elektronik, Eching, Germany). The total volume of the BSTc was calculated according to the Cavalieri principle (Gundersen et al., 1988).

Estimation of neuronal density and total neuronal number. Somatostatin-stained sections of the BSTc from adult males and females (between 22 and 49 years) (Table 2) were counterstained with Nissl staining to reveal all cells and to estimate total neuronal number in the adult BSTc. Cross-sectional digital images (every 50th to 100th section) were made using a 2.5× objective (Plan-Neofluar) on a Zeiss Axioskop microscope, mounted with a Sony B/W CCD camera (model XC77CE), that was connected to an IBAS imaging analysis system (Kontron Elektronik). The somatostatin-stained BSTc was outlined at 2.5× magnification; subsequently, the imaging analysis system overlaid a grid of rectangular fields within the outlined cross-sectional area. Each field was equal in size to the area displayed by the camera at 63× objective (Plan-Apochromat). For analysis, 25% of the rectangular fields (each field covering at least 10% of the outlined area) was selected by a random systematic sampling procedure. To prevent double counting, only neurons containing a nucleolus (~2 μm diameter) were counted. This counting procedure is first based on the assumption that the cell nucleus only contains one nucleolus. No multi-nucleolated nuclei were observed in our sections, confirming the observation of Kruijver et al. (2000) for the BSTc. Second, nucleoli are considered to be hard particles that will not be sectioned by a microtome knife but instead are pushed either in or out the paraffin when hit by a microtome knife (Jones, 1937; Cammermeyer, 1967; Koningsmark, 1970; Braendgaard and Gundersen, 1986). All visible neurons with a nucleus containing a clear nucleolus, within the exclusion lines, were counted using a 63× objective. The neuronal density was calculated by multiplying the total number of nucleoli counted by the sampled volume. The total number of neurons was then estimated for the adult BSTc by multiplying neuronal density with the total BSTc volume. The measurements were made without knowledge of age and sex.

Statistical analysis. The data were categorized in a fetal/neonatal period (between the 25th and 41th weeks of gestation), an infant/pubertal period (between 3 months and 16 years), and an adult period (between 22 and 49 years) and were tested for significant differences using one-way ANOVA and *t* tests (see Fig. 2). A $p < 0.05$ was considered as significant.

RESULTS

BSTc volume defined by VIP immunostaining was ~60.7 ± 3.1% (SEM) smaller than BSTc volume defined by somatostatin immunostaining across all age groups (Figs. 1, 2) because of the

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Table 2. Total number of neurons in the BSTc

	NBB	Sex	Age (years)	Brain weight (gm)	Postmortem delay (hr)	Fixation (d)	Neuronal density (mm^3)	Total number of BSTc neurons
Males (n = 8)	97083	m	22	1334	<16:29	26	12930	76249
	97173	m	24	1364	<33:30	31	17012	114120
	86042	m	28	1450	<17:00	46	18240	96200
	96406	m	35	1430	13:30	1214	18095	119383
	99071	m	39	1400	<16:30	130	16346	113095
	88011	m	41	1500	20:30	33	15158	102247
	92011	m	47	1500	<89:00	77	18267	89782
	97159	m	48	1500	5:30	42	15070	89630
Females (n = 7)	85041	f	28	nd	5:25	44	16255	103774
	85027	f	29	1150	13:10	60	19597	61353
	86032	f	33	1035	<41:00	20	19541	81669
	84002	f	36	1420	85:40	51	20204	74509
	97131	f	43	1345	<92:00	63	20639	75268
	89104	f	49	1260	<41:00	32	13552	88245
	96423	f	49	1253	<17:00	806	17443	92717

NBB, Netherlands Brain Bank; F, female; M, male; SOM, somatostatin.

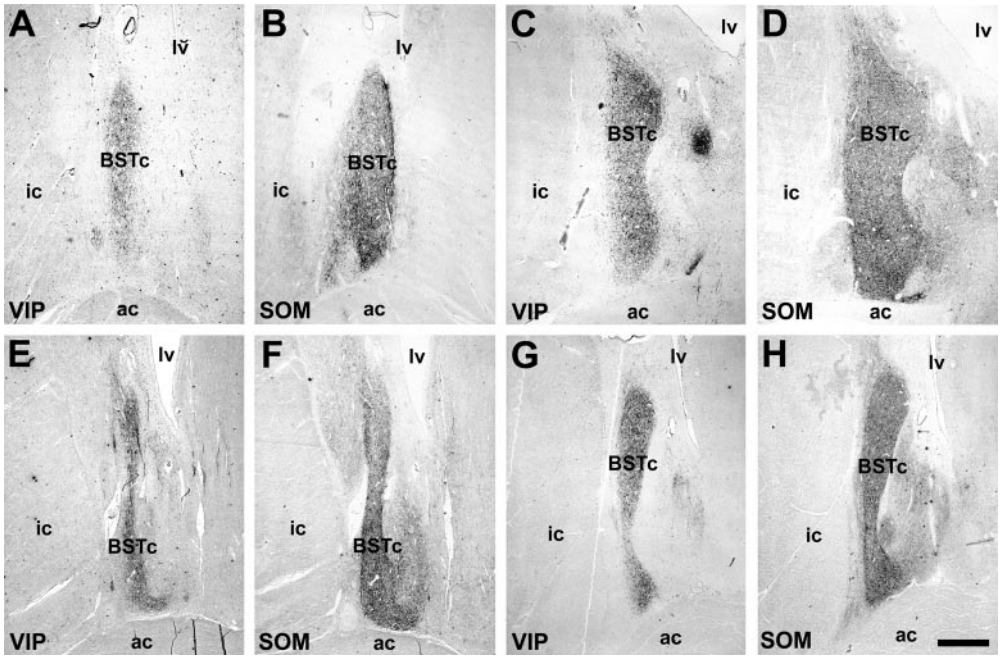

Figure 1. Representative photomicrographs depicting the BSTc in males (*top row*) and females (*bottom row*) in sections stained immunocytochemically for VIP (*A*, *C*, *E*, *G*) and somatostatin (*SOM*) (*B*, *D*, *F*, *G*) during development. *A*, *B*, #87036, 14 years old; *C*, *D*, #99071, 39 years old; *E*, *F*, #99060, 16 years old; *G*, *H*, #92037, 32 years old. Note that the BSTc in males is larger than in females only in adulthood (#99071 vs #92037). Scale bar, 1 mm. *ac*, Anterior commissure; *ic*, internal capsule; *lv*, lateral ventricle.

presence of somatostatin-IR fibers in the cell-sparse shell that surrounds the VIP-IR fibers in the BSTc core. No postmortem delay or fixation time effects on the immunocytochemical staining were observed. Regression analysis showed that BSTc volume in both males and females defined by VIP immunocytochemistry is correlated with BSTc volume defined by somatostatin immunocytochemistry (in males, $r = 0.96$, $p < 0.0001$; in females $r = 0.73$, $p < 0.0001$) (Fig. 2).

One-way ANOVA showed that the male BSTc volume significantly increased with age as based on its VIP ($F_{(2,24)} = 27.4$; $p < 0.0001$) or somatostatin ($F_{(2,23)} = 28.2$; $p < 0.0001$) immunocytochemical staining. *Post hoc* analysis showed that the fetal/neonatal, infant/pubertal, and adult age groups significantly differed from each other ($p < 0.05$). The female BSTc volume significantly increased with age as based on its VIP staining ($F_{(2,24)} = 22.2$; $p < 0.0001$) or somatostatin staining ($F_{(2,23)} = 18.1$; $p < 0.0001$). *Post hoc* analysis showed that only the fetal/neonatal–infant/pubertal age groups and the fetal/neonatal–adult age groups ($p < 0.05$), but not the infant/pubertal–adult age group, significantly differed from each other (Fig. 2*A*,*B*). Consequently, adult BSTc volume was on average 39% larger in males than in females ($t = 2.14$, $p < 0.001$ for VIP; $t = 2.14$, $p < 0.01$ for somatostatin; t test), thereby confirming previous studies, which showed that the adult BSTc size is larger in males than in females (Zhou et al., 1995; Kruijver et al., 2000) (Fig. 2*C*,*D*). Moreover, the total number of BSTc neurons in adulthood (i.e., between 22 and 49 years) was significantly ($t = 2.16$; $p < 0.05$) larger in males (100,088 ± 5247) than in females (82,505 ± 5242) (Fig. 2*E*), which is consistent with the larger number of somatostatin-IR neurons found in males compared with females in adulthood (Kruijver et al., 2000).

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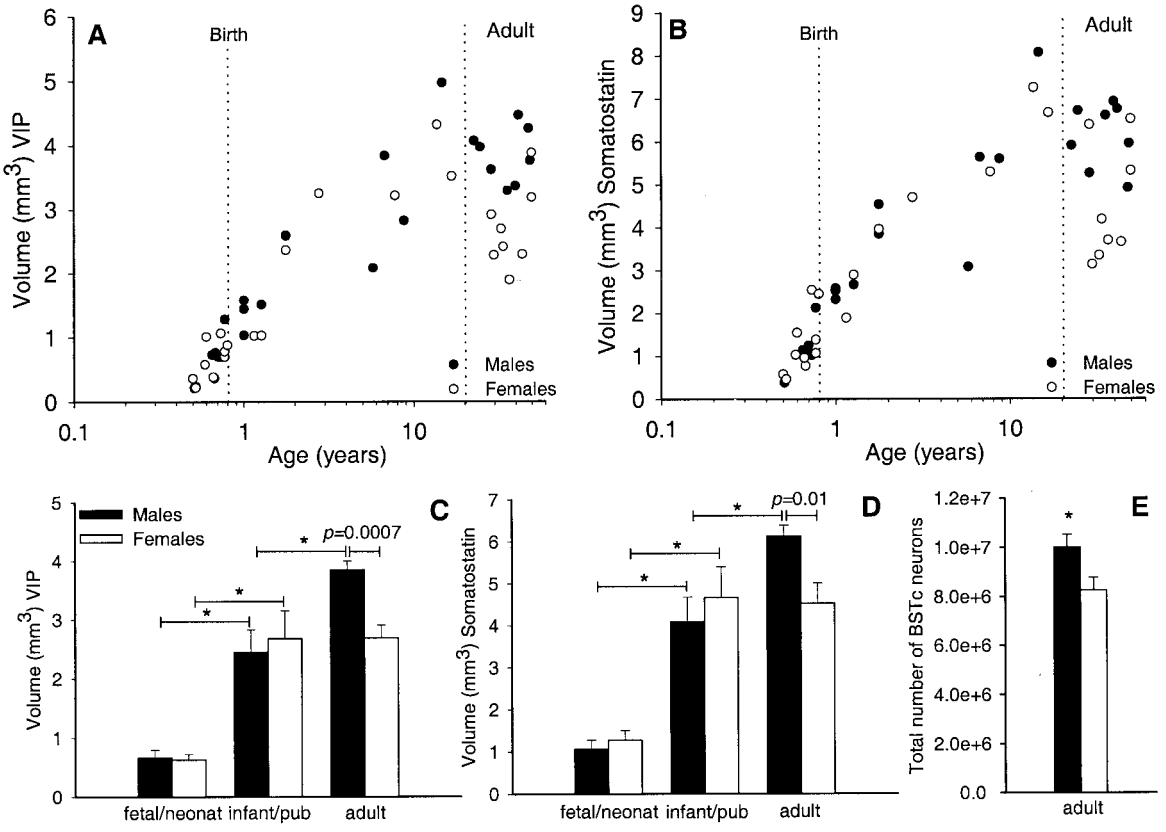

Figure 2. BSTc development in males and females. *A*, *C*, BSTc volume as delineated by its VIP innervation. *B*, *D*, BSTc volume as delineated by its somatostatin innervation. *E*, Total number of BSTc neurons in males and females in adulthood.

DISCUSSION

The sex difference in BSTc volume, which reached significance only in adulthood, developed much later than we expected. Sexual differentiation of the rat BST occurs in the first weeks after birth and requires perinatal sex differences in testosterone levels (Del Abril et al., 1987; Chung et al., 2000). In humans, testosterone levels during fetal and neonatal development are higher in males than in females (Abramovich and Rowe, 1973; Winter, 1978). In addition, dramatic alterations in adult testosterone levels have no obvious effects on the volume of the BSTc in either males or females (Zhou et al., 1995; Kruijver et al., 2000). Therefore, the BSTc was presumed to diverge between males and females early on in development. Moreover, sexual differentiation of the sexually dimorphic nucleus of the preoptic area and other areas in the human anterior hypothalamus occurs between 4 and 10 years of age (Swaab and Hofman, 1988; Swaab et al., 1994).

The late divergence of BSTc volume in males and females may be a general characteristic of the human BST. The human BST-dspm seems to become sexually dimorphic at approximately puberty, as suggested by the developmental time points that were included in the study by Allen and Gorski (1990). Indeed, the BST-dspm appeared to be smaller in females than in males from ~14 years of age (Allen and Gorski, 1990). Relatively late sexual differentiation has also been observed in the pig hypothalamus. The number of cells in the sexually dimorphic vasopressin and oxytocin-containing nucleus in the pig hypothalamus increases in (post)adolescent females but not in males (Van Eerdenburg and Swaab, 1994). Recent studies also showed that several regions in the adult human and primate brain continuously produce new neurons and change in gray and white matter volume (Eriksson et al., 1998; Gould et al., 1999; Gur et al., 1999; Sowell et al., 1999). Therefore, marked morphological changes in the human brain, including sexual differentiation, may not be limited to childhood but may extend into adulthood.

There are several possible explanations for the lack of a sex difference in the BSTc volume shortly after fetal or neonatal sex differences in testosterone levels emerge. Organizational effects of testosterone on sexual differentiation may become clear much later in life. An example of a long delay in organizational effects of gonadal steroids is the development of the sexually dimorphic anteroventral periventricular nucleus (AVPv) in the rat brain, which is larger in females than in males. Although, perinatal sex differences in testosterone cause this sex difference in AVPv size, its volume becomes only significantly different at approximately puberty (Davis et al., 1996). Alternatively, it is possible that sex differences in peripubertal or adult gonadal steroid levels establish the sex difference in BSTc volume in adulthood. Although androgens and estrogens in puberty cause the development of secondary sexual characteristics in peripheral body structures, as far as we know, no data exist on similar effects on human brain structures. However, data from six cases reported in previous studies suggest that the BSTc volume, as delineated by VIP or somatostatin immunocytochemical staining, is not affected by marked increases or decreases in gonadal steroid levels in adulthood. A normal female-sized BSTc was found in one control female with increased androgen levels and in two postmenopausal control females with low gonadal steroid levels. Furthermore, a normal male-sized BSTc was found in a control male with high

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estrogen levels caused by a feminizing adrenal tumor and in two control males who were orchidectomized as a result of prostate cancer. The possibility that gonadal steroid-dependent changes in VIP or somatostatin neuropeptide expression underlie the changes BSTc volume, such as, in quail preoptic area, rat medial amygdala and human amygdala (Panzica et al., 1987; Giedd et al., 1996; Cooke et al., 1999), is also not supported by these six cases who had marked changes in gonadal steroid levels, although their the BSTc volume was normal for their gender (Zhou et al., 1995; Kruijver et al. 2000).

In addition to direct actions of gonadal steroids on the BSTc, the late emergence of sex differences in BSTc volume may reflect relatively late sex-dependent changes in brain areas that supply the BST with its VIP-IR innervation, such as the amygdala (Eiden et al., 1985), which increases in size at a higher rate in males than in females between 4 and 18 years of age (Giedd et al., 1996). Although sex differences in gonadal steroids are the most likely factor to cause sexual differentiation of the BSTc and the areas that innervate the BSTc, we cannot exclude gonadal steroid-independent mechanisms on brain sexual differentiation, such as local expression of sex chromosomal genes (Reisert and Pilgrim, 1991). A candidate gene for such an effect is the *SRY* gene, which was shown to be transcribed in the adult human hypothalamus and cortex of males but not in females (Mayer et al., 1998).

Late sexual differentiation of the human BSTc volume also affects our perception about the relationship between BSTs volume and transsexuality. Interestingly, transsexuals receive their first consultation between the ages of 20 and 45 years, which coincides with the period of sex-dependent divergence of BSTc volume found in the present study (Van Kesteren et al., 1996). However, epidemiological studies show that the awareness of gender problems is generally present much earlier. Indeed, ~67–78% of transsexuals in adulthood report having strong feelings of being born in the wrong body from childhood onward (Van Kesteren et al., 1996), supporting the idea that disturbances in fetal or neonatal gonadal steroid levels underlie the development of transsexuality. Moreover, observations that phenobarbital or diphantoin usage during pregnancy, which affect gonadal steroid levels, increases the prevalence of transsexuality in the offspring support this idea (Dessens et al., 1999). Also, girls who had been exposed to high androgen levels as infants caused by congenital adrenal hyperplasia show an increased incidence of gender problems, which supports early developmental programming of this disorder (Meyer-Bahlburg et al., 1996; Zucker et al., 1996). The lack of marked sexual differentiation of the BSTc volume in our study before birth and in childhood certainly does not rule out early gonadal steroid effects on BSTc functions. As suggested by animal experiments, fetal or neonatal testosterone levels in humans may first affect synaptic density, neuronal activity, or neurochemical content during early BSTc development (Döhler, 1991; Park et al., 1997). Changes in these parameters could affect the development of gender identity but not immediately result in overt changes in the volume or neuronal number of the BSTc. Alternatively, it must also be taken into consideration that changes in BSTc volume in male-to-female transsexuals may be the result of a failure to develop a male-like gender identity. In summary, our finding of a sex difference in BSTc volume only in adulthood suggests that marked sex-dependent organizational changes in brain structure are not limited to early development but may extend into adulthood.

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Exhibit 8

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Meta-Analysis

Meta-Analysis

Hormone Therapy, Mental Health, and Quality of Life Among Transgender People: A Systematic Review

Kellan E. Baker,[1,3] Lisa M. Wilson,[1,3] Ritu Sharma,[1,3] Vadim Dukhanin,[1,3] Kristen McArthur,[1,3] and Karen A. Robinson[2,3]

[1]Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, USA; [2]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA; and [3]Johns Hopkins Evidence-Based Practice Center, 615 North Wolfe Street, Baltimore, MD 21205, USA

ORCiD number: 0000-0002-9716-7936 (K. E. Baker).

Abbreviations: BDI, Beck Depression Inventory; ENIGI, European Network for the Investigation of Gender Incongruence; GnRH, gonadotropin-releasing hormone; HADS, Hospital Anxiety and Depression Scale; QOL, quality of life; RCT, randomized controlled trial; SF-36, Short Form-36 Health Survey; WPATH, World Professional Association for Transgender Health.

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Abstract

We sought to systematically review the effect of gender-affirming hormone therapy on psychological outcomes among transgender people. We searched PubMed, Embase, and PsycINFO through June 10, 2020 for studies evaluating quality of life (QOL), depression, anxiety, and death by suicide in the context of gender-affirming hormone therapy among transgender people of any age. We excluded case studies and studies reporting on less than 3 months of follow-up. We included 20 studies reported in 22 publications. Fifteen were trials or prospective cohorts, one was a retrospective cohort, and 4 were cross-sectional. Seven assessed QOL, 12 assessed depression, 8 assessed anxiety, and 1 assessed death by suicide. Three studies included trans-feminine people only; 7 included trans-masculine people only, and 10 included both. Three studies focused on adolescents. Hormone therapy was associated with increased QOL, decreased depression, and decreased anxiety. Associations were similar across gender identity and age. Certainty in this conclusion is limited by high risk of bias in study designs, small sample sizes, and confounding with other interventions. We could not draw any conclusions about death by suicide. Future studies should investigate the psychological benefits of hormone therapy among larger and more diverse groups of transgender people using study designs that more effectively isolate the effects of hormone treatment.

Key Words: Transgender, hormone therapy, sex hormones, mental health, systematic review

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Transgender people are those whose gender identity is different from the sex they were assigned at birth. Estimates of the size of the transgender population vary depending on how the data are collected [1]. In studies that rely on clinical records, estimates range between 1 and 30 people per 100 000 (0.001% to 0.03%) [2]. Studies that focus instead on self-report among nonclinical populations find estimates that range between 0.1% and 2% [2].

Many transgender people seek medical services to affirm their gender identity. According to the *Standards of Care for Transsexual, Transgender, and Gender Non-Conforming People* maintained by the World Professional Association for Transgender Health (WPATH), gender-affirming medical care is different for each individual and may include a variety of services and procedures, such as psychological support, hormone therapy, and surgeries [3]. Hormone therapy, which typically involves estrogens and anti-androgens for transgender women and other trans-feminine people and testosterone for transgender men and other trans-masculine people, is a common component of medical gender affirmation [4]. Because hormone treatment can have a powerful effect on physical appearance, it is often a priority for transgender people seeking medical gender affirmation [5]. Gender-affirming hormone therapy can be managed for most patients by primary care providers, as it typically involves long-term maintenance on doses similar to those used for cisgender patients with conditions such as hypogonadism [6, 7]. Some clinicians require a minimum period of psychological counseling before hormone therapy can be initiated, while others provide hormone therapy on the basis of informed consent [8].

The need for gender-affirming care is often characterized using psychiatric diagnoses such as gender dysphoria, which replaced gender identity disorder in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [9]. The 11th International Classification of Diseases (ICD-11) replaces these terms with a diagnosis called gender incongruence (codes: HA60, HA61, HA6Z), which is located in a new chapter on sexual health. These changes clarify that the target of gender-affirming medical interventions is not the person's gender identity itself but rather the clinically significant distress that can accompany a misalignment between gender identity and sex assigned at birth [10]. Some countries have further underscored that transgender identity is not a pathology by recognizing gender affirmation as fundamental to the human right to self-definition and removing requirements that transgender people seeking gender-affirming medical care present with a diagnosis such as gender dysphoria [11].

Several previous reviews have indicated that gender-affirming hormone therapy is associated with psychological benefits that include reductions in depression and anxiety and improvements in quality of life (QOL) among transgender people [12-17]. Most of these reviews did not require a minimum duration of hormone therapy [14-17]. One review that did impose a minimum follow-up requirement is 10 years old [12]. The other that required a minimum of 3 months of therapy included only uncontrolled prospective cohorts, which resulted in a sample of only 3 studies [13]. A comprehensive review without a minimum follow-up period assessed gender-affirming hormone therapy and surgeries only in adolescents [17]. By requiring a minimum duration of hormone treatment but considering all ages and a variety of study designs, we sought to update and more completely summarize the growing evidence base regarding the relationship between gender-affirming hormone therapy and psychological outcomes in transgender people.

Search Strategy and Selection Criteria

This review is one of a series of systematic reviews on gender-affirming care conducted for WPATH to inform the eighth revision of the *Standards of Care*. The protocol is registered on PROSPERO (CRD42018115379) [18], and we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in reporting our findings [19].

We searched PubMed, Embase, and PyscINFO from inception to October 2018 and updated the search through June 10, 2020, for studies assessing QOL, depression, anxiety, and death by suicide among transgender participants of any age in the context of gender-affirming hormone therapy [20]. We also reviewed the reference lists of previous reviews and hand-searched the *International Journal of Transgenderism*. Using DistillerSR [21], 2 reviewers independently screened titles, abstracts, and full-text articles. Differences were resolved through consensus adjudication.

We included studies that evaluated the psychological effects of any testosterone, estrogen, or anti-androgen formulation used for gender affirmation. We also considered gonadotropin-releasing hormone (GnRH) analogues used as anti-androgens or for puberty delay. Study participants must have been on hormone therapy for at least 3 months in order to reflect a minimum time for expected onset of effects [3]. Health care provider supervision was not required. We excluded studies that did not state therapy type and duration, including the range for cross-sectional studies. We included studies regardless of language (the search terms were in English) and country of origin, and we accepted any study design except case reports.

We created standardized forms for data extraction using the Systematic Review Data Repository system. The data extracted included participant demographics; study design

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and methods; hormone therapy type, dose, and duration; potential confounders such as gender-affirming surgery status; outcome scales [20]; and psychological outcomes. From studies that used the Short Form-36 Health Survey (SF-36) to measure QOL, we extracted scores in all domains [22]. For studies that used measures with depression or anxiety subscales, we extracted only the subscale scores corresponding to the psychological outcomes of interest (eg, the depression subscale of the Minnesota Multiphasic Personality Inventory [MMPI]). We extracted comparisons with cisgender controls or general population norms only when longitudinal findings in a transgender population or comparisons with an untreated transgender control group were not reported. We used WebPlotDigitizer to extract data reported only in figures [23].

Two reviewers independently assessed risk of bias [20]. For randomized controlled trials (RCTs), we used the revised Cochrane tool [24]. For non-randomized studies, we used the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ROBINS-I) [25]. One reviewer graded strength of evidence for each outcome using the Agency for Healthcare Research and Quality Methods Guide for Conducting Comparative Effectiveness Reviews [26]. We considered the directionality and magnitude of effects reported in cross-sectional studies as additional context for our evaluation of evidence from trials and prospective and retrospective cohorts. Each strength of evidence assessment was confirmed by a second reviewer.

WPATH provided the research question and reviewed the protocol, evidence tables, and report. WPATH had no role in study design, data collection, analysis, interpretation, or drafting. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication. The authors are responsible for all content, and statements in this report do not necessarily reflect the official views of or imply endorsement by WPATH.

Results

We retrieved 1753 nonduplicate studies for the broader systematic review project of which this review was a part (Fig. 1). After screening and full-text review for the specific research question on the psychological effects of gender-affirming hormone therapy, 20 studies reported in 22 publications were included (Table 1): 1 RCT [27], 2 before-after trials [28, 29], 12 prospective cohorts reported in 13 publications [30-42], 1 retrospective cohort reported in 2 publications [43, 44], and 4 cross-sectional studies [45-48]. De Vries (2014) [35] reported on a subset of the participants in de Vries (2011) [34] who continued in care. We counted these publications as a single study but extracted and reported data separately because the characteristics of the study's adolescent population changed substantially in the period between the 2 publications. Similarly, Asscheman (2011) [44] reported on an extension of Asscheman (1989) [43]; we counted these as a single study but extracted data separately. In Table 1 and in the subsequent tables for each outcome, studies are ordered first by study design (RCTs, before-after trials, prospective cohorts, retrospective cohorts, and cross-sectional studies); within these categories, studies are presented in the following order according to how the study results were reported: adult transgender women only, adult transgender men only, adult transgender women and transgender men together, and transgender adolescents (no study reported separate results by gender identity for transgender youth). Where multiple studies shared the same study design and population, they are additionally ordered chronologically.

The time frame covered in the included studies began in 1972 [43], but most studies dated from post-2000. Eight studies were conducted in Italy [27-29, 31, 32, 36, 39, 41]; 2 each in Belgium [37, 48], the Netherlands [34, 35, 43, 44], the United States [30, 47], and Spain [38, 45]; and 1 in the United Kingdom [33], Turkey [42], and France [46]. One study recruited participants from Switzerland and Germany [40]. One study was part of the European Network for the Investigation of Gender Incongruence (ENIGI), which is a research collaborative between clinics providing gender-affirming care to transgender people in Ghent (Belgium), Amsterdam (Netherlands), Oslo (Norway), and Hamburg (Germany). The ENIGI study included in this review drew participants only from the Ghent clinic [37].

The study sizes ranged from 20 to 1331, although most had fewer than 60 participants. Fourteen studies reported on testosterone formulations in adult transgender men [27, 29, 31-33, 36, 39-46, 48]. These formulations were typically injectable testosterone cypionate or enanthate, although some studies used long-acting injectable testosterone undecanoate or daily transdermal gels. Ten studies reported on estrogen formulations in adult transgender women, usually in conjunction with an anti-androgen such as cyproterone acetate or spironolactone [28, 31, 33, 36, 37, 39, 43-47]. Estrogen formulations included transdermal, oral, or injectable estradiol (commonly estradiol valerate) or conjugated estrogens. Three studies reported on the psychological effects of GnRH therapy for puberty delay among mixed-gender groups of transgender adolescents [30, 34, 35, 38]. No study reported on hormone therapy among nonbinary people.

All studies that reported information about recruitment drew their participants largely or exclusively from specialized clinics dedicated to providing gender-affirming care for transgender people. These clinics were typically part of larger systems such as university hospitals. Clinic-based

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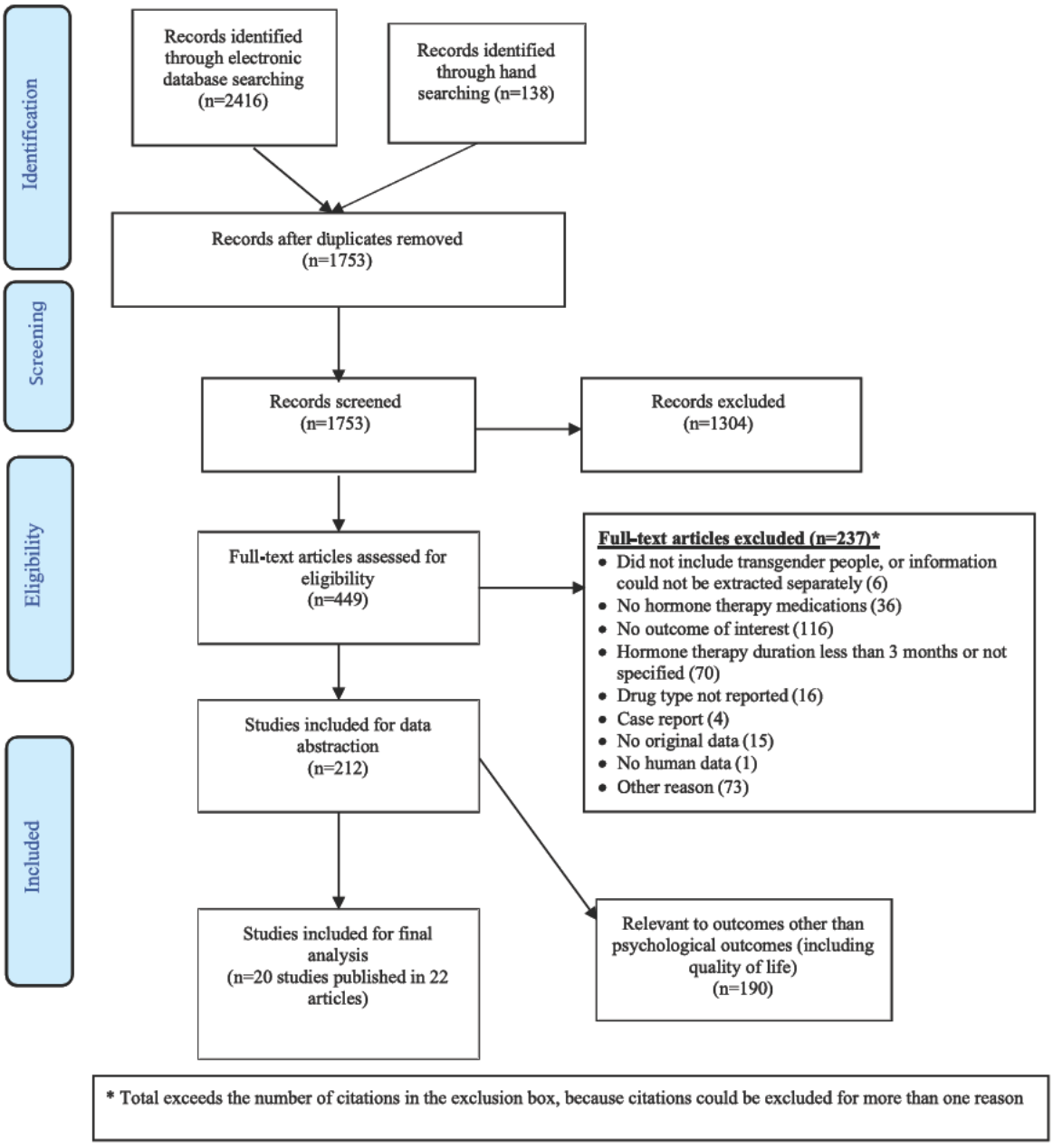

Figure 1. PRISMA flow diagram.

studies often applied strict eligibility criteria that included a period of psychiatric evaluation and a formal diagnosis of gender dysphoria before hormone therapy was initiated. Some studies also reported that psychological counseling was either available or required during the course of hormone therapy. In many cases, hormone therapy was considered a prerequisite for gender-affirming surgeries. The type and timing of gender-affirming surgeries and the proportion of participants for whom hormone therapy and surgeries were assessed simultaneously varied widely: some studies assessed only participants who had not had any type of gender-affirming surgery [27, 28, 30-32, 34, 36, 38-40, 42, 46, 47], while in others some or all participants underwent gender-affirming surgeries during the study period [29, 33, 35, 43-45, 48].

Quality of Life

Seven studies, including 1 RCT [27], 2 before-after trials [28, 29], 2 prospective cohorts [30, 39], and 2 cross-sectional studies [46, 48], assessed QOL (Table 2). An RCT found an improvement of approximately 5.5 points on a 10-point measure of life satisfaction across 3 groups of transgender men (n = 15 each) after 1 year of testosterone treatment ($P < 0.05$) [27]. A before-after trial similarly reported that life satisfaction scores almost

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Table 1. Studies Reporting Effects of Gender-Affirming Hormone Therapy on Psychological Outcomes Among Transgender People

Author, year Location Study name	Study design	Start year	Transgender population	Overall N	Age in years	Baseline HT status	Outcomes	GAS status	Risk of bias
Pelusi, 2014 [27] Italy	Randomized controlled trial[a]	NR	Men	45	Mean: 29.5	No previous HT	QOL	No GAS before or during study	High
Gava, 2016 [28] Italy	Before-after trial	NR	Women	40	Mean: 3.2 (range, 19–55)	No previous HT	QOL, Depression	No GAS before or during study	Low
Gava, 2018 [29] Italy	Before-after trial[a]	NR	Men	50	Mean: 30.1 (range, 21–42)	No previous HT	QOL	72% (n = 36) had gonadectomy during study	Serious
Fuss, 2015 [37] Belgium ENIGI (NCT01072825)	Prospective cohort	2010	Women	20	Mean: 33.9 (range, 17–48)	No previous HT	Anxiety	NR	Serious
Costantino, 2013 [32] Italy	Prospective cohort	2001	Men	50	Mean: 29.8	No previous HT	Depression	No GAS before or during study	Serious
Motta, 2018 [41] Italy	Prospective cohort	2013	Men	52	Mean: 28.3	No previous HT	Anxiety	NR	Moderate
Turan, 2018 [42] Turkey	Prospective cohort[b]	NR	Men	37	Mean: 24.6	No previous HT	Depression, Anxiety	No GAS before or during study	Moderate
Metzger, 2019 [40] Switzerland, Germany	Prospective cohort[b]	2013	Men	23	Mean: 27.2 (range, 18–51)	No previous HT	Depression	No GAS before or during study	Moderate
Colizzi, 2014 [31] Italy	Prospective cohort	2008	Women and men	107	Mean: 29.2	No previous HT	Depression, Anxiety	No GAS before or during study	Low
Manieri, 2014 [39] Italy	Prospective cohort	NR	Women and men	83	Mean: 32.7 (women), 30.2 (men)	No previous HT	QOL	No GAS before or during study	Moderate
Fisher, 2016 [36] Italy	Prospective cohort	2012	Women and men	54	Mean: 32.5 (women), 26.3 (men)	No previous HT	Depression	No GAS before or during study	Low
Defreyne, 2018 [33] UK	Prospective cohort	2012	Women and men	155	Median: 27 (range, 18–52)	No previous HT	Depression, Anxiety	Some had GAS during study; % and type NR	Serious
Asscheman, 1989 [43] Netherlands	Retrospective cohort[b,d]	1972	Women and men	425	Median: 32 (women, range, 16–67); 25.4 (men, range, 16–54)	Previous HT for at least 6 months	Death by suicide	78% (n = 235) of transgender women had GAS during study; data NR for transgender men	Serious

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Table 1. Continued

Author, year Location Study name	Study design	Start year	Transgender population	Overall N	Age in years	Baseline HT status	Outcomes	GAS status	Risk of bias
Asscheman, 2011 [44] Netherlands	Retrospective cohort[b,d]	1975	Women and men	1331	Mean: 31.4 (women, range, 16–76); 26.1 (men, range, 16–57)	Previous HT for at least 1 year	Death by suicide	87% (n = 834) of transgender women and 94% (n = 343) of transgender men had GAS during study	Serious
Leavitt, 1980 [47] US	Cross-sectional	1976	Women	41	Range, 18–35	54% (n = 22) on HT	Depression	No previous GAS	Serious
Wierckx, 2011 [48] Belgium	Cross-sectional[b]	2009	Men	47	Mean: 37 (range, 22–54)	100% on HT	QOL	100% had GAS, but not within previous year	Serious
Gómez-Gil, 2012 [45] Spain	Cross-sectional	NR	Women and men	187	Mean: 29.9 (range, 15–61)	64% (n = 120) on HT	Depression, Anxiety	42% (n = 79) of all participants and 64% (n = 77) of participants on HT had previous GAS	Serious
Gorin-Lazard, 2012 [46] France	Cross-sectional[b]	NR	Women and men	61	Mean: 34.7	72% (n = 44) on HT	QOL	No previous GAS	Serious
de Vries, 2011 [34] Netherlands	Prospective cohort	2000	Girls and boys	70	Mean: 14.8 (range, 11.3–18.6)	No previous HT	Depression, Anxiety	No GAS before or during study	Moderate
de Vries, 2014 [35] Netherlands	Prospective cohort[b,c]	2000	Girls and boys	55	Mean: 14.8 (range, 11.5–18.5)	No previous HT	Depression, Anxiety	100% had GAS during study	Serious
Achille, 2020 [30] US	Prospective cohort	2013	Girls and boys	50	Mean: 16.2	No previous HT	QOL, Depression	No GAS before or during study	Moderate
López de Lara, 2020 [38] Spain	Prospective cohort[b]	2018	Girls and boys	23	Mean: 16 (range, 14-18)	No previous HT	Depression, Anxiety	No GAS before or during study	Moderate

Abbreviations: ENIGI, European Network for the Investigation of Gender Incongruence; GAS, gender-affirming surgery; HT, hormone therapy; NR, not reported; QOL, quality of life.

[a]25 participants were included in both Pelusi [27] and Gava (2018) [29]

[b]Included a cisgender control group or a comparison to general population norms

[c]All participants were also included in de Vries (2011) [34]

[d]An unknown number of participants were included in both Asscheman (1989) [43] and Asscheman (2011) [44]

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Table 2. Effects of Gender-Affirming Hormone Therapy on Quality of Life Among Transgender People

Author, year Study design	Transgender population	Treatment / comparison (n)	QOL measures	Length of treatment	Findings
Pelusi, 2014 [27] RCT[a]	Men	Testoviron depot (15) vs testosterone gel (15) vs testosterone undecanoate (15)	VAS (general life satisfaction)	54 weeks	Mean QOL scores increased from 2.8 to 8.5 ($P < 0.05$) in the testoviron depot arm, from 3.2 to 8.9 ($P < 0.05$) in the testosterone gel arm, and from 2.6 to 8.0 ($P < 0.05$) in the testosterone undecanoate arm.[d] There was no difference across arms.
Gava, 2016 [28] Before-after trial	Women	Cyproterone acetate + estradiol (20) vs leuprolide acetate + estradiol (20)	VAS (general life satisfaction) SF-36	12 months	Mean QOL scores did not change in either arm. No comparisons across arms were reported.
Gava, 2018 [29] Before-after trial[a]	Men	Testosterone undecanoate (25)[c] vs testosterone enanthate (25)[c]	VAS (general satisfaction)	5 years	Mean QOL scores increased from 4.3 ± 3.1 to 8.1 ± 1.8 ($P < 0.001$) in the testosterone undecanoate arm and from 4.3 ± 3.8 to 8.3 ± 1.7 ($P < 0.001$) in the testosterone enanthate arm. No comparisons across arms were reported.
Manieri, 2014 [39] Prospective cohort	Women	HT (56)	WHOQOL	12 months	Mean QOL scores increased from 62.5 to 72.2 ($P < 0.05$).[d]
Manieri, 2014 [39] Prospective cohort	Men	HT (27)	WHOQOL	12 months	Mean QOL scores did not change.
Wierckx, 2011 [48] Cross-sectional[b]	Men	HT (47)[c]	SF-36	At least 3 years	Mean QOL scores on the VT and MH subscales were lower for transgender men than cisgender men (VT subscale: 62.1 ± 20.7 vs 71.9 ± 18.3, $P = 0.002$; MH subscale: 72.6 ± 19.2 vs 79.3 ± 16.4, $P = 0.020$). There were no other differences between transgender men and either cisgender men or cisgender women.
Gorin-Lazard, 2012 [46] Cross-sectional[b]	Women and men	HT (44) vs no HT (17)	SF-36	Median: 20 months (range, 12–42 months)	Mean QOL scores were generally higher in the group receiving HT vs the group not receiving HT (MCS: 51.0 ± 7.7 vs 39.8 ± 12.7, $P = 0.003$; MH subscale: 76.4 ± 14.1 vs 59.1 ± 19.6, $P = 0.004$; RE subscale: 88.6 ± 22.7 vs 54.9 ± 40.7, $P = 0.001$; SF subscale: 83.2 ± 23.3 vs 69.9 ± 24.2, $P = 0.026$). There were no differences in the other subscales.
Achille, 2020 [30] Prospective cohort	Girls and boys	GnRH treatment + HT (47)	Q-LES-Q-SF	12 months	Mean QOL scores did not change.

Abbreviations: GnRH, gonadotropin-releasing hormone; HT, hormone therapy; MCS, Mental Component Summary; MH, mental health; QOL, quality of life; RCT, randomized controlled trial; RE, role functioning/emotional; SF, social functioning; SF-36, Short Form-36 Health Survey; VAS, visual analog scale; VT, vitality; WHOQOL, World Health Organization Quality of Life measure.

[a]10 participants on testosterone enanthate and 15 participants on testosterone undecanoate were included in both Pelusi [27] and Gava (2018) [29]

[b]Included a cisgender control group or a comparison to general population norms

[c]Included participants who had undergone gender-affirming surgery/surgeries, or surgery status not reported

[d]No standard deviations reported

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doubled among transgender men (n = 50) over 5 years [29]. A prospective study found a 16% improvement in QOL scores among transgender women (n = 56) after 1 year of treatment ($P < 0.05$) but no change among transgender men (n = 27) [39]. Another before-after trial reported no difference in SF-36 scores among 2 groups of transgender women (n = 20 each) after 1 year [28]. Among adolescents, a mixed-gender prospective cohort (n = 50) showed no difference in QOL scores after a year of endocrine interventions, which included combinations of GnRH analogues and estrogen or testosterone formulations [30]. No study found that hormone therapy decreased QOL scores. We conclude that hormone therapy may improve QOL among transgender people. The strength of evidence for this conclusion is low due to concerns about bias in study designs, imprecision in measurement because of small sample sizes, and confounding by factors such as gender-affirming surgery status.

Depression

Twelve studies, including 1 before-after trial [28], 9 prospective cohorts [30-36, 38, 40, 42], and 2 cross-sectional studies [45, 47], assessed depression (Table 3). A prospective study found that the proportion of transgender men and transgender women (n = 107) showing symptoms of depression decreased from 42% to 22% over 12 months of treatment ($P < 0.001$) [31]. In 2 other prospective cohorts, Beck Depression Inventory (BDI-II) scores improved by more than half among both transgender men (n = 26) and transgender women (n = 28) after 24 months of therapy ($P < 0.001$) [36] and improved from 15.7 ± 12.3 to 8.1 ± 6.2 among transgender men (n = 23) after 6 months ($P < 0.001$) [40]. A fourth prospective study reported improvements of 1.05 points (95% CI: −1.87, −0.22) and 1.42 points (95% CI: −2.61, −0.24) on the 21-point Hospital Anxiety and Depression Scale (HADS) among 91 transgender women and 64 transgender men after 12 months ($P = 0.013$ and $P = 0.019$, respectively) [33]. A before-after trial, however, found no change in BDI-II scores among 2 groups of transgender women (n = 20 each) after 1 year [28]. Two prospective studies reported no difference among transgender men (n = 37) after 24 weeks [42] or among transgender men (n = 50) after 12 months [32], although in the latter study this outcome did not change from a baseline median of 0.0 ("not at all depressed") on an unvalidated 4-point scale. Among adolescents, 2 mixed-gender prospective cohorts (n = 50 and n = 23, respectively) showed improvements in depression scores after 1 year of treatment with GnRH analogues and estrogen or testosterone formulations (both $P < 0.001$) [30, 38]. Another prospective study reported that BDI scores improved almost by half among adolescents (n = 41) after a mean of 1.88 years of treatment with GnRH analogues to delay puberty ($P = 0.004$) [34]. The overall improvement after several subsequent years of testosterone or estrogen therapy in this cohort (n = 32) was smaller, however, resulting in no significant change from baseline [35]. No study found that hormone therapy increased depression. We conclude that hormone therapy may decrease depression among transgender people. The strength of evidence for this conclusion is low due to concerns about study designs, small sample sizes, and confounding.

Anxiety

Eight studies, including 7 prospective cohorts [31, 33-35, 37, 38, 41, 42] and 1 cross-sectional study [45], assessed anxiety (Table 4). One prospective study found that Symptom Checklist 90-Revised scores indicating a probable anxiety disorder among a mixed-gender group of adults (n = 107) improved from borderline to normal over 12 months ($P < 0.001$) [31]. Another prospective study, however, did not find a difference in HADS anxiety scores among either transgender men (n = 64) or transgender women (n = 91) after 1 year [33], and a third study reported no change in the number of transgender men (6/52, 12%) with a diagnosed anxiety disorder after 7 months [41]. Likewise, 2 other prospective studies found no difference in anxiety scores among transgender men (n = 37) after 24 weeks of treatment [42] or transgender women (n = 20) after 12 months [37], although this latter finding represented no change from a baseline median score of 0 (answering "no" to the question, "do you feel anxious?") on an unvalidated 3-point scale. Among adolescents, 1 prospective study saw mean anxiety scores in a mixed-gender group (n = 23) improve from 33.0 ± 7.2 to 18.5 ± 8.4 after 1 year ($P < 0.001$) [38], but another reported no changes in anxiety after approximately 2 years of puberty delay treatment with GnRH analogues and 4 years of hormone therapy (n = 32) [35]. No study found that hormone therapy increased anxiety. We conclude that hormone therapy may decrease anxiety among transgender people. The strength of evidence for this conclusion is low due to concerns about study designs, small sample sizes, and confounding.

Death by Suicide

One retrospective study reported in 2 publications assessed death by suicide (Table 5) [43, 44]. The first publication reported that 3 transgender women in the Amsterdam gender dysphoria study cohort (n = 303) died by suicide between 1972 and 1986 [43]. The authors calculated the number of suicide deaths expected in an age-matched stratum of

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Table 3. Effects of Gender-Affirming Hormone Therapy on Depression Among Transgender People

Author, year Study design	Transgender population	Treatment / comparison (n)	Depression measures	Length of treatment	Findings
Gava, 2016 [28] Before-after trial	Women	Cyproterone acetate + estradiol (20) vs Leuprolide acetate + estradiol (20)	BDI-II	12 months	Mean depression scores did not change in either arm. No comparisons across arms were reported.
Fisher, 2016 [37] Prospective cohort	Women	HT (28)	BDI-II	24 months	Mean depression score decreased from 10.12 to 4.58 ($P < 0.001$).[d,e]
Defreyne, 2018 [33] Prospective cohort	Women	HT (91)[c]	HADS (depression subscale)	1 year	Median depression score decreased by 1.05 (95% CI: −1.87, −0.22) on a 21-point scale ($P = 0.013$).
Costantino, 2013 [32] Prospective cohort	Men	HT (50)	Ad hoc questionnaire	12 months	Depression score did not change from a median of 0.0 at baseline (IQR: 0.0, 1.0).
Fisher, 2016 [36] Prospective cohort	Men	HT (26)	BDI-II	24 months	Mean depression score decreased from 9.31 to 4.25 ($P < 0.001$).[d,e]
Defreyne, 2018 [33] Prospective cohort	Men	HT (64)[c]	HADS (depression subscale)	1 year	Median depression score decreased by 1.42 (95% CI: −2.61, −0.24) on a 21-point scale ($P = 0.019$).
Turan, 2018 [42] Prospective cohort[b]	Men	HT (37)	SCL-90-R (depression subscale)	24 weeks	Mean depression score did not change.
Metzger, 2019 [40] Prospective cohort[b]	Men	HT (23)	BDI-II	6 months	Mean depression score decreased from 15.7 ± 12.3 to 8.1 ± 6.2 ($P < 0.001$).
Colizzi, 2014 [31] Prospective cohort	Women and men	HT (107)	Zung SDS SCL-90-R (depression subscale)	12 months	Mean Zung SDS score improved from 48.40 ± 10.5 to 39.98 ± 10.79 ($P < 0.001$), and the proportion with Zung SDS scores indicating mild, moderate, or severe depression (vs no depression) decreased from 42% to 22% ($\chi^2 = 19.05$, $P < 0.001$). Mean SCL-90-R score decreased from 0.83 ± 0.74 to 0.51 ± 0.49 ($P < 0.001$), which represents an improvement from possible borderline depression to no depression.
Leavitt, 1980 [47] Cross-sectional	Women	HT (22) vs No HT (19)	MMPI (depression subscale)	At least 12 months	Mean depression score was lower in the group receiving HT vs the group not receiving HT (53.1 ± 14.7 vs 65.7 ± 11.2, $P = 0.004$).

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Table 3. Continued

Author, year Study design	Transgender population	Treatment / comparison (n)	Depression measures	Length of treatment	Findings
Gómez-Gil, 2012 [45] Cross-sectional	Women and men	HT (120)[c] vs No HT (67)[c]	HADS (depression subscale)	Mean: 11.0 years (women, range, 1–46 years); 4.7 years (men, range, 1–22 years)	Mean depression score was lower in the group receiving HT vs the group not receiving HT (3.3 ± 3.2 vs 5.2 ± 4.2, $P = 0.002$).[f] The proportion with scores indicating depression (vs no depression) was larger in the group not receiving HT (31% vs 8%, $\chi^2 = 16.46$, $P = 0.001$).[f]
de Vries, 2011 [34] Prospective cohort	Girls and boys	GnRH treatment (41)	BDI	1.88 years	Mean depression score decreased from 8.31 ± 7.12 to 4.95 ± 6.72 ($P = 0.004$).
de Vries, 2014 [35] Prospective cohort[a,b]	Girls and boys	GnRH treatment + HT (32)[c]	BDI	5.9 years	Mean depression score did not change.
Achille, 2020 [30] Prospective cohort	Girls and boys	GnRH treatment + HT (47)	CESD-R, PHQ-9 (modified for adolescents)	12 months	Mean CESD-R score decreased from 21.4 to 13.9 ($P < 0.001$);[d] a score of <16 indicates no clinical depression. Mean PHQ-9 score decreased from 9.0 to 5.4 ($P < 0.001$).[d]
López de Lara, 2020 [38] Prospective cohort[b]	Girls and boys	GnRH treatment + HT (23)	BDI-II	1 year	Mean depression score decreased from 19.3 ± 5.5 to 9.7 ± 3.9 ($P < 0.001$).

Abbreviations: BDI/BDI-II, Beck Depression Inventory; GAS, gender-affirming surgery; GnRH, gonadotropin-releasing hormone; HADS, Hospital Anxiety and Depression Scale; HT, hormone therapy; IQR, interquartile range; MMPI, Minnesota Multiphasic Personality Inventory; NA, not applicable; SCL-90-R, Symptom Checklist 90-Revised; Zung SDS, Zung Self-Rating Depression Scale.

[a]All participants were also included in de Vries (2011) [34]

[b]Included a cisgender control group or a comparison to general population norms

[c]Included participants who had undergone gender-affirming surgery/surgeries, or surgery status not reported

[d]No standard deviations reported

[e]Adjusted for age, gender role, and surgery status

[f]Adjusted for age, gender, and education level

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Table 4. Effects of Gender-Affirming Hormone Therapy on Anxiety Among Transgender People

Author, year	Transgender population	Treatment / comparison (n)	Anxiety measures	Length of treatment	Findings
Fuss, 2015 [37] Prospective cohort	Women	HT (20)[c]	Ad hoc questionnaire	12 months	Anxiety score did not change from a median of 0.0 at baseline.
Defreyne, 2018 [33] Prospective cohort	Women	HT (91)[c]	HADS (anxiety subscale)	1 year	Median anxiety score did not change.
Defreyne, 2018 [33] Prospective cohort	Men	HT (64)[c]	HADS (anxiety subscale)	1 year	Median anxiety score did not change.
Motta, 2018 [41] Prospective cohort	Men	HT (46)[c]	DSM	7 months	Proportion diagnosed with an anxiety disorder (6/46, 12%) did not change.
Turan, 2018 [42] Prospective cohort[b]	Men	HT (37)	SCL-90-R (anxiety subscale)	24 weeks	Mean anxiety score did not change.
Colizzi, 2014 [31] Prospective cohort	Women and men	HT (107)	SCL-90-R (anxiety subscale) Zung SAS	12 months	Mean SCL-90-R score decreased from 1.05 ± 0.95 to 0.54 ± 0.56 ($P < 0.001$), which represents an improvement from borderline anxiety disorder to no anxiety disorder. Mean Zung SAS score improved from 44.91 ± 9.59 to 37.90 ± 8.97 ($P < 0.001$), and the proportion with Zung SAS scores indicating mild, moderate, or severe anxiety (vs no anxiety) decreased from 50% to 17% ($\chi^2 = 33.03$, $P < 0.001$).
Gómez-Gil, 2012 [45] Cross-sectional	Women and men	HT (120)[c] vs No HT (67)[c]	HADS (anxiety subscale) SADS	Mean: 11.0 years (women, range, 1-46 years); 4.7 years (men, range, 1-22 years)	Mean HADS and SADS scores were lower in the group receiving HT vs the group not receiving HT (6.4 ± 3.7 vs 9.0 ± 4.0, $P = 0.001$; 8.5 ± 7.8 vs 11.0 ± 7.3, $P = 0.038$, respectively).[d] The proportion with scores indicating anxiety (vs no anxiety) was higher in the group not receiving HT ($\chi^2 = 14.46$, $P < 0.001$).[d]
de Vries, 2011 [34] Prospective cohort	Girls and boys	GnRH treatment (41)	STAI (trait subscale)	1.88 years	Mean anxiety score did not change.
de Vries, 2014 [35] Prospective cohort[a,b]	Girls and boys	GnRH treatment + HT (32)[c]	STAI (trait subscale)	5.9 years	Mean anxiety score did not change.
López de Lara, 2020 [38] Prospective cohort[b]	Girls and boys	GnRH treatment + HT (23)	STAI (trait subscale)	1 year	Mean anxiety score decreased from 33.0 ± 7.2 to 18.5 ± 8.4 ($P < 0.001$).

Abbreviations: BAI, Beck Anxiety Inventory; DSM, Diagnostic and Statistical Manual of Mental Disorders; GAS, gender-affirming surgery; GnRH, gonadotropin-releasing hormone; HADS, Hospital Anxiety and Depression Scale; HT, hormone therapy; IQR, interquartile range; SADS, Social Avoidance and Distress Scale; SCL-90-R, Symptom Checklist 90-Revised; STAI, State-Trait Anxiety Inventory; Zung SAS, Zung Self-Rating Anxiety Scale.

[a]All participants were also included in de Vries (2011) [34]

[b]Included a cisgender control group or a comparison to general population norms

[c]Included participants who have undergone gender-affirming surgery/surgeries, or surgery status not reported

[d]Adjusted for age, gender, and education level

the general male Dutch population over this period to be 0.208. No data were reported for transgender men (n = 122). An update to this study reported 17 deaths by suicide among transgender women (n = 966) and 1 among transgender men (n = 365) between 1975 and 2007 [44]. The age- and sex-stratified standardized mortality ratios were 5.70 (95% CI: 4.93, 6.54) and 2.22 (95% CI: 0.53, 6.18), respectively. The risk of bias for this study was serious due to the difficulty of identifying appropriate comparison groups and uncontrolled confounding by surgery

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Table 5. Effects of Gender-Affirming Hormone Therapy on Death by Suicide Among Transgender People

Author, year	Transgender population	Treatment / comparison (n)	Measures	Length of treatment	Findings
Asscheman, 1989 [43] Retrospective cohort[a,b]	Women	HT (303)[c]	Death by suicide (confirmed by autopsy report)	Median: 4.4 years (range, 6 months to 13 years)	3 transgender women (1%) died by suicide between 1972 and 1986. The adjusted number of suicide deaths expected among the general Dutch male population was 0.208.
Asscheman, 2011 [44] Retrospective cohort[a,b]	Women	HT (966)[c]	Death by suicide (confirmed by medical report or physician information)	Median: 18.6 years (range, 0.7–44.5 years)	17 transgender women (2%) died by suicide between 1975 and 2007. The age-stratified SMR compared to the general Dutch male population was 5.70 (95% CI: 4.93, 6.54).
Asscheman, 1989 [43] Retrospective cohort[a,b]	Men	HT (122)[c]	Death by suicide (confirmation procedure NR)	Median: 3.6 years (range, 6 months to 13 years)	No deaths by suicide among transgender men were reported during the study period.
Asscheman, 2011 [44] Retrospective cohort[a,b]	Men	HT (365)[c]	Death by suicide (confirmed by medical report or physician information)	Median: 18.4 years (range, 4.7–42.6 years)	1 transgender man (0.3%) died by suicide between 1975 and 2007. The age-stratified SMR compared to the general Dutch female population was 2.22 (95% CI: 0.53, 6.18).

Abbreviations: HT, hormone therapy; NR, not reported; SMR, standardized mortality ratio.
[a]An unknown number of participants were included in both Asscheman (1989) [43] and Asscheman (2011) [44]
[b]Included a cisgender control group or a comparison to general population norms
[c]Includes participants who had undergone gender-affirming surgery/surgeries, or surgery status not reported

status and socioeconomic variables such as unemployment. We cannot draw any conclusions on the basis of this single study about whether hormone therapy affects death by suicide among transgender people.

Discussion

This systematic review of 20 studies found evidence that gender-affirming hormone therapy may be associated with improvements in QOL scores and decreases in depression and anxiety symptoms among transgender people. Associations were similar across gender identity and age. The strength of evidence for these conclusions is low due to methodological limitations (Table 6). It was impossible to draw conclusions about the effects of hormone therapy on death by suicide.

Uncontrolled confounding was a major limitation in this literature. Many studies simultaneously assessed different types of gender-affirming care and did not control for gender-affirming surgery status, making it difficult to isolate the effects of hormone therapy. Others failed to report complete information about surgery status. Additional factors that may influence both access to care and psychological outcomes, including extent of social or legal gender affirmation and exposure to determinants of health such as discrimination, were typically not considered. In addition, some evidence indicates that cyproterone acetate, a common anti-androgen assessed in many studies alongside estrogen therapy, may increase depression, which may be a source of confounding [49].

Another source of potential bias was recruitment of participants from specialized clinics that impose strict diagnostic criteria as a prerequisite for gender-affirming care. The dual role of clinicians and researchers as both gatekeepers and investigators may force transgender study participants to over- or understate aspects of their mental health in order to access gender-affirming care [8]. Similarly, transgender clinic patients may feel that they cannot opt out of research-related activities, which is a serious concern for the validity of psychological outcome measurements.

Clinic-based recruitment also overlooks transgender people who cannot access these clinics for financial or other reasons and misses those whose need for gender affirmation does not fit into current medical models. This is a particular concern for nonbinary and other gender-diverse people, for whom a model of gender affirmation as a linear transition from one binary gender to another is inaccurate [50].

Most studies used well-known scales for measuring psychological outcomes. None of these scales, however, have been specifically validated for use in transgender populations [51]. Furthermore, many scales are normed

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Table 6. Strength of Evidence of Studies that Evaluate the Psychological Effects of Hormone Therapy Among Transgender People

Outcome	Number of studies (n)	Strength of evidence	Summary[a]
Quality of life	1 randomized controlled trial [27] (45)[b] 2 before-after trials [28, 29] (65)[b] 2 prospective cohorts [30, 39] (133) 2 cross-sectional studies [46, 48] (108)	Low[e]	Hormone therapy may improve quality of life among transgender people.[g]
Depression	1 before-after trial [28] (40) 9 prospective cohorts [30-36, 38, 40, 42] (569)[c] 2 cross-sectional [45, 47] (228)	Low[e]	Hormone therapy may alleviate depression among transgender people.[g]
Anxiety	7 prospective cohorts [31, 33-35, 37, 38, 41, 42] (464)[c] 1 cross-sectional [45] (187)	Low[e]	Hormone therapy may alleviate anxiety among transgender people.[g]
Death by suicide	1 retrospective cohort [43, 44] (1756)[d]	Insufficient[f]	There is insufficient evidence to draw a conclusion about the effect of hormone therapy on death by suicide among transgender people.

[a]Due to similarity of findings, the summary is the same for transgender men and transgender women and for adolescents and adults
[b]25 participants are included in both Pelusi [27] and Gava (2018) [29] and are counted once
[c]All 55 participants in de Vries (2014) [35] were also included among the 70 participants in de Vries (2011) [34] and are counted once
[d]An unknown number of participants were included in both Asscheman (1989) [43] and Asscheman (2011), [44] so the unique sample size is smaller than indicated here
[e]Evidence downgraded due to study limitations, including uncontrolled confounding, and imprecision because of small sample sizes
[f]Evidence downgraded due to study limitations, including confounding and a lack of meaningful comparison groups, and imprecision in measurement of a rare event
[g]The body of cross-sectional evidence tended to align with the conclusion

separately for (presumed cisgender) men and women [52]. Inconsistency in identification of appropriate general population norms hinders comparisons between transgender and cisgender groups, which is a major related research question that requires further investigation.

Beyond methodological concerns in the studies we assessed, our review has other limitations. First, it is likely subject to publication bias, as we may have missed studies not published in the peer-reviewed literature. Second, a number of potentially relevant studies could not be included because the authors did not report on a minimum of 3 months of treatment or did not clearly state the type and/or duration of therapy, including the range for cross-sectional studies [53-65]. Finally, even where outcome measurements were similar across studies, heterogeneity in study designs, study populations, intervention characteristics, and reporting of results (ie, some studies reported results separately by gender identity, while others did not), prevented us from quantitatively pooling results.

More research is needed to further explore the relationship between gender-affirming hormone therapy and QOL, death by suicide, and other psychological outcomes, especially among adolescents. Future studies should investigate these outcomes in larger groups of diverse participants recruited outside clinical settings. Studies assessing the relationship between gender-affirming hormone therapy and mental health outcomes in transgender populations should be prospective or use strong quasi-experimental designs; consistently report type, dose, and duration of hormone therapy; adjust for possible confounding by gender-affirming surgery status; control for other variables that may independently influence psychological outcomes; and report results separately by gender identity. Despite the limitations of the available evidence, however, our review indicates that gender-affirming hormone therapy is likely associated with improvements in QOL, depression, and anxiety. No studies showed that hormone therapy harms mental health or quality of life among transgender people. These benefits make hormone therapy an essential component of care that promotes the health and well-being of transgender people.

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Additional Information

Correspondence: Kellan E. Baker, MPH, MA, Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, 624 North Broadway, Baltimore, MD 21205, USA. Email: kbaker39@jhu.edu.

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Kenneth J. Zucker PhD , Susan J. Bradley MD , Allison Owen-Anderson PhD , Devita Singh MA , Ray Blanchard PhD & Jerald Bain MD

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Puberty-Blocking Hormonal Therapy for Adolescents with Gender Identity Disorder: A Descriptive Clinical Study

KENNETH J. ZUCKER, PhD, SUSAN J. BRADLEY, MD, ALLISON OWEN-ANDERSON, PhD, and DEVITA SINGH, MA

Gender Identity Service, Child, Youth, and Family Program, Centre for Addiction and Mental Health, Toronto, Ontario, Canada

RAY BLANCHARD, PhD

Law and Mental Health Program, Centre for Addiction and Mental Health, Toronto, Ontario, Canada

JERALD BAIN, MD

Department of Endocrinology, Mt. Sinai Hospital, Toronto, Ontario, Canada

The use of puberty-delaying or blocking hormonal treatment of adolescents with gender identity disorder (GID) has become increasingly common. In the present study, we examined demographic, behavior problem, and psychosexual measures to see if any of them correlated with the clinical decision to recommend, or not recommend, puberty-blocking hormonal therapy in a consecutive series of 109 adolescents (55 females, 54 males) with GID evaluated between 2000 and 2009. Of the 109 adolescents, 66 (60.6%) were recommended for puberty-blocking hormonal therapy and 43 (39.4%) were not. A combination of five (of 15) demographic, behavior problem, and psychosexual measures were identified in a logistic regression analysis to significantly predict this clinical recommendation. The quantitative data were complemented by clinical case descriptions and some follow-up information. We discuss our data in relation to the Dutch model of early biomedical treatment for youth with GID and consider areas that require further clinical and empirical examination.

Address correspondence to Kenneth J. Zucker, PhD, Gender Identity Service, Child, Youth, and Family Program, Centre for Addiction and Mental Health, 250 College Street, Toronto, Ontario M5T 1R8, Canada. E-mail: Ken_Zucker@camh.net

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KEYWORDS gender identity disorder, adolescents, hormonal therapy

INTRODUCTION

For many years, it has been recognized that hormonal and sex-reassignment surgery (SRS) is the treatment of choice for many adults with gender identity disorder (GID). A number of literature reviews have documented that SRS reduces, if not eliminates, gender dysphoria in adults, which perhaps is the primary aim of such treatment (e.g., Gijs & Brewaeys, 2007; Green & Fleming, 1990; Pfäfflin & Junge, 1998). Only a small percentage of adults with GID who receive SRS regret it, suggesting that it is an effective biomedical treatment.

Over the past 15 years, there has been an increase in attention to the treatment of GID in adolescents (see, e.g., Cohen-Kettenis, van Goozen, & Cohen, 1998). In part, this has been the result of an apparent increase in the number of adolescents who seek out professional help for their gender dysphoria (Zucker, Bradley, Owen-Anderson, Kibblewhite, & Cantor, 2008). In contrast to natural history data on children with GID, which suggest that the majority will have a desistance of their gender dysphoria when followed up in adolescence or adulthood (Drummond, Bradley, Badali-Peterson, & Zucker, 2008; Green, 1987; Singh, Zucker, & Bradley, 2010c; Steensma, Biemond, de Boer, & Cohen-Kettenis, in press; Wallien & Cohen-Kettenis, 2008; Zucker, 2008; Zucker & Bradley, 1995), there is reasonable evidence that untreated gender dysphoria in adolescents is a relatively stable trait. Although some gender-dysphoric adolescents who present for clinical assessment do not necessarily desire hormonal treatment and/or SRS, the majority do.

Since the mid-1990s, one model of therapeutic care, developed by Dutch clinicians and researchers, has been to initiate the biomedical aspects of sex-reassignment in early- to mid-adolescence rather than to wait for the legal age of adulthood (18 years in many countries) or even later. After careful psychologic evaluation, adolescents deemed appropriate for such treatment are prescribed hormonal medication to delay or suppress somatic puberty (prior to the age of 16 years). If the gender dysphoria persists, then cross-sex hormonal therapy is offered at the age of 16 and, if the adolescent so desires, surgical sex change procedures are then offered at a lower bound age of 18 (see Cohen-Kettenis, Delemarre-van de Waal, & Gooren, 2008; Cohen-Kettenis & Pfäfflin, 2003; Cohen-Kettenis & van Goozen, 1998; Delemarre-van de Waal & Cohen-Kettenis, 2006; Gooren & Delemarre-van de Waal & Gooren, 1996).

The rationale for this treatment protocol includes the following: (1) there is the assumption that, for some adolescents with GID (and, perhaps, even

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the majority), there is little systematic empirical evidence that psychologic interventions can resolve the gender dysphoria, even if the adolescent desires this (Cohen-Kettenis et al., 2008; Zucker, 2006; Zucker & Bradley, 1995); (2) the use of hormonal blockers can be helpful to the adolescent because it reduces the incongruence between the development of natal sex secondary physical characteristics (e.g., in males: facial hair growth, hair growth on other parts of the body, deepening of the voice; in females: breast development, menstruation) and the felt psychologic gender, thereby reducing stress; (3) reduction of the incongruence makes it easier for adolescents to present socially in the cross-gender identity/role (when they so desire), which is also helpful in reducing stress during the gender transition process (see, e.g., Smith, van Goozen, Kuiper, & Cohen-Kettenis, 2005a). Because the suspension of the patient's biological puberty reduces the preoccupation with it, it has also been argued that this affords the adolescent greater opportunity to explore his or her longer-term gender identity options in psychosocial counseling or psychotherapy in a more reflective and less pressured manner.

The sequence of this biomedical treatment is progressively irreversible. On the one hand, the use of hormonal medication to suppress or delay puberty is a reversible procedure; on the other hand, surgical interventions (e.g., in males, penectomy and castration; in females, bilateral mastectomy) are irreversible. Accordingly, if clinicians are going to support adolescents with gender dysphoria to move down a pathway that, in the end, results in a completely irreversible intervention, it is, as with adults, important to have a relatively high degree of confidence that the likelihood of regret will be low.

In the Dutch model, several factors have been identified as important in deeming an adolescent eligible for early biomedical treatment. According to Cohen-Kettenis et al. (2008), these include the following: (1) the presence of gender dysphoria from early childhood on; (2) an increase in the gender dysphoria after the first signs of puberty; (3) the absence of psychiatric comorbidity that would interfere with a diagnostic evaluation or treatment; (4) adequate psychological and social support during treatment; and (5) a demonstration of knowledge of the sex reassignment process.

Several empirical studies by the Dutch group have evaluated the effectiveness of biomedical interventions for adolescents with GID. Cohen-Kettenis and van Goozen (1997) assessed 22 adolescents with GID at a baseline mean age of 17.5 years (range, 15–20). Of these, 12 had been prescribed some form of hormonal therapy between the ages of 16 and 18 (e.g., hormonal blockers and/or cross-sex hormones). All 22 patients subsequently received at least some form of SRS and were followed up at a mean age of 22 (range, 19–27); the follow-up occurred at least one year after the SRS procedure (M interval, 2.6 years; range, 1–5 years). At the time of the baseline evaluation, eight other adolescents were not diagnosed with "transsexualism" and, therefore, were not recommended to start the "real-life"

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test of living in the cross-gender role. Three other adolescents were diagnosed with "transsexualism," but their real-life test was postponed because of "severe concurring psychopathology and/or adverse social circumstances." Thus, in this sample, 22 (66.6%) of 33 adolescents received SRS at a relatively young age. A series of psychological tests were administered to the patients at baseline and at follow-up, including measures of gender dysphoria and psychopathology.

The pre-post design used by Cohen-Kettenis and van Goozen (1997) was applied to 19 of 22 patients who agreed to participate in the follow-up assessment. None of the patients regretted the SRS and, on the Utrecht Gender Dysphoria Scale (UGDS), a dimensional measure, showed a substantial decrease in their mean score between baseline and follow-up (the latter score was comparable to that of a nonpatient control group). On two measures of psychopathology and personality functioning (the Dutch version of the MMPI and the Dutch Personality Questionnaire), there were significant improvements between baseline and follow-up on 4 of 12 scales (e.g., increased Extroversion, decreased Inadequacy). There was no instance of a significant increase in psychopathology or personality dysfunction on any of the scales between baseline and follow-up; however, at the time of follow-up, 21% of the patients were unemployed and were not in school.

In a second study, Smith, van Goozen, and Cohen-Kettenis (2001) examined another cohort of 20 adolescents with GID who received early SRS and were compared to 14 nontreated and 6 delayed-treatment adolescents. Systematic follow-up data were not available on an additional 7 nontreated patients. Of the 21 nontreated patients, it was reported that they were not diagnosed with "transsexualism," and it was noted that many of these patients had "psychological or environmental problems" that were "too serious to make an accurate diagnosis." Thus, in this sample, 20 (42.5%) of 47 adolescents received SRS at a relatively young age. At baseline, the mean age of the treated group was 16.6 (range, 15–19) and, at follow-up, the mean age was 21.0 (range, 19–23). Of these, 10 patients had started on some form of hormone therapy between 16 and 18 years, and the follow-up occurred at least one year after the SRS procedure (M interval, 1.3 years; range, 1–4 years). At baseline, the mean age of the nontreated group was 17.3 years (range, 13.7–20.2) and at follow-up the mean age was 21.6 (range, 15.7–26.2). A series of psychological tests were administered to the patients at baseline and at follow-up, including measures of gender dysphoria and psychopathology.

None of the 20 treated patients regretted the SRS and on the UGDS showed a substantial decrease in their mean score between baseline and follow-up. Of the 14 nontreated patients, only one reported to have seriously regretted not having received SRS. The nontreated group also showed a significant decrease in their mean UGDS; however, the nontreated group had, on average, a significantly higher mean UGDS score than the treated group ($p < .0001$, our analysis based on data reported in Smith et al., 2001, Table 2).

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On two measures of psychopathology (the Dutch versions of the MMPI and the Symptom Checklist-90), there were both similarities and differences between the treated and nontreated groups. On the MMPI, there were no significant changes in either group between baseline and follow-up on 5 scales; however, the nontreated group had significantly higher scores than the treated group on the Psychopathology scale at both baseline and at follow-up. On the SCL-90, the treated group showed significant improvement on 3 of 9 scales (Anxiety, Depression, and Hostility) whereas there were no significant changes in the nontreated group. On several of the SCL-90 scales, the treated group had significantly less symptomatology than the nontreated group.

In a third study, de Vries, Steensma, Doreleijers, and Cohen-Kettenis (2010b) examined a cohort of 70 adolescents with GID evaluated at a baseline mean age of 13.6 (SD = 1.8 years), who were subsequently started on a hormonal blocker at a mean age of 14.8 (SD = 1.1) and then followed-up at mean age of 16.6 (SD = 1.2), prior to the onset of cross-sex hormonal treatment. Of these 70 patients, 41–54 had data on measures of behavioral problems via the Child Behavior Checklist and the Youth Self-Report form, on specific measures of depression, anger, and anxiety, and a clinician rating on the Children's Global Assessment Scale, a measure of functional impairment. Between baseline and follow-up, there were significant reductions in psychopathology on 8 of 10 scales. Unlike the previous two studies, de Vries et al. did not report on the number of referred adolescents seen during the time frame of the study (2000–2008) who were not recommended for puberty-blocking hormonal treatment.

Several key conclusions can be drawn from these three studies of adolescents with GID:

1. For the adolescents recommended for early SRS, there was virtually no evidence of regret, suggesting that the intervention was effective. For adolescents recommended for puberty-blocking hormonal therapy, there was also evidence of improvement in general psychologic problems at follow-up and certainly no evidence of deterioration in psychological well-being.
2. For the adolescents not recommended for early SRS, the majority of patients were apparently content with this clinical decision (Smith et al., 2001), but such information was not reported on in the earlier study by Cohen-Kettenis and van Goozen (1997).
3. In the study by de Vries et al. (2010b), it should be noted that the absence of a comparison group of GID adolescents who were not placed on hormonal blockers makes it difficult to fully evaluate the specificity of this treatment in reducing general behavioral and emotional problems (it is conceivable, for example, that a trial of supportive therapy without any type of biomedical intervention might have been equally effective).

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The use of hormonal blockers to treat adolescents with GID has been well-received in the professional literature (e.g., Baltieri, Cortez, & de Andrade, 2009; Giordano, 2008; Hembree et al., 2009; Spriggs, 2004). There are, however, a number of uncertainties that require further explanation. Perhaps the most acute issue is how to best identify adolescents deemed eligible for early biomedical treatment from those who are not. As noted earlier, one criterion used by the Dutch group is a history of gender dysphoria from early childhood on. Yet in clinics such as ours, we see some adolescents with GID who show little or absolutely no evidence of GID in early childhood. In many respects, these adolescents resemble the "late-onset" form of GID that has been described in the literature on adults (see Lawrence, 2010). The gender dysphoria appears to emerge, at least in the eyes of significant others (e.g., parents, therapists who have known the patient since childhood), only after the onset of puberty. It is not clear if this late-onset group should be deemed ineligible for early hormonal therapy. Other adolescents have a history of pervasive cross-gender behavior during childhood but without apparent gender dysphoria until adolescence (see, e.g., Zucker, 2006, Case 1, pp. 539–540). It is unclear if a childhood history of pervasive cross-gender behavior without the explicit wish to be of the other gender would count as an example of "early-onset" in the Dutch model.

Another issue concerns the diagnosis of GID itself. In the first two studies by the Dutch group, the diagnostic term "transsexualism" was used, but it is unclear if this was used synonymously with the *Diagnostic and Statistical Manual* (DSM-IV) diagnosis of GID or if something else was meant. In our clinic, virtually all of the adolescents that we see who present with gender dysphoria meet the DSM criteria for GID, but there is still variation in severity. It is not entirely clear if such variation should be taken into account when making a recommendation for hormonal treatment. In Smith et al. (2001, Table 1), virtually all patients in the nontreated group were noted to *not* have the diagnosis of "transsexualism," but it is unclear if this meant that the patients did not meet the DSM-IV criteria for GID or something else. If these adolescents did not have a GID, it is reasonable to ask why they had been referred to a specialized gender clinic. It is, of course, possible that the nontreated group had some traits suggestive of a GID but were below the threshold for the diagnosis, but this was not made clear in the Smith et al. report.

A final issue that deserves consideration concerns the Dutch group's view on the role of psychiatric comorbidity in making treatment decisions about early biomedical interventions. It is, for example, unclear what is meant when it is stated that the presence of such comorbidity interferes with a diagnostic evaluation or in what ways the presence of such comorbidity interferes with treatment. In Smith et al. (2001, Table 1), brief descriptive information was provided about psychiatric comorbidity. For example, Case 8 was diagnosed with schizophrenia, which might well be a reason to delay treatment of the gender dysphoria (the patient subsequently committed

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suicide). Case 14 was noted to have a pathological gambling problem and had dropped out of school. Perhaps this is an example of behavior problems that would interfere with treatment compliance. Three patients were noted to have a Pervasive Developmental Disorder (PDD), but it was not made clear why the presence of a PDD should be a rule out for early hormonal treatment (see, e.g., de Vries, Noens, Cohen-Kettenis, van Berckelaer-Onnes, & Doreleijers, 2010a). For a number of other cases, no specific psychiatric comorbidity was noted, and Smith et al. did not provide any specific information about the kinds of psychiatric comorbidity in their early-treated group. Inspection of the psychopathology data in Smith et al. (2001, Table 2) shows a lot of overlap between the treated and nontreated groups, suggesting that psychiatric comorbidity is a difficult parameter per se to use in deciding whether or not to institute early treatment. On this point, more detailed clinical examples would be useful.

The purpose of the present study was to provide descriptive information on our clinic's therapeutic recommendation to institute puberty-blocking hormonal treatment in a cohort of adolescents with GID. Adolescents who were recommended for this treatment were compared to adolescents who did not receive this recommendation with regard to demographic, behavior problem, and psychosexual measures to see if the clinical decision was reliably associated with any of these quantitative parameters. We also conducted a logistic regression analysis to identify how these parameters worked in concert in predicting the clinical recommendation regarding hormonal treatment. Last, this article provides some clinical vignettes to characterize, in a qualitative manner, the decision whether or not to recommend hormonal therapy as well as to provide some preliminary information on the course of our patients' gender development.

METHOD

Participants

The patients were 109 adolescents (54 males, 55 females) referred consecutively to, and then assessed in, the Gender Identity Service, which is housed within the Child, Youth, and Family Program at the Centre for Addiction and Mental Health, between 2000 and 2009. Referrals were initiated either by the youth or by parents or professionals (e.g., mental health clinicians, pediatricians, teachers). During this same time period, our clinic also evaluated another 56 adolescent patients who were referred for other reasons: adolescents with transvestic fetishism without co-occurring gender dysphoria (N = 35), adolescents with cross-gender behavior but without an explicit desire to be of the other sex and who had not yet differentiated a sexual orientation (N = 6), and adolescents with a gay/lesbian or bisexual sexual orientation (N = 15), which was experienced as ego-dystonic, was of concern to the

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parents, and/or was associated with psychosocial problems, such as risky sexual behavior. These latter three groups of patients were not the focus of the present study.

Procedure and Measures

Youth and their families (or a guardian, such as a child protection agency worker) were seen for a diagnostic assessment that typically involved a family interview, interviews with parents, and an interview with the youth. Parents were not involved in the assessment if either the youth did not wish to have them participate or the youth was in-care (e.g., in residential treatment) or living independently and the parents were not available to be seen. As part of the assessment, the youth were seen for psychological testing, which consisted of a battery of tests and tasks, including cognitive testing, projective testing, and gender-specific measures.

Demographics

Eight demographic variables were coded for the present study: (1) the patient's biological sex,[1] (2) age at assessment, (3) year of assessment (YOA), (4) Full-Scale IQ on an age-appropriate Wechsler Intelligence Scale, (5) parents' social class (Hollingshead, 1975), (6) parents' marital status, (7) race/ethnicity, and (8) whether or not the youth was in-care (e.g., via a child protection society and living in a group home, residential treatment, a foster family).

Behavior Problems

The Child Behavior Checklist (CBCL) is a parent-report questionnaire designed to assess behavior problems in children and youth (Achenbach & Edelbrock, 1983). Each of 118 items was rated on a 3-point scale (0–2) for frequency of occurrence, where 0 = not true, 1 = somewhat or sometimes true, and 2 = very true or often true. Revised versions of the CBCL have moved the upper-bound for age to 18 years from 16 years (Achenbach, 1991a). For adolescents over the age of 18, the Adult Behavior Checklist for Ages 18–59 (Achenbach & Rescorla, 2003) was used. We utilized maternal ratings for the majority of patients but, if the mother was not available, we utilized ratings by a stepmother, adoptive mother, aunt, grandmother or a mental health professional if the youth was in-care. The CBCL has two specific items pertaining to cross-gender behavior: "Behaves like opposite sex" (Item 5) and "Wishes to be of opposite sex" (Item 110). In addition to these items, it is not unusual for parents to endorse other items on the CBCL that reflect a youth's cross-gender identification. For example, a parent might endorse "Strange ideas" (Item 85) and then provide an example such as "He

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wants to die and come back as a girl." For the analyses reported here, these items were scored as 0's to avoid any artificial inflation of general behavior problems. For the present study, we coded for the sum of items rated as a 1 or a 2 and the percentage of patients with a Total *T* score in the clinical range (>90th percentile).

The Youth Self-Report (YSR) is a self-report questionnaire designed for youth between the ages of 11 and 18 (Achenbach, 1991b; Achenbach & Edelbrock, 1986). For adolescents over the age of 18, the Adult Self-Report for Ages 18–59 (Achenbach & Rescorla, 2003) was used. On the YSR, a total of 118 items were rated on a 3-point scale (0–2) for frequency of occurrence; of these, 102 items constitute potential behavior problems (16 other items are considered to be "socially desirable" items). The YSR also contains the same two gender-specific items (Item 5: "I act like the opposite sex" and Item 110: "I wish I were of the opposite sex") and these, along with any other responses specifically pertaining to gender identity issues, were scored as 0s to avoid any artificial inflation of general behavior problems. For the present study, we coded for the sum of items rated as a 1 or a 2 and the percentage of patients with a Total *T* score in the clinical range (>90th percentile).

Psychosexual Variables

For the present study, we examined six psychosexual measures that are part of our assessment protocol.

The Gender Identity Questionnaire for Adolescents (GIQ-Ad) is a 13-item parent-report questionnaire pertaining to various aspects of concurrent sex-typed behavior (e.g., sex-of-peer affiliation preference, masculine vs. feminine interests, cross-dressing, the desire to be of the other sex). Eleven of the items were rated on a 5-point scale (e.g., from "never" to "every day"), one item was rated on a 4-point scale, and one item was calculated as a difference score based on the number of male versus female close friends. Factor analysis of the GIQ-Ad was based on a sample of 371 youth, including youth with GID, transvestic fetishism, and sibling or clinical controls. A principal axis factor analysis identified a one-factor solution, accounting for 37.46% of the variance. A total of 10 items from the questionnaire, all with factor loadings ≥.38 (range, .38–.82), were used to construct a unit-weighted mean total score, with a lower score reflecting more cross-gender behavior. Cronbach's alpha for this measure was .88. More detailed psychometric information on the GIQ-Ad is reported elsewhere (Zucker, Bradley, Owen-Anderson, & Singh, 2010).

With the Draw-a-Person test, after each youth had drawn a house and a tree, he or she was asked to "draw a person" and to identify its sex. The youth was then asked to draw a person of the sex opposite to that of the first drawing. The sex of the first-drawn person was recorded. If the youth gave an ambivalent or vague response (e.g., "It could be either" or "I don't know"),

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he or she was asked to think a bit and then to decide if the drawing was that of a boy/man or girl/woman. In nonclinical populations of adolescents, it has been shown that the sex of the first drawn person is reliably associated with the drawer's sex (Bieliauskas, 1960; Butler & Marcuse, 1959; Swensen & Newton, 1955).

The Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults (GIDYQ) is a 27-item questionnaire pertaining to concurrent gender identity and gender dysphoria (Deogracias et al., 2007). Item content was based on prior measures, expert panels, and clinical experience. There are parallel versions for males and females. Each item was rated on a 5-point response scale ranging from *Never* to *Always* based on a time frame of the past 12 months. Item examples include: "In the past 12 months, have you felt unhappy about being a boy?" and "In the past 12 months, have you wished to have an operation to change your body into a man's (e.g., to have your breasts removed or to have a penis made)?" Factor analysis identified a strong one-factor solution that accounted for 61.3% of the variance. All 27 items had factor loadings ≥.30 (median, .86; range, .34–.96). Psychometric evidence for discriminant validity, sensitivity and specificity, and clinical utility have been reported elsewhere (Deogracias et al., 2007; Singh et al., 2010a; Singh, McMain, & Zucker, 2010b). Participants' GIDYQ total score was calculated by summing scores on the completed items and dividing by the number of marked responses.

The Recalled Childhood Gender Identity/Gender Role Questionnaire (RCGI) (Zucker et al., 2006) is a 23-item questionnaire pertaining to various aspects of sex-typed behavior as well as relative closeness to mother and father during childhood. Items were rated on a 5-point response scale. Each participant was instructed to make ratings for their behavior as a child ("between the years 0 and 12"). Factor analysis identified two factors, accounting for 37.4% and 7.8% of the variance, respectively (all factor loadings ≥.40). Factor 1 consisted of 18 items that pertained to childhood gender role and gender identity, and Factor 2 consisted of three items that pertained to parent-child relations (relative closeness to one's mother vs. father). Information on normative sex differences and discriminant validity has been reported elsewhere (Drummond et al., 2008; Singh et al., 2010a; Zucker et al., 1996, 2006). For the present study, the mean Factor 1 score was computed for each participant.

The Erotic Response and Orientation Scale (EROS) is a 16-item self-report measure assessing sexual orientation in fantasy over the past six months (Storms, 1980). Half of the questions pertained to heterosexual fantasy (e.g., for females, "How often have you had any sexual feelings (even the slightest) while looking at a boy?") and the other half pertained to homosexual fantasy (e.g., for females, "How often have you had any sexual feelings (even the slightest) while looking at a girl?"). Each item was rated on a 5-point scale for frequency of occurrence, ranging from "none" to "almost

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every day." Mean homoerotic and heteroerotic fantasy scores were derived for each participant. Previous use of the EROS has shown good evidence of discriminant validity (Drummond et al., 2008; Storms, 1980; Zucker et al., 1996). Youth were classified as homosexual in relation to their birth sex if their mean homoerotic score exceeded their mean heteroerotic score; youth were classified as nonhomosexual (i.e., heterosexual, bisexual, or asexual) in relation to their birth sex if their mean homoerotic score was equal to or less than their mean heteroerotic score.

The Sexual History Questionnaire (SHQ) is a 20-item self-report measure assessing sexual orientation in behavior. Items were selected from Langevin's (1985) longer 36-item SHQ for males and a parallel version was created for females (see Drummond et al., 2008). Half the items were about sexual experience with boys and half the items were about sexual experience with girls. For each item, the participant was asked to report his or her sexual behavior experience since the age of 13. Sample items include: "How many girls have you touched on the naked breasts since the age of 13?" and "Since the age of 13, how many boys have you touched on their private parts with your hands?" Each item was rated on a 5-point response scale (where 1 = "none or never," 2 = "only one," 3 = "2–5", 4 = "6–10", and 5 = "11 or more"). In the present study, Cronbach's alpha was .93. As for the EROS, youth were classified as homosexual in relation to their birth sex if their mean homoerotic score exceeded their mean heteroerotic score; youth were classified as nonhomosexual in relation to their birth sex if their mean homoerotic score was equal to or less than their mean heteroerotic score (i.e., heterosexual, bisexual, or asexual).

Hormonal Blocker Treatment Recommendation

At the end of the clinical assessment, the attending clinician (KJZ, SJB, or AO-A) provided the youth and his or her family with feedback, including diagnostic impressions and therapeutic recommendations. For the present study, we reviewed each clinical file and coded whether or not the attending clinician recommended a trial of hormonal therapy to suppress somatic masculinization (in the case of biological males) or somatic feminization (in the case of biological females). For the present study, a recommendation against hormonal blockers was dummy coded as 0 and a recommendation for hormonal blockers was coded as 1.

RESULTS

After the baseline assessment, hormonal therapy to suppress the patient's biological puberty was recommended for 66 (60.6%) youth and not recommended for 43 (39.4%) youth. In the following series of analyses, we

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TABLE 1 Demographic Characteristics as a Function of Hormonal Blocker Recommendation

Variable		Hormonal Blocker Recommendation			
		Yes	No	t or χ^2	p
Age (in yrs)	M	17.01	16.59	1.23	ns
	SD	1.74	1.74		
	N	66	43		
Sex				7.95	.005
Male	N (%)	25 (46.3)	29 (53.7)		
Female	N (%)	41 (74.5)	14 (25.5)		
Year of Assessment	M	2005.83	2005.63	<1	ns
	SD	2.70	2.45		
	N	66	43		
Full-Scale IQ[a]	M	104.25	101.60	<1	ns
	SD	17.91	18.60		
	N	65	42		
Social Class[b]				4.04	.132
I-II	N (%)	38 (69.1)	17 (30.9)		
III	N (%)	17 (56.7)	13 (43.3)		
IV-V	N (%)	11 (45.8)	13 (54.2)		
Parent's Marital Status[c]				<1	ns
Both Parents	N (%)	33 (64.7)	18 (35.3)		
Other	N (%)	33 (56.9)	25 (43.1)		
Ethnicity				2.45	.117
Caucasian	N (%)	47 (56.0)	37 (44.0)		
Other	N (%)	19 (76.0)	6 (24.0)		
In Care				3.11	.077
Yes	N (%)	6 (37.5)	10 (62.5)		
No	N (%)	60 (64.5)	33 (35.5)		

Note. Row values add up to 100% of the sample.

[a]Participants were administered age-appropriate versions of the Wechsler Intelligence scales.

[b]Hollingshead's (1975) Four-Factor Index of Social Status (absolute range, 8–66); I-II (40–66), III (30–39); IV-V (8–29). Higher scores represent a combination of greater educational attainment and higher occupational status.

[c]For marital status, the category "Other" included the following family constellations: single parent, separated, divorced, widowed, reconstituted (e.g., mother and step-father), etc.

examined whether or not there were any significant differences on the demographic variables, the behavior problem measures, and the psychosexual measures as a function of this recommendation. Tables 1 and 2 show the quantitative results as a function of the hormonal treatment recommendation, along with the statistical test value and p value.

Demographic Variables

For the eight demographic variables, there was only one significant difference as a function of the hormonal treatment recommendation: biological females were significantly more likely to receive a recommendation for hormonal suppression than biological males. As can be seen in Table 1, there was also a borderline statistical effect for the in-care variable: youth who were in-care

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TABLE 2 Behavior Problem and Psychosexual Measures as a Function of Hormonal Blocker Recommendation

Variable		Hormonal Blocker Recommendation			
		Yes	No	t or χ^2	p
CBCL: Sum Items[a]	M	61.02	63.59	<1	ns
	SD	27.17	32.55		
	N	62	39		
% Clinical Range		83.9	69.2		
YSR: Sum Items[b]	M	60.95	75.17	2.78	.006
	SD	24	28		
	N	65	42		
% Clinical Range		40.0	42.9		
Draw-a-Person					
Cross-Sex Drawn First	N (%)	47 (69.1)	21 (30.8)	3.43	.064
Same-Sex Drawn First	N (%)	18 (48.6)	19 (51.3)		
GIQ-Ad[c]	M	2.17	2.94	5.06	<.001
	SD	0.74	0.70		
	N	60	37		
GIDYQ[d]	M	2.21	2.61	4.74	<.001
	SD	0.35	0.47		
	N	60	39		
RCGI[e]	M	2.05	2.84	5.48	<.001
	SD	0.67	0.79		
	N	65	42		
Sexual Orientation (in fantasy)				7.51	.006
Homosexual	N (%)	45 (72.6)	17 (27.4)		
Non-Homosexual	N (%)	20 (44.4)	25 (55.6)		
Sexual Orientation (in behavior)				12.96	<.001
Homosexual	N (%)	43 (78.2)	12 (21.8)		
Non-Homosexual	N (%)	22 (42.3)	30 (57.7)		

[a]Absolute range, 0–236
[b]Absolute range, 0–204
[c]Absolute range, 1–5
[d] For this measure, the absolute range for 9 of the items was 1–5, but there was no formal absolute range for the difference score between number of male vs. female friends.
[e]Absolute range, 1–5

were less likely to receive a recommendation for hormonal suppression than were youth not in-care. Nonwhite youth were also more likely to receive a recommendation for hormonal therapy than Caucasian youth, as were youth from a higher social class background, but these differences only approached significance, with p values of .11 and .13, respectively. Age at assessment, year of assessment, Full-Scale IQ, and parent's marital status did not differ significantly as a function of hormonal treatment recommendation.

Behavior Problems

There was no significant difference on the CBCL mean sum score as a function of hormonal treatment recommendation, but youth not recommended

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for hormonal therapy had a significantly higher YSR mean score than youth who were recommended.

Psychosexual Variables

All of the psychosexual variables examined in the current study showed significant differences as a function of our recommendation for hormonal therapy. Youth who were recommended for hormonal therapy were more likely to draw an opposite sex person first on the DAP, had, on average, a more extreme mean score on the parent-report GIQ-Ad measure of concurrent cross-sex-typed behavior, self-reported more gender dysphoria on the GIDYQ, recalled more cross-gender behavior during childhood on the RCGI, and were more likely to be classified as homosexual (on both the EROS and the SHQ) than as non-homosexual.

Logistic Regression

In order to examine which of our demographic, behavior problem, and psychosexual variables might collectively contribute to the hormonal blocker recommendation, all 16 measures were examined in a logistic regression analysis with the hormonal blocker recommendation as the criterion variable. Because there were missing data for some of the variables (see Tables 1–2), we used the multiple imputation procedure in SPSS (Version 17) to produce the regression equation (see Graham, 2009).[2]

The results of the logistic regression analysis are shown in Table 3. Of the 16 predictor variables, 5 were significant at $p < .10$, with p values ranging from .016 to .096: ethnicity, the GIDYQ, the GIQ-Ad, the RCGI, and the YSR sum score. A recommendation for hormonal blockers was more likely to be made when the patients were of a visible minority ethnicity, when parent-report indicated more concurrent cross-gender behavior, when the patients self-reported more concurrent gender dysphoria, recalled more cross-gender behavior in childhood, and had a lower YSR behavior problem sum score.[3]

Descriptive and Qualitative Clinical Data

In this section, we provide descriptive information on what we know about the subsequent life-course of our patients following the baseline assessment, when this information was available to us. Of course, this information should be viewed as provisional, since some patients were only recently assessed; the longest interval between assessment and follow-up was 10 years, since the lower bound YOA was 2000. We also provide clinical vignettes to illustrate our reasoning behind the decision to recommend or not recommend hormonal therapy to suppress the patient's biological puberty.

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TABLE 3 Logistic Regression Predicting Hormonal Recommendation

Variable	β	SE	p
GIQ-Ad	1.63	0.67	.016
GIQAA	2.79	1.23	.025
RCGI	1.17	0.58	.045
Ethnicity	1.91	0.95	.047
YSR Sum	−0.02	0.01	.096
Sex	0.01	0.79	.990
Age at assessment	0.22	0.22	.319
YOA	−0.08	0.13	.532
Full-Scale IQ	0.03	0.03	.295
Parent's Marital Status	−0.53	0.76	.478
Social Class	−0.76	0.49	.127
In-Care	0.13	1.19	.910
CBCL Sum	−0.01	0.01	.419
Draw-a-Person	−1.20	0.91	.193
EROS	−0.18	0.82	.820

Note. Dichotomous variables were dummy coded. For Ethnicity, 1 = White; 2 = Visible Minority; for Sex, 1 = female; 2 = male; for Parent's Marital Status, 1 = Two-parent; 2 = Other; for Social Class, 1 = I-II, 2 = III, 3 = IV-V (see Table 1); for In-Care, 1 = Not In-Care; 2 = In-Care; for Draw-a-Person, 1 = same-sex person drawn first; 2 = opposite-sex person drawn first; for EROS, 1 = non-homosexual sexual orientation (in relation to birth sex), 2 = homosexual orientation (in relation to birth sex).

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Patients Who Were Recommended for Hormonal Therapy at Baseline

Of the 38 female patients for whom we recommended hormonal therapy to suppress somatic feminization (excluding the additional three patients who were already receiving cross-sex hormonal therapy at the time of the baseline evaluation), 24 (63.1%) started the treatment, 6 (15.7%) decided against it, and we did not have follow-up information for the remaining 8 (21.0%). Of the 23 male patients for whom we recommended hormonal therapy to suppress somatic masculinization (excluding two additional patients who were either already on blockers or were receiving cross-sex hormonal therapy at the time of the baseline evaluation), 16 (69.5%) started the treatment, 2 (8.6%) decided against it, 2 (8.6%) did not attend for a feedback session and thus did not receive our recommendation, and we did not have follow-up information for the remaining 3 (13.0%).

Patients Who Were Not Recommended for Hormonal Therapy at Baseline

Of the 14 female patients for whom we did not recommend hormonal therapy at the baseline assessment, there was no subsequent change in this recommendation for 12 (for 2 other patients, we had no follow-up data available). Of the 29 male patients for whom we did not recommend hormonal therapy at the baseline assessment, we subsequently recommended blockers for 5 patients (a sixth patient went on blockers at the

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recommendation of his therapist), made no change in this recommendation for 17, one patient committed suicide after our assessment was completed (while on a waiting list for counseling at a mental health clinic near his place of residence and who had made at least one serious suicide attempt prior to our assessment), and for 5 other patients, we had no follow-up data.

Case Vignettes: Blockers Not Recommended

Rhianna was a 16-year-old Caucasian biological female with a Full-Scale IQ of 88. She lived with her parents and a younger brother. Parent's social class was middle-class. Unlike many female adolescents with GID, Rhianna did not present with a phenotypic masculine appearance (e.g., short hair, male-typical clothing style). Rather, Rhianna had more of a "goth" look and would be perceived by naive others as an adolescent girl. In terms of her developmental history, there was no evidence for cross-gender identification or GID in childhood. At the time of assessment, Rhianna was in a romantic/sexual relationship with a gay adolescent male and the main reason that she gave for wanting a sex-change was that she feared that if she did not become male that she might lose her boyfriend. Rhianna self-identified as bisexual. Apart from Rhianna's gender dysphoria, her psychiatric history was complex. At the time of referral, she was depressed and suicidal. Her grades had dropped precipitously since entering high school. In general, Rhianna felt quite alienated from other youth her age. Rhianna reported experimenting with a lot of recreational drugs (e.g., marijuana, Ecstasy, LSD, and Oxy-Contin). Rhianna reported some auditory hallucinations. Rhianna read a lot about "abnormal psychology" and wondered if she had schizophrenia. She reported an intense dislike of her parents and only grudgingly consented to their participation in our assessment. At the time of referral, she had been prescribed Prozac by the family physician. For a long time, the parents noted that Rhianna had the propensity to "take on other people's personalities." As a child, she would take on the characters of bad witches or characters from Disney movies and then would remain in this "role" for a long time. A year prior to the assessment, Rhianna became "obsessed" with a character from a current film and, according to the parents, had now taken on this character's personality. We did not recommend hormonal blockers for Rhianna. We felt that there were several reasons to be cautious about this: (1) her primary reason for wanting a sex change struck as dubious (i.e., to reduce the likelihood that her gay boyfriend would reject her); (2) the absence of a history of cross-gender identification and GID in childhood caused us to wonder if her current gender dysphoria was a kind of fantasy solution to other problems and/or that it was not a fixed identity status, immutable to psychosocial interventions; and (3) her very vulnerable psychiatric state, including a query of a psychotic process *in statu nascendi*. Rhianna entered supportive

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psychotherapy and was treated pharmacologically with risperidone. At age 20, the time of last follow-up, the gender dysphoria had desisted, Rhianna was in a heterosexual relationship, and was attending college to complete the requirements for a specific occupation. The psychiatrist who has followed Rhianna has suggested a working diagnosis of bipolar disorder, which has been successfully controlled with medication.

Melvin was a 15-year-old Caucasian biological male with a Full-Scale IQ of 87. He had lived with his mother and an older brother. Socioeconomic background of the family was lower class. Due to physical abuse, his mother left his father shortly after Melvin was conceived, and there has never been any contact with the father. His mother has had chronic and severe mental health problems. Due to the severe family dysfunction, Melvin has been in the care of a child protection agency since the age of 5. He has had a long and complex psychiatric history, with multiple admissions to inpatient units. Various psychiatric diagnoses had been considered: Conduct Disorder, Attention-Deficit Hyperactivity Disorder, Asperger's Disorder, Reactive Attachment Disorder, and a learning disability. Over the years, he had been prescribed various psychotropic medications. At the time of assessment, Melvin presented in the female gender role, wearing casual feminine clothing and with shoulder-length hair. It was our impression that Melvin would be perceived by naive others to be an adolescent female, but his given name would "mark" him as a boy. There was no childhood history of cross-gender identification or GID. Indeed, the extensive psychiatric reports available to us from Melvin's childhood made no reference at all to gender identity issues. Melvin reported an adolescent onset of his gender dysphoria, with co-occurring transvestic fetishism and autogynephilia. Sexual orientation was gynephilic. Melvin was taken into care for various reasons, including the concern that his mother would kill him if she discovered that he was cross-dressing. At the time of our assessment, Melvin's living situation was precarious as his volatile behavior made it very difficult for him to be managed in either group homes or in foster families. He barely attended school and was failing all of his subjects. We did not recommend hormonal blockers for Melvin. Although Melvin reported intense gender dysphoria, we were concerned that his living situation was unstable and that his volatile behavior would make it difficult to explore in supportive therapy the gender identity issues. Indeed, after our assessment, Melvin was arrested for assaulting his foster parents, with whom he had been placed, and was court-ordered to a juvenile detention facility (that provided psychiatric care) for a year. At the age of 17, Melvin had been placed in a foster family that was supportive of his desire to live in the female gender role. Although his general psychiatric well-being was still unstable, we recommended hormonal blockers at this point in time, along with the recommendation for continued supportive therapy to help manage Melvin's volatility and to help him cope in special education in high school.

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Case Vignettes: Blockers Recommended

Beth was a 13-year-old Caucasian biological female with a Full-Scale IQ of 101. She lived with her mother and two younger siblings. Socioeconomic background of the family was middle class. Her parents, who had been in a common-law relationship, separated when Beth was 6, following a long period of marital discord, including physical abuse of the mother by the father. At the time of assessment, Beth presented as an overweight youth, whose phenotypic social appearance was stereotypically masculine (in terms of hair-style and clothing style). Because Beth has a female-typical name, she was known to her schoolmates as a girl, but naive others would have perceived her to be a young adolescent boy. Beth had a childhood history of marked cross-gender behavior, which her mother understood to be "tomboyism" that she presumed Beth would "grow out of." During childhood, the mother did not recall that Beth ever verbalized the desire to be a boy. By middle school, Beth had become increasingly oppositional and depressed. The mother-daughter relationship was extremely volatile and conflicted. Because of Beth's mental state, including suicidal feelings, she was admitted to a psychiatric unit for youth. In the course of this treatment, an astute clinician gently explored with Beth her feelings about being a girl and she was able to acknowledge intense feelings of gender dysphoria. This lifted Beth's depression and a referral was made to our clinic for further evaluation. After our assessment, we recommended hormonal therapy to suppress somatic feminization and a trial of supportive psychotherapy to explore further Beth's gender identity, help her to deal with her anxiety and depression (which was also being treated with a selective serotonin reuptake inhibitor), work with the mother in helping Beth negotiate a social gender change within the family and at school, and to explore with Beth her sexual orientation (which was "asexual" at the time of the baseline assessment). We were of the view that the supportive psychotherapy could, among other things, explore with Beth whether she could imagine the idea of a lesbian sexual identity as opposed to moving towards gender reassignment.[4] This was not "our" goal, but we viewed it as an important parameter to examine since Beth's sexual orientation was undifferentiated at the baseline assessment. At age 16, the time of her last follow-up, Beth has successfully transitioned to the male gender role (including a legal name change to Seth), has progressed to cross-sex hormonal therapy, functioned reasonably well at school, and reported an emerging gynephilic sexual orientation in fantasy; unfortunately, Seth struggles with his weight (281 lbs.) and requires on-going nutritional counseling.

Wayne was a 16-year-old Black Caribbean biological male with a Full-Scale IQ of 68. He lived with his mother and several siblings. Socioeconomic background of the family was lower middle class. Wayne's parents separated when he was 12, in part due to his father's excessive gambling, which left

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the family in dire financial straits. His mother had a history of brief psychotic episodes, although she was stable at the time of our assessment. At assessment, Wayne presented in the male gender role with notable "effeminate" mannerisms (he did, however, make efforts to pass in the female gender role when not in the presence of his family). Wayne had a history of childhood cross-gender identification although he had never verbalized the desire to be a female until early adolescence. Sexual orientation was androphilic. Wayne did not do well in school and was often ostracized because of his effeminacy. He was quite depressed at the time of our evaluation. The parents were distraught about Wayne's desire to be a girl. Although they were not aware of his sexual orientation, they reported that homosexuality was completely unacceptable because of their cultural and religious heritage (cf. Rosario, 2009). We hypothesized that the combination of internalized, familial, and cultural-religious homophobia was a contributing factor in Wayne's gender dysphoria, since living in the female gender role would "normalize" his sexual orientation. We recommended hormonal therapy to suppress Wayne's somatic masculinization and also saw him in supportive psychotherapy. Shortly after treatment began, Wayne began to live more fully in the female gender role and adopted the given name of Jane. The treatment focused on Jane's difficulties at school, worked on her mood state, examined whether or not she could entertain identifying as a gay male, and explored with Jane her propensity to put herself at risk in sexual situations (e.g., meeting heterosexual men in clubs who were not aware of her biological sex). At age 20, the time of her last follow-up, Jane was living with her mother, was working, was less depressed, and had been living in the female gender role for about three years (with a legal name change). Cross-sex hormonal therapy was instituted at the age of 18. Jane hopes to obtain sex-reassignment surgery in the next couple of years.

DISCUSSION

The primary aim of the present study was to examine whether or not our clinical recommendation to institute hormonal-blocking treatment for adolescents with GID was reliably associated with a series of demographic, behavior problem, and psychosexual measures that were part of our diagnostic assessment protocol. In this consecutive series of adolescents, hormonal blockers were recommended (although not necessarily instituted) for 60.6% of the sample. This percentage was similar to the 66.6% reported on by Cohen-Kettenis and van Goozen (1997) but somewhat higher than the 42.5% reported on by Smith et al. (2001).

The clinical decision to recommend hormonal blockers was reliably associated with several of our quantitative measures. We were more likely to recommend blockers for biological females and less likely to recommend

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blockers for youth who were in-care (Table 1). None of the other demographic variables (age at assessment, YOA, IQ, parent's social class and marital status, and ethnicity) were significantly associated with this recommendation. We were less likely to recommend blockers for youth who reported, on average, higher mean behavior problem scores on the YSR, but there was no significant difference in this recommendation as a function of the parent-report CBCL score (Table 2). The recommendation for blockers was also reliably associated with more extreme concurrent and recalled gender dysphoria and cross-gender behavior (across a number of measures) and for youth with a homosexual sexual orientation (in relation to their birth sex) (Table 2). In the logistic regression, five variables (out of 15) were predictive of our recommendation for hormonal treatment, including several measures related to degree of cross-gender behavior and gender dysphoria, a lower YSR score, and a visible ethnic minority status (Table 3).

It should be recognized that the current data set does not provide a formal algorithm that can be used in considering hormonal blockers for adolescents with GID, but the data provide suggestive evidence of the factors that seemed related to our clinical decision. It was clear, for example, that we were more likely to recommend blockers for those adolescents who had both a history and a concurrent clinical presentation of relatively more extreme cross-gender behavior and gender dysphoria. This seems consistent with Cohen-Kettenis et al.'s (2008) argument that the presence of gender dysphoria from "early childhood on" is one consideration for the institution of early hormonal treatment.

In Table 2, it can be seen that we were also more likely to recommend blockers for adolescents with a homosexual sexual orientation. Sexual orientation did not, however, survive as a significant predictor in the logistic regression (Table 3). There is considerable evidence that a homosexual sexual orientation, compared to a non-homosexual sexual orientation, among both adolescents and adults with GID, is associated with more recalled cross-gender behavior in childhood although not necessarily correlated with degree of concurrent gender dysphoria (Deogracias et al., 2007; Singh et al., 2010a; Smith et al., 2005a). It would appear, therefore, that our recommendation for hormonal blockers was more strongly linked to our patients' degree of gender dysphoria and recalled cross-gender behavior than sexual orientation per se.

One important difference between our adolescent sample and the adolescent samples reported on by the Dutch group is that we see many adolescents who do not have a homosexual sexual orientation whereas this appears to be quite uncommon in the Dutch samples. The reasons for this are not clear because many Dutch adults with gender dysphoria have a nonhomosexual sexual orientation (Smith et al., 2005a; Smith, van Goozen, Kuiper, & Cohen-Kettenis, 2005b). Because many adolescents with a nonhomosexual sexual orientation do not have the "early-onset" form of GID

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(cf. Lawrence, 2010; Smith et al., 2005b), it is important to recognize that "late-onset" GID was not necessarily a rule-out for hormonal blockers in our sample (cf. Cohen-Kettenis et al., 2008).

We were also more likely to recommend blockers for female patients than male patients, but biological sex did not survive the logistic regression as a significant predictor. It is likely the case that biological sex was related to our clinical recommendation because, in our sample, females reported, on average, more recalled cross-gender behavior and concurrent gender dysphoria and were more likely to have a homosexual sexual orientation than males (Singh et al., 2010a).

As noted earlier, the Dutch group is less likely to recommend early hormonal therapy when the patient has severe concurrent psychopathology. Our data were somewhat consistent with this in that we were less likely to recommend early hormonal therapy for youth who had higher scores on the YSR and youth who were in-care (a likely proxy for comorbidity), but the recommendation was unrelated to CBCL scores. Thus, the evidence was inconsistent about the role of comorbid psychopathology in making this clinical recommendation. It is likely that measures such as the YSR and CBCL are not precise enough with regard to assessing the potentially interfering role of concurrent psychopathology. Accordingly, in future studies, it would be important to augment these quantitative metrics with other measures, such as degree of functional impairment, and qualitative analysis to identify what exactly it is about co-occurring psychopathology that is linked to decisions about early biomedical treatment. On this latter point, the clinical material from the Dutch group is fairly sketchy (see Smith et al., 2001); in the present study, we attempted to provide more detailed qualitative information for two adolescents for whom we did not recommend hormonal treatment, but clearly more systematic data are urgently needed.

Finally, the logistic regression identified ethnicity as a significant predictor of our hormonal treatment recommendation, with youth of non-White ethnicity more likely to be recommended for suppression. It is not entirely clear how to understand this finding. On the one hand, ethnicity was not significantly correlated with any of our measures of gender dysphoria or cross-gender behavior and our measures of behavior problems (data not shown). On the other hand, non-White ethnicity was marginally correlated with both Full-Scale IQ ($r = -.18$, $p = .064$) and a homosexual sexual orientation on the EROS ($r = .19$, $p = .055$). IQ and sexual orientation (via the EROS) were not, however, significant predictors of our hormonal treatment recommendation in the logistic regression (Table 3). Perhaps the significant relation between ethnicity and sexual orientation (Table 2) influenced the recommendation of the clinician, but on this point, further research is required, including a more detailed qualitative analysis.

Our study represents the first systematic analysis of a North American cohort of adolescents with GID who were considered for hormonal blocker

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treatment. Given the relative novelty of this treatment (Hembree et al., 2009), it will be important to follow closely the developmental course of our patients in order to examine the long-term effectiveness of it in contributing to the clinical aim of reducing gender dysphoria and improving general psychosocial well-being. It is equally important to track the developmental course of those patients who were not recommended this form of intervention to see whether or not their gender dysphoria persisted or desisted and to evaluate their general psychologic adaptation and functioning.

NOTES

1. Two of the patients had a co-occurring disorder of sex development: one patient was a genetic female with congenital adrenal hyperplasia, who had been assigned female shortly after birth; the second patient was a genetic male with penile agenesis, who had also been assigned female shortly after birth (and surgically castrated). Both of these patients are included in our sample as females based on their assigned gender. Two other female patients had co-occurring polycystic ovarian syndrome.

2. For sexual orientation, we arbitrarily selected the EROS measure as the metric of sexual orientation, not the SHQ. These two variables were highly correlated, with a Phi coefficient of .61 (Nunnally, 1978, pp. 132–133).

3. A logistic regression that only included the participants with no missing data on any of the variables ($N = 88$) yielded very similar findings as the multiple imputation procedure. The results of this logistic regression analysis are available from the corresponding author upon request.

4. There is considerable clinical evidence that some women with a lesbian sexual orientation can "migrate" to a transgendered gender identity and vice-versa. For lesbian women, this is particularly common among those who self-identify as "butch." One can also make the same clinical observation for men with a gay sexual orientation, particularly those who are behaviorally very feminine. Thus, it is important consider that an adolescent might fluctuate between these two kinds of identity statuses and thus is an appropriate topic for exploration in supportive psychotherapy (see, e.g., Brown, 2010; Devor, 1997; Diamond & Butterworth, 2008; Lee, 2001; McCarthy, 2003; Rosario, 2009).

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Association between gender confirmation treatments and perceived gender congruence, body image satisfaction and mental health in a cohort of transgender individuals

Ashli A. Owen-Smith, PhD, SM[1,2], **Joseph Gerth, MPH**[3], **R. Craig Sineath, MPH**[10], **Joshua Barzilay, MD**[2], **Tracy A. Becerra-Culqui, PhD**[4], **Darios Getahun, MD, PhD, MPH**[4], **Shawn Giammattei, PhD**[5], **Enid Hunkeler, MA, FAHA**[6], **Timothy L. Lash, DSc, MPH**[3], **Andrea Millman, MA**[7], **Rebecca Nash, MPH**[3], **Virginia P. Quinn, PhD**[8], **Brandi Robinson, MPH**[2], **Douglas Roblin, PhD**[9], **Travis Sanchez, PhD**[3], **Michael J. Silverberg, PhD, MPH**[7], **Vin Tangpricha, MD, PhD**[10,11], **Cadence Valentine, MSW**[4], **Savannah Winter**[2], **Cory Woodyatt**[3], **Yongjia Song, MPH**[3], and **Michael Goodman, MD, MPH**[3]

[1]Georgia State University, School of Public Health, Department of Health Management and Policy, Atlanta GA

[2]Kaiser Permanente Georgia, Center for Clinical and Outcomes Research, Atlanta GA

[3]Emory University, Rollins School of Public Health, Department of Epidemiology, Atlanta GA

[4]Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA

[5]The Rockway Institute, Alliant International University, San Francisco, CA

[6]Emeritus, Division of Research, Kaiser Permanente Northern California, Oakland, CA

[7]Division of Research, Kaiser Permanente Northern California, Oakland, CA

[8]Emeritus, Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA

[9]Mid-Atlantic Permanente Research Institute, Kaiser Permanente Mid-Atlantic States, Rockville, MD

[10]Emory University, School of Medicine, Atlanta, GA

[11]The Atlanta VA Medical Center, Atlanta GA

Abstract

Background—Transgender individuals sometimes seek gender confirmation treatments (GCTs), including hormone therapy (HT) and/or surgical change of the genitalia and other secondary sex

Corresponding Author Ashli Owen-Smith, PhD, SM, Assistant Professor of Health Management & Policy, School of Public Health, Georgia State University, P.O. Box 3984, Atlanta, GA 30302-3984, Phone: 404-413-1139, Fax: 404-413-2343, aowensmith@gsu.edu.

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characteristics (gender confirmation surgeries; GCS). These treatments, which alter the body so that it is more compatible with one's identity, may ameliorate distress resulting from the incongruence between one's physical appearance and gender identity.

Aim—The aim was to examine the degree to which individuals' body-gender congruence, body image satisfaction, depression and anxiety differed by GCT groups in cohorts of transmasculine (TM) and transfeminine (TF) individuals.

Methods—The "Study of Transition, Outcomes & Gender (STRONG)" is a cohort study of transgender individuals recruited from three XXX health plans located in Georgia, Northern California and Southern California; cohort members were recruited to complete a survey between 2015–2017. Participants were asked about: history of GCTs; body-gender congruence; body image satisfaction; depression; and anxiety. Participants were categorized as having received: 1) no GCT to date; 2) HT only; 3) HT + top surgery; 4) HT + partial bottom surgery; and 5) HT + definitive bottom surgery.

Outcomes—Outcomes of interest included body-gender congruence, body image satisfaction, depression and anxiety.

Results—Of the 2,136 individuals invited to participate, 697 subjects (33%) completed the survey, including 347 TM and 350 TF individuals. The proportion of participants with low body-gender congruence scores was significantly higher in the "no treatment" group (prevalence ratio [PR]=3.96, 95% confidence interval [CI] 2.72–5.75) compared to the "definitive bottom" surgery group. The PR for depression comparing participants who reported no treatment relative to those who had definitive surgery was 1.94 (95% CI: 1.42–2.66); the corresponding PR for anxiety was 4.33 (95% CI 1.83–10.54).

Clinical Implications—Withholding or delaying GCTs until depression or anxiety have been treated may not be the optimal treatment course given the benefits of reduced levels of distress after undergoing these interventions.

Strengths & Limitations—Strengths include the well-defined sampling frame, which allowed correcting for non-response, a sample with approximately equal numbers of TF and TM participants, and the ability to combine data on HT and GCS. Limitations include the cross-sectional design and the fact that participants may not be representative of the transgender population in the US.

Conclusion—Body-gender congruence and body image satisfaction were higher, and depression and anxiety were lower among individuals who had more extensive GCTs compared to those who have received less treatment or no treatment at all.

Keywords

Transgender; gender confirmation treatments; mental health; body image

INTRODUCTION

Transgender is a term used to describe individuals whose gender identity differs from the male or female sex designation usually occurring at birth.[1, 2] A person whose gender identity differs from a female sex designation is referred to as female-to-male or

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transmasculine (TM) and a person whose gender identity differs from a male sex designation is referred to as male-to-female or transfeminine (TF). The terms TM/TF include a broad spectrum of identities that differ from the gender assigned at birth and can apply to individuals who do not identify with binary categories.[3]

Some transgender individuals experience gender dysphoria (GD), defined as a feeling of distress resulting from the incongruence between physical appearance and gender identity.[4, 5] This distress, compounded by commonplace experiences of stigma, victimization and discrimination, may partly explain the disproportionately high rates of depression and anxiety among TM and TF individuals compared with the general population.[6–8] These mental health issues not only affect an individual's quality of life but are associated with other health problems and higher mortality rates.[9–12] Among transgender individuals, depression has been linked to substance abuse, high risk sexual behaviors, and most notably, suicide.[13–15]

Transgender individuals may seek medical gender confirmation treatments (GCTs), including administration of hormone therapy (HT) to achieve desired masculinization or feminization, and/or surgical change of the genitalia and other secondary sex characteristics. HT may include estrogens for TF and testosterone for TM individuals. Examples of gender confirmation surgeries (GCS) include breast augmentation and vaginoplasty for TF individuals and mastectomy and hysterectomy for TM individuals.[16] Historically, individuals seeking these interventions receive HT first and may choose to undergo surgeries later, after 12 months of continuous HT[17], although not all individuals follow this sequence.

Given that one source of GD is the incongruence between the physical body and gender identity, it follows that medical interventions that alter the body to be more compatible with one's identity could ameliorate this distress. Lindgren and Pauly, the first to explore the effectiveness of GD treatment, found that after HT and/or GCS, body dissatisfaction levels were reduced in both TF and TM study participants.[18, 19] More recent studies have provided additional support that both HT and GCS can decrease the level of overall body dissatisfaction[20, 21] and/or increase body satisfaction.[22] Similarly, a recent systematic review suggests that HT may lead to improvements in psychological functioning, including reductions in depression and anxiety.[23]

Although these studies offer insights regarding the associations between GCTs and body dissatisfaction/body image, depression and anxiety, they have been limited by several factors. First, the sample sizes were relatively small (22 to 162 participants) and each was based at a single clinical site.[16, 18, 21, 22, 24, 25] Second, data have rarely been presented separately for both TM *and* TF individuals, thus obscuring differences that may exist between these distinct populations.[20] Third, most studies have focused on HT *or* GCS (or assessed HT and GCS together) rather than examining the extent to which individuals at different stages of medical GCT may differ with respect to experiences of body-gender incongruence, body image satisfaction, depression and anxiety.

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With these considerations in mind, the aim of the present study was to examine the degree to which body-gender congruence, body image satisfaction, depression and anxiety differed by GCT groups among TM and TF individuals.

MATERIALS AND METHODS

Study population

The present study is based upon the cohort of participants used in the "Study of Transition, Outcomes & Gender (STRONG)." This cohort was recruited from XXX Health Plans located in Georgia (XXX), Northern California (XXX) and Southern California (XXX). The primary goal of STRONG is to assess morbidity among transgender and gender nonconforming individuals overall and among TM/TF subgroups. The three participating XXX health plans are integrated health care systems that currently provide comprehensive health services to approximately 8 million members. Enrollees are socio-demographically diverse and broadly representative of the communities in the corresponding areas.[26]

The study was conducted in partnership with XXX University, which served as the coordinating center. All activities were reviewed and approved by the Institutional Review Boards (IRB) of the four participating institutions. The three XXX organizations use similar electronic medical record (EMR) systems, and have comparably organized databases with identical variable names, formats, and specifications across sites.

The methods of cohort ascertainment were described in detail previously.[27, 28] Briefly, EMR data pertaining to all participating health plan members of all ages enrolled between January 1, 2006 and December 31, 2014 were used to identify two types of evidence supporting transgender/gender non-conforming status: 1) relevant International Classification of Diseases, Ninth Edition (ICD-9) codes; and 2) presence of specific keywords in free-text notes. Eligibility status was independently verified by two trained reviewers with disagreements adjudicated by a committee that included the project manager and two investigators.

Survey recruitment

The survey eligibility criteria included: age 18 years or older, current enrollment in one of the participating health plans, at least one relevant ICD-9 diagnostic code, and text string-confirmed transgender status. Participants were excluded from the survey if their ICD codes and text strings were limited to mental health records, their XXX physicians did not provide consent for initiating the contact, or in their responses to the screening questions, their gender identity was the same as natal sex. All initial invitations were sent via regular mail. The letter included a website and a unique password linked to the Study ID; participants were asked to read and electronically sign the consent form online prior to survey completion. Subjects who did not respond to the initial invitation were sent up to two reminders.

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Survey goal and content

As not all data elements of interest could be ascertained from the EMR data alone, the project also included a cross-sectional survey which collected self-report data via an online survey software tool or by paper for those who did not want/were not able to complete the survey on the internet.

Gender identity (TM and TF status) was determined based on a two-step question: first inquiring about participants' natal (assigned at birth) sex and then asking about their current gender identity. If the gender identity was different from the natal female sex the participant was considered TM; if the gender identity was different from the natal male sex, the participant was considered TF. Five persons who reported being born with intersex conditions were excluded from the current analysis.

GCTs received were determined by asking participants about past, current and planned HT and their history of GCS. Based on reported history of these GCTs, each participant was placed in one of the following five ordered categories: 1) no gender confirmation therapy to date; 2) HT only; 3) Top surgery (e.g., mastectomy or breast augmentation); 4) Partial bottom surgery (e.g., hysterectomy without vaginectomy or orchiectomy without vaginoplasty); and 5) Definitive bottom surgery (e.g., vaginectomy or vaginoplasty). These categories were ordered in this way based on the level of medical intervention involved (e.g., hormone therapy was considered the least extensive intervention, followed by top surgeries, which typically require one clinician referral; bottom surgeries were considered the most extensive medical interventions, as they are more medically complex procedures, have a higher risk of surgical complications and typically require two clinician referrals).[29] Although nearly all participants who underwent top or bottom surgery also reported receiving hormones, a history of HT was not required in order for an individual to be classified in a subsequent category. The five-category GCT status was used as the main independent variable of interest. Participants were also asked about their history of procedures aimed at changing secondary sex characteristics such as laryngeal shave, facial feminization, and electrolysis.

Body-gender congruence was measured using the Transgender Congruence Scale (TCS), a validated 15-item instrument aimed at measuring a transgender person's level of comfort with gender identity.[30] Body image satisfaction was measured using the body attractiveness subscale of the previously validated Revised Physical Self-Perception Profile.[31] Information about the participants' depression and anxiety levels was collected using the 10-item Center for Epidemiologic Studies Depression (CESD-10) scale and the Beck Anxiety Index (BAI), respectively.[32, 33] For TCS and body image, the binary outcome of interest was defined as the total score being less than the overall study population median value. For depression and anxiety, the binary outcome was defined using the previously proposed clinically relevant cutoffs of 10 for CESD-10, and 21 for BAI.[32, 34]

Data analyses

The objectives of these analyses were to compare body-gender congruence, body image satisfaction, and levels of depression, and anxiety across categories of subjects at different

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stages of GCT. The distributions of dependent variables of interest were compared across GCT categories by calculating category-specific median and interquartile range (IQR) values. The differences in the distributions were examined using Kruskall-Wallis tests separately for TM and TF participants.

Multivariable logistic regression models were used to examine the association between GCT categories and each outcome of interest. The covariates in the model included age, study site, race/ethnicity, TM/TF status, and receipt of procedures for changing secondary sex characteristics (e.g., laryngeal shave or facial electrolysis for TF and "facial masculinization" for TM).

To address the effect of survey non-response on study results, each logistic regression analysis was replicated using weighted models. The weights for the models represented inverse selection probabilities. The selection probabilities were obtained from a separate logistic model, which included all STRONG cohort members who were invited to participate in the survey. The binary dependent variable in this model was response to the survey and independent variables included age, TM/TF status, race/ethnicity, study site and receipt of HT and GCS.

The results of both weighted and unweighted multivariable analyses were expressed as adjusted prevalence ratios (PR) and corresponding 95% confidence intervals (CI) using the 'rlogist' procedure in the SAS-callable SUDAAN® statistical software package (RTI International, Research Triangle Park, NC).

RESULTS

Of the 2,136 individuals invited to participate, 697 subjects (33%) completed the survey: 347 were TM and 350 were TF individuals. TM respondents were younger than their TF counterparts (73% vs. 35% under the age of 40 years, Table 1). More than half of survey respondents (55% of TM and 57% of TF respondents) were non-Hispanic Whites. The proportion of Hispanics (19%) was similar to that reported in the overall cohort, but the proportions of Blacks and Asians were lower (3% and 7% respectively) than in the EMR-based study. Only 4% of survey respondents (n=28) had no history of GCT and approximately one-third (n=234) received HT without any surgery. Top surgery category included 41% of TM subjects, but only 8% of TF participants. By contrast, definitive bottom surgery was more common among TF (33%) compared to TM (11%) study subjects. Only 7 individuals reported receiving surgery but not HT; most of those were TM who underwent top surgery. Receipt of procedures aimed and changing secondary sex characteristics was reported in 11.5% of participants (1.2 % of TM and 21.7% of TF individuals).

Table 2 compares the distributions of the four dependent variables of interest: total TCS score, body image satisfaction score, CESD-10 depression score, and BAI anxiety score by TM/TF status and by GCT category. As the extent of GCTs increased (from no treatment to definitive bottom surgery), the TCS and body image satisfaction scores also increased (i.e., were more favorable), with no appreciable difference between TM and TF participants. The

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results were generally similar in the analyses that examined distributions of the CESD-10 and BAI scores.

The bivariate associations were similar to the results obtained in the multivariable logistic regression analyses. There was no evidence of an important multiplicative interaction between gender identity and GCT, and for this reason all models include TM/TF status as a covariate.

The association of GCTs with the outcomes of interest was evident in all models, but particularly pronounced for the TCS score. The proportion of participants with low (below median) TCS scores was nearly four times higher in the “no reported treatment” category (PR=3.96, 95% CI 2.72–5.75) compared to the “definitive bottom” surgery group (Table 3). The overall patterns were similar, but the PR estimates were of lower magnitude, in the regression models that assessed body image satisfaction (Table 3). In the analyses of the CESD-10 score (Table 4) the PR for moderate/severe depression (>10 points) comparing participants who reported no treatment relative to those who had definitive surgery was 1.94 (95% CI: 1.42–2.66). The corresponding PR for clinically significant anxiety (BAI >21 points) was 4.33 (95% CI 1.83–10.54; Table 4). Procedures used to change secondary sex characteristics were not associated with TCS scores, body image satisfaction, depression or anxiety (Tables 3–4). The results of the weighted models adjusting for non-response were generally similar to those of the main analyses (Tables 3–4).

DISCUSSION

For both TM and TF participants, body-gender congruence and body image satisfaction were higher among individuals who had more extensive GCT compared to those who have received less treatment or no treatment at all. These findings are consistent with previous evidence that HT[20] and GCS[21, 22, 24] lead to improved body satisfaction among transgender individuals. This result is consistent with our understanding of GD in that one of the roots of GD is a high level of body image dissatisfaction[35] and this distress may be alleviated by receiving interventions that result in a more closely-aligned physical body with gender identity. GCTs may also increase one’s confidence in passing as a member of the preferred gender. For example, TM taking testosterone experience a redistribution of fat, increased muscle mass and a deepened voice, which promotes a more masculine appearance; similarly, TF individuals taking estrogens and antiandrogens experience reduced facial hair growth, an increase in fat deposits around the hips and buttocks, breast growth and reduced muscle mass, which promotes a more feminine appearance.[36] Previous research has underscored the importance of social “passing” for positive body image and body satisfaction and feelings of “passing” have been associated with a higher quality of life and self-esteem.[37]

Evidence suggests that in addition to exacerbating symptoms of GD, body image dissatisfaction can lead to secondary health problems among transgender individuals. For example, a study conducted among German, Swiss and Austrian participants showed that TM individuals displayed higher degrees of restrained eating patterns, weight and shape concerns, body dissatisfaction, and body checking (e.g., frequent weighing, looking in the

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mirror, pinching the stomach, waist, thighs or arms, etc.) than male controls: TF individuals showed more restrained eating, bulimic behavior, and body checking than male controls, and higher degrees of weight and shape concerns, body image dissatisfaction, and body checking than female controls.[38] Body dissatisfaction and poor body image can also predispose individuals to chronic depression, substance use/abuse, and several affective spectrum and somatic disorders.[39] Clearly, body dissatisfaction can lead to significant morbidities in this population and thus interventions that reduce risk for these conditions, such as GCTs, warrant serious consideration.

Our results also indicate that depression, and especially anxiety, were lower among individuals who received a more extensive GCTs compared to those who received less treatment or no treatment at all. These findings are consistent with and extend results from previous studies that have similarly reported that HT and GCS can result in lower levels of depression and anxiety.[16, 40–42] Historically, standard clinical practice has been to first treat any comorbid psychological conditions such as depression and anxiety prior to referring a transgender individual for GCTs.[43] As medical GCTs can be both physically and psychologically taxing[40] individuals with well-managed mental health issues may be best prepared to undergo this treatment. On the other hand, withholding HT or GCS until depression or anxiety have been treated may not be the optimal treatment course given the benefits of reduced levels of distress after undergoing GCT. The more recent clinical guidelines such as the World Professional Association for Transgender Health (WPATH) Standards of Care now recognize that HT may improve overall mental health status.[29] Given the alarmingly high rates of suicide attempts among transgender populations[7, 44–46] and recent evidence suggesting that suicide attempt rates decrease after GCS, [47] it is critical to consider all possible interventions with the potential to ameliorate psychological distress in this population. Healthcare providers must balance these potential benefits against possible adverse events related to HT (e.g., thromboembolism) and GCS (e.g., infections or other complications) as well as patient preferences/values and the availability/affordability of treatments.

Health insurance coverage for GCTs, particularly surgery, remains an area of controversy. For example, in 2016 the Centers for Medicare and Medicaid Services (CMS) announced the decision to not issue a National Coverage Determination on gender reassignment surgery for Medicare beneficiaries with GD because the clinical evidence was deemed inconclusive. In its decision memo, the CMS indicated that it “encourages robust clinical studies that will fill the evidence gaps and help inform which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.”[48] Findings from this study indicate that GCTs may be particularly beneficial for psychosocial conditions. However, additional research is needed to ascertain the benefits and harms of these interventions. Of particular concern are the effects on different subgroups such as those with more severe pre-existing psychiatric illness and individuals with varying levels of social support.

Several limitations of the present study should be recognized. The cross-sectional design of the survey does not allow for causal inferences with respect to the association between stage

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of GCT and body-gender congruence, body image satisfaction, depression, and anxiety. For example, individuals who are less depressed/anxious could be more likely to seek GCTs than those who are more depressed/anxious. However, a recent prospective study reported that, over the course of HT, participants with gender dysphoria reported significant reductions in general psychopathology and depressive symptoms, providing some evidence for the temporal association between GCTs and improvements in mental health-related outcomes.[49] The current study sample included only a small proportion of individuals who received no GCTs at all. These individuals were underrepresented because of the IRB requirement that eligible subjects had to have both a diagnostic code and a text string-confirmed transgender status, and could not receive transgender care exclusively from mental health providers. Additional prospective studies with large sample sizes and longer follow-up periods are needed to assess these constructs before and after receipt of GCTs. We also recognize that transgender individuals enrolled through integrated health care systems such as KP represent a cohort of individuals with health insurance that may not be representative of the transgender population in the US. It is expected that some of the results may differ among transgender individuals from different socioeconomic strata. Weighing against this concern is the demonstrated ability to cost-effectively identify a large cohort of transgender subjects with a high degree of internal validity. The availability of the well-defined sampling frame and extensive data on both respondents and non-respondents permitted quantitative adjustment for selection bias. Further, the present study, in contrast to prior research, included approximately equal numbers of TF and TM participants, which allowed us to examine differences and similarities of these two populations. The ability to combine data on HT and GCS allowed us to investigate the extent to which individuals *at different stages of GCT* may differ with respect to experiences of body-gender congruence, body image satisfaction, depression and anxiety.

CONCLUSIONS

In sum, results from the present study provide evidence for an association between participants' stage of GCT and their perceived body-gender incongruence and body image satisfaction as well as their symptoms of depression and anxiety. These findings were consistent for both TM and TF participants. Future research is needed to assess the temporal association between GCTs and psychosocial outcomes employing robust study designs, including larger-scale longitudinal cohort studies, and utilizing standardized scales and clinician-delivered mental health outcome measures in order to facilitate inferences and draw more definitive conclusions.

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Table 1

Characteristics of the STRONG survey participants

Participant characteristics	All subjects	Transmasculine	Transfeminine
	n (col %)	n (col %)	n (col %)
Total, n (row %)	697 (100.0)	347 (50.0)	350 (50.0)
Age at time of survey			
18–29	217 (31.1)	148 (42.7)	69 (19.7)
30–39	157 (22.5)	105 (30.3)	52 (14 9)
40–54	168 (24.1)	69 (19.9)	99 (28 3)
55 or older	155 (22.2)	25 (7.2)	130 (37.1)
Presents as a woman			
Never	330 (47.3)	310 (89.3)	20 (5.7)
Part-time	67 (9.6)	22 (6.3)	45 (12 9)
Full-time	273 (39.2)	5 (1.4)	268 (76.6)
Declined to respond	27 (3.9)	10 (2.9)	17 (4.9)
Presents as a man			
Never	277 (39.7)	16 (4.6)	261 (74.6)
Part-time	63 (9.0)	22 (6.3)	41 (11.7)
Full-time	323 (46.3)	297 (85.6)	26 (7.4)
Declined to respond	34 (4.9)	12 (3.5)	22 (6.3)
Race/ethnicity			
Non-Hispanic Whites	392 (56.2)	191 (55.0)	201 (57.4)
Non-Hispanic Blacks	20 (2.9)	13 (3.7)	7 (2.0)
Asian/Pacific islanders	48 (6.9)	25 (7.2)	23 (6.6)
Hispanics	133 (19.1)	68 (19.6)	65 (18.6)
Mixed race/ethnicity	18 (2.6)	8 (2.3)	10 (2.9)
"Other" race/ethnicity	49 (7.0)	27 (7.8)	22 (6.3)
Declined to respond	37 (5.3)	15 (4.3)	22 (6.3)
Education			
High school graduate or less	74 (10.6)	45 (13.0)	29 (8.3)

Participant characteristics	All subjects	Transmasculine	Transfeminine
	n (col %)	n (col %)	n (col %)
At least some college	242 (34.7)	100 (28.8)	142 (40.6)
College graduate	197 (28.3)	104 (30.0)	93 (26.6)
Graduate/professional school	150 (21.5)	81 (23.3)	69 (19.7)
Declined to respond	34 (4.9)	17 (4.9)	17 (4.9)
Individual income			
Less than $25,000	127 (18.2)	69 (19.9)	58 (16.6)
$25,000 – $49,999	138 (19.8)	65 (18.7)	73 (20.9)
$50,000 – $74,999	120 (17.2)	65 (18.7)	55 (15.7)
$75,000 – $99,999	93 (13.3)	47 (13.5)	46 (13.1)
Greater than $100,000	128 (18.4)	51 (14.7)	77 (22.0)
Prefer not to answer or unsure	91 (13.1)	50 (14.4)	41 (11.7)
History of GCT [a]			
No GCT	28 (4.0)	11 (3.2)	17 (4.9)
HT only	234 (33.6)	76 (21.9)	158 (45.1)
Top surgery	171 (24.5)	142 (40.9)	29 (8.3)
Partial bottom surgery	80 (11.5)	64 (18.4)	16 (4.6)
Definitive bottom surgery	153 (22.0)	39 (11.2)	114 (32.6)
Missing information	31 (4.4)	15 (4.3)	16 (4.6)
Procedures to change secondary sex characteristics			
Yes	80 (11.5)	4 (1.2)	76 (21.7)
No	617 (88.5)	343 (98.8)	274 (78.3)

[a] Only 7 individuals reported receiving surgery but not HT. Most of those were TM who underwent top surgery.

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Table 2

The distributions of outcome measures by transgender status and by gender confirmation category

Outcome measure by gender confirmation category	Transmasculine			Transfeminine		
	Median	IQR[e]	p-value[f]	Median	IQR[e]	p-value[f]
Transgender congruence score[a]						
No treatment	30	22–36	<0.0001	30	25–46	<0.0001
HT only	43	32–51		44	33–50	
Top surgery	50	44–56		44	39–52	
Partial bottom surgery	49	42–55		51	37–57	
Definitive bottom surgery	55	49–59		53	48–57	
Body image satisfaction score[b]						
No treatment	9	9–16	<0.0001	11	6–18	0.0065
HT only	12	7–18		15	10–20	
Top surgery	17	12–22		12	9–19	
Partial bottom surgery	15	9–18		14	10–22	
Definitive bottom surgery	16	13–21		18	13–22	
CESD-10 depression score[c]						
No treatment	16	13–23	0.0016	14	10–21	0.0002
HT only	12	8–18		10	5–16	
Top surgery	8	4–13		11	6–16	
Partial bottom surgery	9	4–15		8	3–16	
Definitive bottom surgery	6	3–14		6	3–11	
BAI anxiety score[d]						
No treatment	25	16–26	0.0006	12	7–25	0.0015
HT only	12	7–26		9	2–17	
Top surgery	7	4–17		7	3–13	
Partial bottom surgery	9	2–17		9	3–13	
Definitive bottom surgery	5	2–13		5	1–10	

[a]Composite of 12 questions, possible range: 12–60; higher scores indicate greater level of comfort with gender identity.

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[b] Composite of 5 questions, possible range: 5–25; higher scores indicate a higher level of body image satisfaction.

[c] Composite of 10 questions, possible range: 0–30; higher scores indicate higher levels of depression.

[d] Composite of 21 questions, possible range: 0–63; higher scores indicate higher levels of anxiety.

[e] Interquartile range

[f] Kruskal-Wallis test

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Table 3

Associations of gender confirmation, gender identity, and procedures aimed at changing secondary sex characteristics with low transgender congruence and body image scores

Variables of interest	Total N	N (%) within treatment category	Unweighted analyses			Weighted analyses		
			PR[a]	95% CI[b]		PR[a]	95% CI[b]	
Transgender congruence score below median[c]								
Gender confirmation category								
Definitive bottom surgery	149	33 (22%)	1.00	(reference)		1.00	(reference)	
Partial bottom surgery	77	34 (44%)	2 11	1.38	3.23	2.15	1.37	3.37
Top surgery	161	71 (44%)	2.06	1.39	3.05	2.10	1.39	3.17
HT only	210	138 (66%)	3.03	2.14	4.30	3.22	2.25	4.61
No treatment	27	23 (85%)	3 96	2.72	5.75	3.66	2.28	5.88
Gender identity								
Transfeminine	306	150 (49%)	1.00	(reference)		1.00	(reference)	
Transmasculine	318	149 (47%)	0 95	0.77	1.15	1.03	0.83	1.28
Changes in secondary sex characteristics								
Yes	75	30 (40%)	1.00	(reference)		1.00	(reference)	
No	549	269 (49%)	0.88	0.68	1.12	0.87	0.68	1.13
Body image score below median[d]								
Gender confirmation category								
Definitive bottom surgery	150	49 (33%)	1.00	(reference)		1.00	(reference)	
Partial bottom surgery	79	39 (49%)	1.42	1.01	2.01	1.58	1.10	2.26
Top surgery	167	67 (40%)	1 19	0.85	1.65	1.25	0.88	1.78
HT only	220	116 (53%)	1 59	1.20	2.10	1.72	1.27	2.32
No treatment	28	17 (61%)	1.81	1.22	2.68	1.75	1.08	2.83
Gender identity								
Transfeminine	319	139 (44%)	1.00	(reference)			(reference)	
Transmasculine	325	149 (46%)	1.09	0.88	1.36	1.11	0.88	1.39
Procedures to change secondary sex characteristics								

Variables of interest	Total N	N (%) within treatment category	Unweighted analyses			Weighted analyses		
			PR[a]	95% CI[b]		PR[a]	95% CI[b]	
Yes	77	24 (31%)	1.00	(reference)			(reference)	
No	567	264 (47%)	1.24	0.87	1.76	1.29	0.87	1.90

[a] PR, prevalence ratio adjusted for age, race, study site, and all variables listed in the table.

[b] CI, confidence interval

[c] Model based on 624 observations

[d] Model based on 644 observations

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Table 4

Associations of gender confirmation, gender identity, and procedures aimed at changing secondary sex characteristics with high CESD-10 depression and anxiety scores

Variables of interest	Total N	N (%) within treatment category	Unweighted analyses			Weighted analyses		
			PR[a]	95% CI[b]		PR[a]	95% CI[b]	
CESD-10 score above 10[c]								
Gender confirmation category								
Definitive bottom surgery	141	50 (35%)	1.00	(reference)		1.00	(reference)	
Partial bottom surgery	75	34 (45%)	1.19	0.84	1.67	1.18	0.84	1.68
Top surgery	158	66 (42%)	1.00	0.73	1.38	0.96	0.69	1.34
HT only	198	113 (57%)	1.40	1.07	1.83	1.38	1.05	1.81
No treatment	26	20 (77%)	1.94	1.42	2.66	2.01	1.51	2.68
Gender identity								
Transfeminine	293	139 (47%)	1.00	(reference)			(reference)	
Transmasculine	305	144 (47%)	0.92	0.74	1.15	0.91	0.73	1.12
Changes in secondary sex characteristics								
Yes	71	30 (42%)	1.00	(reference)			(reference)	
No	527	253 (48%)	0.91	0.69	1.18	0.93	0.72	1.21
Anxiety score above 21[d]								
Gender confirmation category								
Definitive bottom surgery	139	8 (5.8%)	1.00	(reference)		1.00	(reference)	
Partial bottom surgery	73	13 (18%)	1.93	0.82	4.53	1.41	0.57	3.46
Top surgery	159	34 (22%)	1.90	0.86	4.18	1.51	0.68	3.37
HT only	195	47 (24%)	2.59	1.21	5.54	2.15	1.02	4.51
No treatment	26	11 (42%)	4.33	1.83	10.54	2.74	1.10	6.80
Gender identity								
Transfeminine	296	42 (14%)	1.00	(reference)		1.00	(reference)	
Transmasculine	296	71 (24%)	1.26	0.81	1.94	1.38	0.87	2.20
Procedures to change secondary sex characteristics								

Variables of interest	Total N	N (%) within treatment category	Unweighted analyses		Weighted analyses	
			PR[a]	95% CI[b]	PR[a]	95% CI[b]
Yes	72	6 (8.3%)	1.00	(reference)	1.00	(reference)
No	520	107 (21%)	1.00	0.48 2.11	1.05	0.49 2.25

[a] PR, prevalence ratio adjusted for age, race, study site, and all variables listed in the table.

[b] CI, confidence interval

[c] Model based on 598 observations

[d] Model based on 592 observations

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