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Appendix A METHODOLOGY

1. Introduction

This version of the Standards of Care (SOC-8) is based upon a more rigorous and methodological evidence-based approach than previous versions. This evidence is not only based on the published literature (direct as well as background evidence) but also on consensus-based expert opinion. Evidence-based guidelines include recommendations intended to optimize patient care and are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options. Evidence-based research provides the basis for sound clinical practice guidelines and recommendations but must be balanced by the realities and feasibility of providing care in diverse settings. The process for development of the SOC-8 incorporated recommendations on clinical practice guideline development from the National Academies of Medicine and The World Health Organization that addressed transparency, the conflict-of-interest policy, committee composition and group process. (Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice, 2011; World Health Organization, 2019a).

The SOC-8 revision committee was multidisciplinary and consisted of subject matter experts, health care professionals, researchers and stakeholders with diverse perspectives and geographic representation. All committee members completed conflict of interest declarations.*

A guideline methodologist assisted with the planning and development of questions, and an independent team undertook systematic reviews that were used to inform some of the statements for recommendations. Additional input to the guidelines was provided by an international advisory committee, legal experts, and feedback received during a public comment period. Recommendations in the SOC-8 are based on available evidence supporting interventions, a discussion of risks and harms, as well as feasibility and acceptability within different contexts and country settings. Consensus of the final recommendations was attained using a Delphi process that included all members of the Standards of Care Revision committee and required that recommendation statements were approved by 75% of members. Supportive and explanatory text of the evidence for the statements were written by chapter members. Drafts of the chapters were reviewed by the Chair and the Co-Chairs of the SOC Revision Committee to ensure the format was consistent, evidence was properly provided, and recommendations were consistent across chapters. An independent team checked the references used in the SOC-8 before the guidelines were fully edited by a single professional. A detailed overview of the SOC-8 Methodology is described below.

2. Difference between the methodology of the SOC-8 and previous editions

The main differences in the methodology of the SOC-8 when compared with other versions of the SOC are:

- The involvement of a larger group of professionals from around the globe;

- A transparent selection process to develop the guidelines steering committee as well as to select chapter leads and members;
- The inclusion of diverse stakeholders in the development of the SOC-8
- Management of conflicts of interest
- The use of a Delphi process to reach agreement on the recommendations among SOC-8 committee members
- The involvement of an independent body from a reputable university to help develop the methodology and undertake independent systematic literature reviews where possible
- Recommendations were graded as either “recommend” or “suggest” based upon the strength of the recommendations.
- The involvement of an independent group of clinical academics to review citations.
- The involvement of international organizations working with the transgender and gender diverse (TGD) community, members of WPATH and other professional organizations as well as the general public who provided feedback through a public comment period regarding the whole SOC-8.

3. Overview of SOC-8 development Process

The steps for updating the Standards of Care are summarized below:

1. Establishing Guideline Steering Committee including Chair, and Co-Chairs (July 19, 2017)
2. Determining chapters (scope of guidelines)
3. Selecting Chapter Members based upon expertise (March 2018)
4. Selecting the Evidence Review Team: John Hopkins University (May 2018)
5. Refining topics included in the SOC-8 and review questions for systematic reviews
6. Conducting systematic reviews (March 2019)
7. Drafting the recommendation statements
8. Voting on the recommendation statements using a Delphi process (September 2019–February 2022)
9. Grading of the recommendations statements
10. Writing the text supporting the statements
11. Independently validating the references used in the supportive text
12. Finalizing a draft SOC-8 (December 1, 2021)
13. Feedback on the statements by International Advisory Committee
14. Feedback on the entire draft of the SOC-8 during a public comment period (November 2021–January 2022)
15. Revision of Final Draft based on comments (January 2022– May 2022)
16. Approval of final Draft by Chair and Co-Chairs (June 10, 2022)
17. Approval by the WPATH Board of Directors
18. Publication of the SOC-8
19. Dissemination and translation of the SOC-8

3.1. Establishment of Guideline Steering Committee

The WPATH Guideline Steering Committee oversaw the guideline development process for all chapters of the Standards of Care. Except for the Chair (Eli Coleman) who was appointed by the WPATH board to maintain a continuity from previous SOC editions, members of the Guideline Steering Committee were selected by the WPATH Board from WPATH members applying for these positions. Job descriptions were developed for the positions of Co-Chairs, Chapter Leads, Chapter Members and Stakeholder. WPATH members were eligible to apply by completing an application form and submitting their CV. The Board of WPATH voted for the position of co-chair (one member of the board did not participate in view of conflict of interest). The chairs and co-chairs selected the chapter leads and members (as well as stakeholders) based on the application form and CVs.

The Guideline Steering Committee for Standards of Care 8th Version are:

- Eli Coleman, PhD (Chair) Professor, Director and Academic Chair, Institute for Sexual and Gender Health, Department of Family Medicine and Community Health, University of Minnesota Medical School (USA)
- Asa Radix, MD, PhD, MPH (Co-chair) Senior Director, Research and Education Callen-Lorde Community Health Center Clinical Associate Professor of Medicine New York University, USA
- Jon Arcelus, MD, PhD (Co-chair) Professor of Mental Health and Well-being Honorary Consultant in Transgender Health University of Nottingham, UK
- Karen A. Robinson, PhD (Lead, Evidence Review Team) Professor of Medicine, Epidemiology and Health Policy & Management Johns Hopkins University, USA

3.2. Determination of topics for chapters

The Guideline Steering Committee determined the chapters for inclusion in the Standards of Care by reviewing the literature and by reviewing the previous edition of the SOC. The chapters in the Standards of Care 8th Version:

1. Terminology
2. Global Applicability
3. Population estimates
4. Education*
5. Assessment of Adults
6. Adolescent
7. Children
8. Nonbinary
9. Eunuch
10. Intersex
11. Institutional environments
12. Hormone Therapy
13. Surgery and Postoperative Care
14. Voice and communication

15. Primary care
16. Reproductive Health
17. Sexual Health
18. Mental Health

* The Education Chapter was originally intended to cover both education and ethics. A decision was made to create a separate committee to write a chapter on ethics. In the course of writing the chapter, it was later determined topic of ethics was best placed external to the SOC8 and required further in-depth examination of ethical considerations relevant to transgender health.

3.3. Selection of chapter members

A call for applications to be part of the SOC-8 review committee (chapter lead or member) was sent to the WPATH membership. The Chairs of the Guideline Steering Committee appointed the members for each chapter, ensuring representation from a variety of disciplines and perspectives.

Chapter Leads and Members were required to be WPATH Full Members in good standing and content experts in transgender health, including in at least one chapter topic. Chapter Leads reported to the Guideline Steering Committee and were responsible for coordinating the participation of Chapter Members. Chapter members reported directly to the Chapter Lead.

Each chapter also included stakeholders as members who bring perspectives of transgender health advocacy or work in the community, or as a member of a family that included a transgender child, sibling, partner, parent, etc. Stakeholders were not required to be full members of WPATH.

The Chapter Members were expected to:

- Participate in the development refinement of review questions
- Read and provide comments on all materials from the Evidence Review Team
- Critically review draft documents, including the draft evidence report
- Review and assess evidence and draft recommendations
- Participate in the Delphi consensus process
- Develop the text to back up the recommendation statements
- Grade each statement to describe the strength of the recommendation
- Review and address the comments from the Chairs during the whole process
- Develop the content of the chapters
- Review comments from public comments and assist in the development of a revision of guidelines
- Provide input and participate in the dissemination of guidelines

Training and orientation for Chapter Leads and Members was provided, as needed. Training content included formulation and refinement of questions (i.e., use of PICO), reviewing the evidence, developing recommendation state-

ments, grading the evidence and the recommendations, and information about the guideline development program and process.

A total of 26 chapter-leads were appointed (some chapters required co-leads), 77 chapter members and 16 stakeholders. A total of 127 were selected. During the SOC process, 8 people left, due to personal or work-related issues. Therefore, there were 119 final authors of the SOC-8.

3.4. Selection of the evidence review team

The WPATH Board issued a request for applications to become the Evidence Review Team. For Standards of Care 8th Version the WPATH Board engaged the Evidence Review Team at Johns Hopkins University under the leadership of Karen Robinson.

- Karen A. Robinson, PhD (Lead, Evidence Review Team) Professor of Medicine, Epidemiology and Health Policy & Management Johns Hopkins University, USA

Dr Robinson also guided the steering committee in the development of the SOC-8 by providing advice and training in the development of PICO questions, statements, and the Delphi process as well as undertaking a very rigorous systematic literature review where direct evidence was available.

Conflict of interest

Members of the Guideline Steering Committee, Chapter Leads and Members, and members of the Evidence Review Team were asked to disclose any conflicts of interest. Also reported, in addition to potential financial and competing interests or conflicts, are personal or direct reporting relationships with a chair, co-chair or a WPATH Board Member or the holding of a position on the WPATH Board of Directors.

3.5. Refinement of topics and review of questions

The Evidence Review Team abstracted the recommendation statements from the prior version of the Standards of Care. With input from the Evidence Review Team, the Guideline Steering Committee and Chapter Leads determined:

- Recommendation statements that needed to be updated
- New areas requiring recommendation statements

3.6. Conduct the systematic reviews

Chapter Members developed questions to help develop recommendation statements. For the questions eligible for systematic review, the Evidence Review Team drafted review questions, specifying the Population, Interventions, Comparisons, and Outcomes (PICO elements). The Evidence Review Team undertook the systematic reviews. The Evidence Review Team presented evidence tables and other

results of the systematic reviews to the members of the relevant chapter for feedback.

Protocol

A separate detailed systematic review protocol was developed for each review question or topic, as appropriate. Each protocol was registered on PROSPERO.

Literature search

The Evidence Review Team developed a search strategy appropriate for each research question including MEDLINE®, Embase™, and the Cochrane Central Register of Controlled Trials (CENTRAL). The Evidence Review Team searched additional databases as deemed appropriate for the research question. The search strategy included MeSH and text terms and was not limited by language of publication or date.

The Evidence Review Team hand searched the reference lists of all included articles and recent, relevant systematic reviews. The Evidence Review Team searched ClinicalTrials.gov for any additional relevant studies.

Searches were updated during the peer review process.

The literature included in the systematic review was mostly based on quantitative studies conducted in Europe, the US or Australia. We acknowledge a bias towards perspectives from the global north that does not pay sufficient attention to the diversity of lived experiences and perspectives within transgender and gender diverse (TGD) communities across the world. This imbalance of visibility in the literature points to a research and practice gap that needs to be addressed by researchers and practitioners in the future in order to do justice to the support needs of all TGD people independent of gender identification.

Study selection

The Evidence Review Team, with input from the Chapter Workgroup Leads, defined the eligibility criteria for each research question *a priori*.

Two reviewers from the Evidence Review Team independently screened titles and abstracts and full-text articles for eligibility. To be excluded, both reviewers needed to agree that the study met at least one exclusion criteria. Reviewers resolved differences regarding eligibility through discussion.

Data extraction

The Evidence Review Team used standardized forms to abstract data on general study characteristics, participant characteristics, interventions, and outcome measures. One reviewer abstracted the data, and a second reviewer confirmed the abstracted data.

Assessment of risk of bias

Two reviewers from the Evidence Review Team independently assessed the risk of bias for each included study. For

randomized controlled trials, the Cochrane Risk of Bias Tool was used. For observational studies, the Risk of Bias in Non-Randomized Studies—of Interventions (ROBINS-I) tool was used. Where deemed appropriate, existing recent systematic reviews were considered and evaluated using ROBIS.

Data synthesis and analysis

The Evidence Review Team created evidence tables detailing the data abstracted from the included studies. The members of the Chapter Workgroups reviewed and provided comments on the evidence tables.

Grading of the evidence

The Evidence Review Team assigned evidence grades using the GRADE methodology. The strength of the evidence was obtained using predefined critical outcomes for each question and by assessing the limitations to individual study quality/risk of bias, consistency, directness, precision, and reporting bias.

3.7. Drafting of the Recommendation Statements

Chapter Leads and Members drafted recommendation statements. The statements were crafted to be feasible, actionable, and measurable.

Evidence-based recommendation statements were based on the results of the systematic, and background literature reviews plus consensus-based expert opinions.

The Chair and Co-Chairs and Chapter Leads reviewed and approved all recommendation statements for clarity and consistency in wording. During this review and throughout the process any overlap between chapters was also addressed.

Many chapters had to work closely together to ensure consistency of their recommendations. For example, as there are now separate chapters for childhood and adolescence, to ensure consistency between both chapters, some authors were part of both chapters. For a similar reason, when applicable, a workgroup collaborated with other Chapter Workgroups on topics shared between the chapters (i.e., Assessment of Children, Assessment of Adults, Hormone Therapy, Surgery and Postoperative Care and Reproductive Health).

3.8. Approval of the recommendations using the Delphi process

Formal consensus for all statements was obtained using the Delphi process (a structured solicitation of expert judgments in three rounds). For a recommendation to be approved, a minimum of 75% of the voters had to approve the statement. A minimum of 65% of the SOC-8 members had to take part in the Delphi process for each statement. People who did not approve the statement had to provide information as to the reasons for their disapproval, so the statement could be modified (or removed) according to this feedback. Once modified, the statement was put through the Delphi process again. If after 3 rounds the statement

was not approved, the statement was removed from the SOC. Every member of the SOC voted for each statement. There was a response rate between (74.79% and 94.96%) for the statements.

3.9. Grading criteria for statements

Once the statements passed the Delphi process, chapter members graded each statement using a process adapted from the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework. This a transparent framework for developing and presenting summaries of evidence and provides a systematic approach for making clinical practice recommendations (Guyatt et al., 2011). The statements were graded based on factors such as:

- The balance of potential benefits and harms
- Confidence in that balance or quality of evidence
- Values and preferences of providers and patients
- Resource use and feasibility

The statements were classified as:

- Strong recommendations (“we recommend”) are for those interventions/therapy/strategies where:
 - the evidence is of high quality
 - estimates of the effect of an intervention/therapy/strategy (i.e., there is a high degree of certainty effects will be achieved in practice)
 - there are few downsides of therapy/intervention/strategy
 - there is a high degree of acceptance among providers and patients or those for whom the recommendation applies.
- Weak recommendations (“we suggest”) are for those interventions/therapy/strategies where:
 - there are weaknesses in the evidence base
 - there is a degree of doubt about the size of the effect that can be expected in practice
 - there is a need to balance the potential upsides and downsides of interventions/therapy/strategies
 - there are likely to be varying degrees of acceptance among providers and patients or those for whom the recommendation applies.

3.10. Writing of the text supporting the statements

Following the grading of the statements, the Chapter Workgroups wrote the text providing the rationale or reasoning for the recommendation. This included providing the available evidence, providing details about potential benefits and harms, describing uncertainties, and information about implementation of the recommendation, including expected barriers or challenges among others. References use APA-7 style, to support the information in the text. Links to resources are also provided, as appropriate. The text, including whether a recommendation has been described as strong or weak, was reviewed and approved by the Chair and Co-Chairs.

3.11. External validation of references used to support the statements

A group of independent clinical academics working in the field of transgender health reviewed the references used in every chapter in order to validate that the references were appropriately used to support the text. Any queries regarding the references were sent back to the chapters for review.

3.12. Finalizing a draft SOC-8

A final SOC-8 draft was made available for comments.

3.13. Distribute Standards of Care for review by international advisors

The statements of the recommendations of Standards of Care 8th were circulated among the broader Standards of Care Revision Committee and the WPATH International Advisory Group, which included the Asia Pacific Transgender Network (APTN), the Global Action for Transgender Equality (GATE), the International Lesbian, Gay, Bisexual, Transgender, Intersex Association (ILGA), and Transgender Europe (TGEU).

3.14. Public comment period

The revised draft version of the Standards of Care document was posted online for comment from the public, including WPATH members, on the WPATH website. A 6-week period was allocated for comments. A total of 1,279 people made comments on the draft with a total of 2,688 comments.

3.15. Revision of final draft based on comments

The Chapter Leads and Guideline Steering Committee considered the feedback and made any necessary revisions. All public comments were read and, where appropriate, integrated into the background text.

As part of this process, 3 new Delphi statements were developed and 2 were modified enough to require a new vote by the SOC-8 committee. This meant a new Delphi process was initiated in January 2022. The results of this

Delphi process were accepted by the chapters, and the new statements were added or modified accordingly. The new supportive text was added.

All the new versions of the chapters were reviewed again by the Chair and Co-Chairs and changes or modifications were suggested. Finally, once the Chairs and the Chapter Members were satisfied with the draft, the chapter was finalized.

All new references were double checked by an independent member.

3.16. Approval of final draft by Chair and Co-Chairs

Modifications were reviewed by the Chairs and were accepted by them.

3.17. Approval by the WPATH Board of Directors

The final document was presented to the WPATH Board of Directors for approval and it was approved on the 20th of June 2022.

3.18. Publication of the SOC-8 and dissemination of the Standards of Care

The Standards of Care was disseminated in a number of venues and in a number of formats including publication in the International Journal of Transgender Health (the official scientific journal of WPATH).

4. Plan to Update

A new edition of the SOC (SOC-9) will be developed in the future, when new evidence and/or significant changes in the field necessitating a new edition is substantial.

*The development of SOC-8 was a complex process at a time of COVID-19 and political uncertainties in many parts of the world. Members of the SOC-8 worked on the SOC-8 on top of their day-to-day job, and most of the meetings took place out of their working time and during their weekends via Zoom. There were very few face-to-face meetings, most of them linked to WPATH, USPATH or EPATH conferences. Committee members of the SOC-8 were not paid as part of this process.

Appendix B GLOSSARY

CISGENDER refers to people whose current gender identity corresponds to the sex they were assigned at birth.

DETRANSITION is a term sometimes used to describe an individual's retransition to the gender stereotypically associated with their sex assigned at birth.

EUNUCH refers to an individual assigned male at birth whose testicles have been surgically removed or rendered non-functional and who identifies as a eunuch. This differs from the standard medical definition by excluding those who do not identify as eunuch.

EUNUCH-IDENTIFIED: An individual who feels their true self is best expressed by the term eunuch. Eunuch-identified individuals generally desire to have their reproductive organs surgically removed or rendered non-functional.

GENDER: Depending on the context, gender may reference gender identity, gender expression, and/or social gender role, including understandings and expectations culturally tied to people who were assigned male or female at birth. Gender identities other than those of men and women (who can be either cisgender or transgender) include transgender, nonbinary, genderqueer, gender neutral, agender, gender fluid, and "third" gender, among others; many other genders are recognized around the world.

GENDER-AFFIRMATION refers to being recognized or affirmed in a person's gender identity. It is usually conceptualized as having social, psychological, medical, and legal dimensions. Gender affirmation is used as a term in lieu of transition (as in medical gender-affirmation) or can be used as an adjective (as in gender-affirming care).

GENDER-AFFIRMATION SURGERY (GAS) is used to describe surgery to change primary and/or secondary sex characteristics to affirm a person's gender identity.

GENDER BINARY refers to the idea there are two and only two genders, men and women; the expectation that everyone must be one or the other; and that all men are males, and all women are females.

GENDER DIVERSE is a term used to describe people with gender identities and/or expressions that are different from social and cultural expectations attributed to their sex assigned at birth. This may include, among many other culturally diverse identities, people who identify as nonbinary, gender expansive, gender nonconforming, and others who do not identify as cisgender.

GENDER DYSPHORIA describes a state of distress or discomfort that may be experienced because a person's gender identity differs from that which is physically and/or socially attributed to their sex assigned at birth. Gender Dysphoria is also a diagnostic term in the DSM-5 denoting an incongruence between the sex assigned at birth and experienced gender accompanied by distress. Not all transgender and gender diverse people experience gender dysphoria.

GENDER EXPANSIVE is an adjective often used to describe people who identify or express themselves in ways that broaden the socially and culturally defined behaviors or beliefs associated with a particular sex. Gender creative is also sometimes used. The term gender variant was used in the past and is disappearing from professional usage because of negative connotations now associated with it.

GENDER EXPRESSION refers to how a person enacts or expresses their gender in everyday life and within the context of their culture and society. Expression of gender through physical appearance may include dress, hairstyle, accessories, cosmetics, hormonal and surgical interventions as well as mannerisms, speech, behavioral patterns, and names. A person's gender expression may or may not conform to a person's gender identity.

GENDER IDENTITY refers to a person's deeply felt, internal, intrinsic sense of their own gender.

GENDER INCONGRUENCE is a diagnostic term used in the ICD-11 that describes a person's marked and persistent experience of an incompatibility between that person's gender identity and the gender expected of them based on their birth-assigned sex.

INTERSEX refers to people born with sex or reproductive characteristics that do not fit binary definitions of female or male.

MISGENDER/MISGENDERING refers to when language is used that does not correctly reflect the gender with which a person identifies. This may be a pronoun (he/him/his, she/her/hers, they/them/theirs) or a form of address (sir, Mr.).

NONBINARY refers to those with gender identities outside the gender binary. People with nonbinary gender identities may identify as partially a man and partially a woman, or identify as sometimes a man and sometimes a woman, or identify as a gender other than a man or a woman, or as not having a gender at all. Nonbinary people may use the pronouns they/them/theirs instead of he/him/his or she/her/hers. Some nonbinary people consider themselves to be transgender or trans; some do not because they consider transgender to be part of the gender binary. The shorthand NB or "enby" is sometimes used as a descriptor for nonbinary. Examples of nonbinary gender identities are genderqueer, gender diverse, genderfluid, demigender, bigender, and agender.

RETRANSITION refers to second or subsequent gender transition whether by social, medical, or legal means. A retransition may be from one binary or nonbinary gender to another binary or nonbinary gender. People may retransition more than once. Retransition may occur for many reasons, including evolving gender identities, health concerns, family/societal concerns, and financial issues.

SEX ASSIGNED AT BIRTH refers to a person's status as male, female, or intersex based on physical characteristics. Sex is usually assigned at birth based on appearance of the external genitalia. AFAB is an abbreviation for "assigned female at birth." AMAB is an abbreviation for "assigned male at birth."

SEXUAL ORIENTATION refers to a person's sexual identity, attractions, and behaviors in relation to people on the basis of their gender(s) and or sex characteristics and those of their partners. Sexual orientation and gender identity are distinct terms.

TRANSGENDER or trans are umbrella terms used to describe people whose gender identities and/or gender expressions are not what is typically expected for the sex to which they were assigned at birth. These words should always be used as adjectives (as in "trans people") and never as nouns (as in "transgenders") and never as verbs (as in "transgendered").

TRANSGENDER MEN or **TRANS MEN** or **MEN OF TRANS EXPERIENCE** are people who have gender identities as men and who were assigned female at birth. They may or may not have undergone any transition. FTM or Female-to-Male are older terms that are falling out of use. **TRANSGENDER WOMEN** or **TRANS WOMEN** or **WOMEN OF TRANS EXPERIENCE** are people who have gender identities as women and who were assigned male at birth. They may or may not have undergone any transition. MTF or Male-to-Female are older terms that are falling out of use.

TRANSITION refers to the process whereby people usually change from the gender expression associated with their assigned sex at birth to another gender expression that better matches their gender identity. People may transition socially by using methods such as changing their name, pronoun, clothing, hair styles, and/or the ways that they

move and speak. Transitioning may or may not involve hormones and/or surgeries to alter the physical body. Transition can be used to describe the process of changing one's gender expression from any gender to a different gender. People may transition more than once in their lifetimes. **TRANSPHOBIA** refers to negative attitudes, beliefs, and actions concerning transgender and gender diverse people as a group. Transphobia may be enacted in discriminatory policies and practices on a structural level or in very specific and personal ways. Transphobia can also be internalized, when transgender and gender diverse people accept and reflect such prejudice about themselves or other transgender and gender diverse people. While transphobia sometimes may be a result of unintentional ignorance rather than direct hostility, its effects are never benign. Some people use the term anti-transgender bias in place of transphobia.

Appendix C GENDER-AFFIRMING HORMONAL TREATMENTS

Table 1. Expected time course of physical changes in response to gender-affirming hormone therapy

Testosterone Based Regimen		
Effect	Onset	Maximum
Skin Oiliness/acne	1–6 months	1–2 years
Facial/body hair growth	6–12 months	>5 years
Scalp hair loss	6–12 months	>5 years
Increased muscle mass/strength	6–12 months	2–5 years
Fat redistribution	1–6 months	2–5 years
Cessation of menses	1–6 months	1–2 years
Clitoral enlargement	1–6 months	1–2 years
Vaginal atrophy	1–6 months	1–2 years
Deepening of voice	1–6 months	1–2 years
Estrogen and testosterone-lowering based regimens		
Effect	Onset	Maximum
Redistribution of body fat	3–6 months	2–5 years
Decrease in muscle mass and strength	3–6 months	1–2 years
Softening of skin/decreased oiliness	3–6 months	Unknown
Decreased sexual desire	1–3 months	Unknown
Decreased spontaneous erections	1–3 months	3–6 months
Decreased sperm production	Unknown	2 years
Breast growth	3–6 months	2–5 years
Decreased testicular volume	3–6 months	Variable
Decreased terminal hair growth	6–12 months	> 3 years
Increased scalp hair	Variable	Variable
Voice changes	None	

Adapted from Hembree et al., 2017.

Table 2. Risks associated with gender affirming hormone therapy (bolded items are clinically significant) (Updated from SOC-7)

RISK LEVEL	Estrogen-based regimens	Testosterone-based regimens
Likely increased risk	Venous Thromboembolism Infertility Hyperkalemia ^a Hypertriglyceridemia Weight Gain	Polycythemia Infertility Acne Androgenic Alopecia Hypertension Sleep Apnea Weight Gain Decreased HDL Cholesterol and increased LDL Cholesterol
Likely increased risk with presence of additional risk factors	Cardiovascular Disease Cerebrovascular Disease Meningioma ^c Polyuria/Dehydration ^a Cholelithiasis	Cardiovascular Disease Hypertriglyceridemia
Possible increased risk	Hypertension Erectile Dysfunction	
Possible increased risk with presence of additional risk factors	Type 2 Diabetes Low Bone Mass/ Osteoporosis Hyperprolactinemia	Type 2 Diabetes Cardiovascular Disease
No increased risk or inconclusive	Breast and Prostate Cancer	Low Bone Mass/ Osteoporosis Breast, Cervical, Ovarian, Uterine Cancer

^ccyproterone-based regimen

^aspironolactone-based regimen

Table 3. Gender-Affirming Hormone Regimens In Transgender And Gender Diverse Youth (Adapted from the Endocrine Society Guidelines; Hembree et al., 2017)

Induction of female puberty (estrogen-based regimen) with oral 17β-estradiol	
Initiate at 5µg/kg/d and increase every 6 months by 5 µg/kg/d up to 20 µg/kg/d according to estradiol levels	Adult dose = 2-6 mg/day
In postpubertal TGD adolescents, the dose of 17β-estradiol can be increased more rapidly:	1 mg/d for 6 months followed by 2 mg/d and up according to estradiol levels
Induction of female puberty (estrogen-based regimen) with transdermal 17β-estradiol	
Initial dose 6.25-12.5 µg/24 h (cutting 24 g patch to ¼ then ½)	Titrate up by every 6 months by 12.5 µg/24 h according to estradiol levels
Adult dose = 50-200 µg/24 hours	For alternatives once at adult dose (Table 4)
Induction of male puberty (testosterone-based regimen) with testosterone esters	
25 mg/m ² /2 weeks (or alternatively half this dose weekly)	Increase by 25 mg/m ² /2 weeks every 6 months until adult dose and target testosterone levels are achieved. See alternatives for testosterone (Table 4)

Table 4. Hormone regimens in transgender and gender diverse adults*

Estrogen-based regimen (Transfeminine)	
Estrogen	
Oral or sublingual	
Estradiol	2.0-6.0 mg/day
Transdermal	
Estradiol transdermal patch	0.025-0.2 mg/day
Estradiol gel various	‡ daily to skin
Parenteral	
Estradiol valerate or cypionate	5-30 mg IM every 2 weeks 2-10 IM every week
Anti-Androgens	
Spironolactone	100–300 mg/day
Cyproterone acetate	10 mg/day**
GnRH agonist	3.75–7.50 mg SQ/IM monthly
GnRH agonist depot formulation	11.25/22.5 mg SQ/IM 3/6 monthly
‡ Amount applied varies to formulation and strength	
Testosterone-Based Regimen (Transmasculine)	
Transgender males	
Testosterone	
Parenteral	
Testosterone enanthate/ cypionate	50–100 IM/SQ weekly or 100–200 IM every 2 weeks
Testosterone undecanoate	1000 mg IM every 12 weeks or 750 mg IM every 10 weeks
Transdermal testosterone	
Testosterone gel	50-100 mg/day
Testosterone transdermal patch	2.5–7.5 mg/day

*Doses are titrated up or down until sex steroid hormone levels are in the therapeutic range. Hormone regimens do not reflect all formulations that are available in all pharmacies throughout the world. Hormone regimens may have to be adapted to what is available in local pharmacies.

**Kuijpers et al (2021).

Table 5. Hormone monitoring of transgender and gender diverse people receiving gender-affirming hormone therapy (Adapted from the Endocrine Society Guidelines)

Transgender male or trans masculine (including gender diverse/nonbinary) individuals

1. Evaluate patient approximately every 3 months (with dose changes) in the first year and 1 to 2 times per year thereafter to monitor for appropriate physical changes in response to testosterone.
2. Measure serum total testosterone every 3 months (with dose changes) until levels are at goal
 - a. For parenteral testosterone, the serum total testosterone should be measured midway between injections. The target level is 400-700ng/dL. Alternatively, measure peak and trough peaks to ensure levels remain in the range of reference men.
 - b. For parenteral testosterone undecanoate, testosterone should be measured just before injection. If the level is < 400ng/dL, adjust the dosing interval.
 - c. For transdermal testosterone, the testosterone level can be measured no sooner than after 1 week of daily application (at least 2 hours after application of product).
3. Measure hematocrit or hemoglobin concentrations at baseline and approximately 3 months (with dose changes) for the first year and then one to two times a year.

Transgender Female or trans feminine (including gender diverse/nonbinary) individuals

1. Evaluate patient approximately every 3 months (with dose changes) in the first year and one to two times per year thereafter to monitor for appropriate physical changes in response to estrogen.
 - a. Serum testosterone levels should be less than 50ng/dL.
 - b. Serum estradiol should be in the range of 100-200pg/mL.
 2. For individuals receiving spironolactone, serum electrolytes, in particular potassium, and kidney function, in particular creatinine, should be monitored.
 3. Follow primary care screening per primary care chapter recommendations
-

Appendix D SUMMARY CRITERIA FOR HORMONAL AND SURGICAL TREATMENTS FOR ADULTS AND ADOLESCENTS

The SOC-8 guidelines are intended to be flexible in order to meet the diverse health care needs of TGD people globally. While adaptable, they offer consensus-based standards derived from the best available scientific evidence for promoting optimal health care and guiding the treatment of people experiencing gender incongruence. As in all previous versions of the SOC, the criteria put forth in this document for gender affirming interventions are clinical guidelines; individual health care professionals and programs, in consultation with the TGD person, may modify them. Clinical departures from the SOC may occur due to a TGD person's unique anatomic, social, or psychological situation; an experienced health care professional's evolving method of handling a common situation; a research protocol; lack of resources in various parts of the world; or the need for specific harm-reduction strategies. These departures should be recognized as such, discussed with the TGD person, and documented. This documentation is also valuable for the accumulation of new data, which can be retrospectively examined to allow for health care—and the SOC—to evolve. This summary criteria needs to be read in conjunction with the relevant chapters (see Adult Assessment and Adolescent chapters).

SUMMARY CRITERIA FOR ADULTS

Related to the assessment process

- Health care professionals assessing transgender and gender diverse adults seeking gender-affirming treatment should liaise with professionals from different disciplines within the field of trans health for consultation and referral, if required*
- If written documentation or a letter is required to recommend gender affirming medical and surgical treatment (GAMST), only one letter of assessment from a health care professional who has competencies in the assessment of transgender and gender diverse people is needed.

Criteria for hormones

- a. Gender incongruence is marked and sustained;
- b. Meets diagnostic criteria for gender incongruence prior to gender-affirming hormone treatment in regions where a diagnosis is necessary to access health care;
- c. Demonstrates capacity to consent for the specific gender-affirming hormone treatment;
- d. Other possible causes of apparent gender incongruence have been identified and excluded;
- e. Mental health and physical conditions that could negatively impact the outcome of treatment have been assessed, with risks and benefits discussed;
- f. Understands the effect of gender-affirming hormone treatment on reproduction and they have explored reproductive options.

Criteria for surgery

- a. Gender incongruence is marked and sustained;
- b. Meets diagnostic criteria for gender incongruence prior to gender-affirming surgical intervention in regions where a diagnosis is necessary to access health care;
- c. Demonstrates capacity to consent for the specific gender-affirming surgical intervention;
- d. Understands the effect of gender-affirming surgical intervention on reproduction and they have explored reproductive options;
- e. Other possible causes of apparent gender incongruence have been identified and excluded;
- f. Mental health and physical conditions that could negatively impact the outcome of gender-affirming surgical intervention have been assessed, with risks and benefits have been discussed;
- g. Stable on their gender affirming hormonal treatment regime (which may include at least 6 months of hormone treatment or a longer period if required to achieve the desired surgical result, unless hormone therapy is either not desired or is medically contraindicated).*

*These were graded as suggested criteria

SUMMARY CRITERIA FOR ADOLESCENTS

Related to the assessment process

- A comprehensive biopsychosocial assessment including relevant mental health and medical professionals;
- Involvement of parent(s)/guardian(s) in the assessment process, unless their involvement is determined to be harmful to the adolescent or not feasible;
- If written documentation or a letter is required to recommend gender-affirming medical and surgical treatment (GAMST), only one letter of assessment from a member of the multidisciplinary team is needed. This letter needs to reflect the assessment and opinion from the team that involves both medical and mental health professionals (MHPs).

Puberty blocking agents

- a. Gender diversity/incongruence is marked and sustained over time;
- b. Meets the diagnostic criteria of gender incongruence in situations where a diagnosis is necessary to access health care;
- c. Demonstrates the emotional and cognitive maturity required to provide informed consent/assent for the treatment;
- d. Mental health concerns (if any) that may interfere with diagnostic clarity, capacity to consent, and gender-affirming medical treatments have been addressed; sufficiently so that gender-affirming medical treatment can be provided optimally.
- e. Informed of the reproductive effects, including the potential loss of fertility and the available options to preserve fertility;
- f. Reached Tanner stage 2.

Hormonal treatments

- a. Gender diversity/incongruence is marked and sustained over time;
- b. Meets the diagnostic criteria of gender incongruence in situations where a diagnosis is necessary to access health care;
- c. Demonstrates the emotional and cognitive maturity required to provide informed consent/assent for the treatment;
- d. Mental health concerns (if any) that may interfere with diagnostic clarity, capacity to consent, and gender-affirming medical treatments have been addressed; sufficiently so that gender-affirming medical treatment can be provided optimally.
- e. Informed of the reproductive effects, including the potential loss of fertility and the available options to preserve fertility;
- f. Reached Tanner stage 2.

Surgery

- a. Gender diversity/incongruence is marked and sustained over time;

- b. Meets the diagnostic criteria of gender incongruence in situations where a diagnosis is necessary to access health care;
- c. Demonstrates the emotional and cognitive maturity required to provide informed consent/assent for the treatment;
- d. Mental health concerns (if any) that may interfere with diagnostic clarity, capacity to consent, and gender-affirming medical treatments have been addressed; sufficiently so that gender-affirming medical treatment can be provided optimally.
- e. Informed of the reproductive effects, including the potential loss of fertility and the available options to preserve fertility;
- f. At least 12 months of gender-affirming hormone therapy or longer, if required, to achieve the desired surgical result for gender-affirming procedures, including breast augmentation, orchiectomy, vaginoplasty, hysterectomy, phalloplasty, metoidioplasty, and facial surgery as part of gender-affirming treatment unless hormone therapy is either not desired or is medically contraindicated.

S258  E. COLEMAN ET AL.**Appendix E GENDER-AFFIRMING SURGICAL PROCEDURES**

As the field's understanding of the many facets of gender incongruence expands, and as technology develops which

allows for additional treatments, it is imperative to understand this list is not intended to be exhaustive. This is particularly important given the often lengthy time periods between updates to the SOC, during which evolutions in understanding and treatment modalities may occur.

FACIAL SURGERY

Brow	<ul style="list-style-type: none"> • Brow reduction • Brow augmentation • Brow lift
Hair line advancement and/or hair transplant	
Facelift/mid-face lift (following alteration of the underlying skeletal structures)	
Facelift/mid-face lift (following alteration of the underlying skeletal structures)	<ul style="list-style-type: none"> • Platysmaplasty
Blepharoplasty	<ul style="list-style-type: none"> • Lipofilling
Rhinoplasty (+/- fillers)	
Cheek	<ul style="list-style-type: none"> • Implant • Lipofilling • Upper lip shortening • Lip augmentation (includes autologous and non-autologous) • Reduction of mandibular angle • Augmentation • Osteoplastic • Alloplastic (implant-based) • Vocal cord surgery (see voice chapter)
Lip	
Lower jaw	
Chin reshaping	
Chondrolaryngoplasty	
BREAST/CHEST SURGERY	
Mastectomy	<ul style="list-style-type: none"> • Mastectomy with nipple-areola preservation/reconstruction as determined medically necessary for the specific patient • Mastectomy without nipple-areola preservation/reconstruction as determined medically necessary for the specific patient
Liposuction	
Breast reconstruction (augmentation)	<ul style="list-style-type: none"> • Implant and/or tissue expander • Autologous (includes flap-based and lipofilling)
GENITAL SURGERY	
Phalloplasty (with/without scrotoplasty)	<ul style="list-style-type: none"> • With/without urethral lengthening • With/without prosthesis (penile and/or testicular) • With/without colectomy/colpocleisis
Metoidioplasty (with/without scrotoplasty)	<ul style="list-style-type: none"> • With/without urethral lengthening • With/without prosthesis (penile and/or testicular) • With/without colectomy/colpocleisis • May include retention of penis and/or testicle • May include procedures described as "flat front"
Vaginoplasty (inversion, peritoneal, intestinal)	
Vulvoplasty	
GONADECTOMY	
Orchiectomy	
Hysterectomy and/or salpingo-oophorectomy	
BODY CONTOURING	
Liposuction	
Lipofilling	
Implants	<ul style="list-style-type: none"> • Pectoral, hip, gluteal, calf
Monsplasty/mons reduction	
ADDITIONAL PROCEDURES	
Hair removal: Hair removal from the face, body, and genital areas for gender affirmation or as part of a preoperative preparation process. (see Statement 15.14 regarding hair removal)	<ul style="list-style-type: none"> • Electrolysis • Laser epilation
Tattoo (i.e., nipple-areola)	
Uterine transplantation	
Penile transplantation	

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<https://www.wsj.com/articles/u-s-becomes-transgender-care-outlier-as-more-in-europe-urge-caution-6c70b5e0>

POLITICS

U.S. Becomes Transgender-Care Outlier as More in Europe Urge Caution

Republicans seize on European doubts over medical interventions to call for restrictions

By *Jathon Sapsford* [Follow](#) and *Stephanie Armour* [Follow](#)

June 19, 2023 at 12:01 am ET



A transgender flag was worn at a Pride festival in Georgia last year. PHOTO: ROBIN RAYNE/ZUMA PRESS

WASHINGTON—The U.S. is becoming an outlier among many Western nations in the way its national medical institutions treat children suffering from distress over gender identity.

For years, the American healthcare industry has staunchly defended medical interventions for transgender minors, including puberty blockers, which suppress the physical changes of adolescence as a treatment for those distressed over their gender.

The European medical community, by contrast, is expressing doubts about that approach. Having allowed these treatments for years, five countries—the U.K., Sweden, Finland, Norway and France—now urge caution in their use for minors, stressing a lack of evidence

that the benefits outweigh the risks. This month, the U.K.'s publicly funded National Health Service limited the use of puberty blockers to clinical trials, putting the drugs beyond the reach of most children.

“These countries have done systematic reviews of evidence,” said Leor Sapir, a fellow who studies transgender care at the conservative-leaning Manhattan Institute think tank. “They’ve found that the studies cited to support these medical interventions are too unreliable, and the risks are too serious.”

Many countries still allow puberty blockers as a clinical option, including Canada, Spain and Australia. Some in those countries also are urging curtailment. In Italy, for example, the president of the Italian Psychoanalytic Society wrote a public letter to the Italian prime minister in January expressing “serious concerns” over the use of puberty blockers.

In a congressional hearing last week, GOP politicians and their expert witnesses repeatedly cited European examples of increased caution and portrayed Democrats and the U.S. medical community as having gone too far in making treatments readily available for minors.

“It’s beneficial to see European countries coming to their senses,” said Rep. Dan Crenshaw, (R., Texas) in an interview after citing U.K. systematic evidentiary reviews of puberty blockers in last week’s hearing. In a sign that Republicans plan to make transgender-care issues a 2024 campaign theme, Crenshaw said at the hearing: “This is the issue of our time. This is a hill we’re gonna die on.”

Republican Rep. Dan Crenshaw says, 'It's beneficial to see European countries coming to their senses' on puberty blockers. PHOTO: TOM WILLIAMS/ZUMA PRESS

Democrats say Republicans are attacking transgender youth to score political points and are backing dangerous bans and restrictions on treatments that will cause children harm.

“They are telling parents that Republican politicians know better than they do what is best for their child,” said Rep. Frank Pallone Jr., (D., N.J.) at the hearing last week. “This is the height of hypocrisy from a group that supposedly believes in limited government.”

A recent poll by the Washington Post and KFF, an independent polling and research firm, showed 68% opposed to the use of puberty blockers in children ages 10 to 14. The poll, published in May, was conducted late last year.

Since then, well over a dozen GOP-run states have issued restrictions on medical interventions as part of transgender care. Health providers in Texas, for example, risk losing their medical licenses if they provide puberty blockers, surgeries or hormone treatments to most transgender minors under a GOP-led law that goes into effect in September.

The U.S. medical community hasn't wavered in its support for medical interventions and continues to recommend puberty blockers and hormones for minors as a clinical option. Unlike the concerns expressed by many authorities in Europe, U.S. medical associations often treat the science behind such medical interventions as settled.

Last week, delegates at the annual meeting of the American Medical Association endorsed a resolution—co-sponsored by the American Academy of Pediatrics, the American Association of Clinical Endocrinology and others—that reiterated support for access to medical interventions, saying that GOP claims about transgender care “do not reflect the

research landscape.”

Other states, reflecting Democratic priorities, are welcoming transgender minors seeking such treatments. Last week, New York introduced new public-school guidance that allowed teachers to keep secret a child’s social transition, in which students change their name or pronouns to reflect an identity other than the gender at birth.

Some students “have not talked to their families about their gender identity because of safety concerns or lack of acceptance and may begin their transition at school without parent/guardian knowledge,” the guidance said.

Some Republicans say parents should be involved. “Parents are the people who are best positioned to make these judgments,” said former New Jersey governor and 2024 Republican presidential candidate Chris Christie, speaking on CNN’s “State of the Union” on Sunday. Christie called for states to ensure “parental involvement at every step along the way.”

Puberty blockers were once embraced by many countries, becoming the international standard with the “Dutch Protocol,” when clinicians in the mid-1990s pioneered the use of drugs to suppress estrogen and testosterone. Their use delays breast growth, the widening of hips, and menstruation in women. In males, they suppress the growth of facial hair and deeper voices.

Some 98% of adolescents who began puberty blockers before the age of 18 continued to use cross-sex hormones into adulthood, based on a 2022 study from the Netherlands. That has some critics saying that, rather than allowing a patient to outgrow the confusions that come with puberty, it locks children into feelings of being the wrong gender.

The U.S. Food and Drug Administration approved puberty blockers in 1993 for children going through puberty at an unusually early age. But the FDA hasn’t approved puberty blockers to treat gender dysphoria, the distress felt over a conflict between a child’s gender identity and the sex recorded at birth.

Given as a shot or an implant, the drugs can lead to less development of genital tissue, complicating future gender-transition surgeries. Other side effects may include hot flashes, weight gain, headaches, decreased bone density and mood changes. They may also affect

later fertility.

Write to Jathon Sapsford at jathon.sapsford@wsj.com and Stephanie Armour at Stephanie.Armour@wsj.com

From: [Blaise Trettis](#)
To: [BOM Public Comment](#)
Subject: Boards should adopt nonemergency rules which delete the previous rules of the Boards which grandfathered-in the ability of physicians to prescribe puberty blockers and cross sex hormones to children
Date: Friday, June 16, 2023 4:17:24 PM
Attachments: [Outlook-ana5qkfp.png](#)

You don't often get email from btrettis@pd18.net. [Learn why this is important](#)

EXTERNAL EMAIL: DO NOT CLICK links or open attachments unless you recognize the sender and know the content is safe.

Dear Board of Medicine (BOM) and Board of Osteopathic Medicine (BOOM):

I understand that the Boards are working quickly on emergency rules which the legislature directed the Boards to promulgate in Ch. 2023-90 Laws of Florida (CS/SB 254). My comment is directed to what the Boards should do after the emergency rules have been promulgated and are in effect. Ch. 2023-90 Laws of Florida amended section 456.52 Florida statute by adding this sentence at subparagraph (6)(b): "Any emergency rules adopted under this section are exempt from s. 120.54(4)(c) and shall remain in effect until replaced by rules adopted under the nonemergency rulemaking procedures of the Administrative Procedure Act." I submit that the BOM and BOOM should adopt nonemergency rules which terminate the emergency rules being adopted now. Additionally, the nonemergency rules should delete part (2) of rules 64B8-9.019 and 64B15-14.014, both of which are titled, "Standards of Practice for the Treatment of Gender Dysphoria in Minors." Part (2) of these rules reads: "Minors being treated with puberty blocking, hormone, or hormone antagonist therapies prior to the effective date of this rule may continue with such therapies." The effect of repealing the emergency rules now being promulgated and part (2) of the aforementioned rules would be to terminate physicians' administration of these drugs to children who were grandfathered-in by the rules to continue to take these harmful drugs. The BOM and BOOM have the authority to repeal these rules notwithstanding the direction by the legislature in Ch. 2023-90 to promulgate emergency rules. The BOM and BOOM did not have any legislature directive to adopt its rules which ended the surgical mutilation of children in the name of transgenderism and which ended puberty blocker drugs and cross-sex hormones prescribed for children. Nothing in Ch. 2023-90 Laws of Fla. should be read to mean that the legislature wishes the BOM and BOOM to end its independent judgment in adopting rules relating to the harmful practice of MD's and DO's prescribing puberty blocker drugs and cross-sex hormones to children.

I personally appeared at the joint meeting of the BOM and BOOM on October 28, 2022, at the Orlando International Airport at which the Boards decided to grandfather-in children currently taking these harmful drugs. What was amazing to me about this decision was that there was no discussion, at all, by the Boards in making this decision. A single member of one of the Boards, I don't know who, simply said the conclusory statement that children who are currently taking these drugs should be allowed to continue taking them because discontinuing the drugs could be harmful. No Board member explained how it could be harmful to a child to discontinue taking these harmful, powerful, drugs. No Board member made any response to this one conclusory statement by a single Board member. I would challenge any member of

the BOM and BOOM to articulate reasons why a child should be allowed to take these drugs which are not approved by the FDA for treatment of gender dysphoria, and for which the FDA, less than one year ago, issued its warning that puberty blocker drugs administered to children cause serious health effects including tumor-like masses in the brain, impairment of brain development, visual disturbances, headache, vomiting, papilledema (swelling of optic nerve), increased blood pressure, and abducens neuropathy (eye paralysis). See "FDA Slaps Warning on Puberty Blockers," by Joshua Arnold, July 28, 2022; https://www.dailysignal.com/2022/08/05/fda-slaps-warning-on-puberty-blockers/?utm_source=TDS_Email&utm_campaign=top5.

By allowing children to continue to take puberty blocker drugs and cross-sex hormones, the BOM and BOOM are increasing the suicide rate of these children. See "Puberty Blockers, Cross-Sex Hormones, and Youth Suicide," The Heritage Foundation, June 13, 2022, by Jay P. Greene, PhD. See <http://report.heritage.org/bg3712>. The two conclusions of this study were: 1) studies finding that sex-change interventions prevent suicide fail to show a causal relationship and have been poorly executed; 2) a superior research design shows that easing access to puberty blockers and cross-sex hormones by minors increases suicide rate.

I recommend that the BOM and BOOM apply cost versus benefit analysis to the question of whether the Boards should allow MD's and DO's to continue to prescribe these harmful drugs to children. On the cost side of this analysis are these costs: The serious, harmful, medical consequences from the drugs described in the FDA's warning described above; increased rate of suicide by children taking these harmful drugs as described in the Heritage Foundation study above; medical sterilization of these children caused by taking puberty blocker drugs followed by cross sex hormones.

On the benefit side of the cost versus benefit analysis is this: there is no benefit to children from taking these harmful drugs. There is also no negative consequence resulting from discontinuing the taking of these harmful drugs. Up to 90% of children who have gender dysphoria will resolve their gender confusion and come to accept their natural sex by adulthood when they do not take puberty blocker drugs and cross-sex hormones.

I respectfully submit that the BOM and BOOM should re-visit their decision to adopt rules which grandfathered-in the ability of MD's and DO's to prescribe these harmful drugs to children. Some of these children may be as young as ten years old and younger, which means that they will be taking these harmful drugs for seven or eight more years or longer. The current rules of the Boards and the emergency rules being promulgated guarantee that these children will become medically sterilized, will commit suicide at a higher rate, and will suffer very serious health consequences. If the BOM and BOOM do not undertake the repeal these rules, then Board members should state on the record their reasons why it is in the best medical/health interest of children to be allowed to take these harmful drugs. In short, the Board members should offer some (any) justification for the rules that they have adopted to date. No justification has been offered to this point in time.

Sincerely,



Blaise Trettis

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64B8-9.019 Standards of Practice for the Treatment of Gender Dysphoria in Minors.

(1) The following therapies and procedures performed for the treatment of gender dysphoria in minors are prohibited.

(a) Sex reassignment surgeries, or any other surgical procedures, that alter primary or secondary sexual characteristics.

(b) Puberty blocking, hormone, and hormone antagonist therapies.

(2) Minors being treated with puberty blocking, hormone, or hormone antagonist therapies prior to the effective date of this rule may continue with such therapies.

Rulemaking Authority 458.331(1)(v) FS. Law Implemented 458.331(1)(v) FS. History--New 3-16-23.

64B15-14.014 Standards of Practice for the Treatment of Gender Dysphoria in Minors.

(1) The following therapies and procedures performed for the treatment of gender dysphoria in minors are prohibited.

(a) Sex reassignment surgeries, or any other surgical procedures, that alter primary or secondary sexual characteristics.

(b) Puberty blocking, hormone, and hormone antagonist therapies.

(2) Minors being treated with puberty blocking, hormone, or hormone antagonist therapies prior to the effective date of this rule may continue with such therapies.

Rulemaking Authority 459.015(1)(z) FS. Law Implemented 459.015(1)(z) FS. History—New 3-28-23.

CHAPTER 2023-90

Committee Substitute for Senate Bill No. 254

An act relating to treatments for sex reassignment; amending s. 61.517, F.S.; granting courts of this state temporary emergency jurisdiction over a child present in this state if the child has been subjected to or is threatened with being subjected to sex-reassignment prescriptions or procedures; amending s. 61.534, F.S.; providing that, for purposes of warrants to take physical custody of a child in certain child custody enforcement proceedings, serious physical harm to the child includes, but is not limited to, being subjected to sex-reassignment prescriptions or procedures; creating s. 286.31, F.S.; defining the term “governmental entity”; prohibiting certain public entities from expending state funds for the provision of sex-reassignment prescriptions or procedures; amending s. 456.001, F.S.; defining the terms “sex” and “sex-reassignment prescriptions or procedures”; creating s. 456.52, F.S.; prohibiting sex-reassignment prescriptions and procedures for patients younger than 18 years of age; providing an exception; requiring the Board of Medicine and the Board of Osteopathic Medicine to adopt certain emergency rules within a specified timeframe; requiring the boards to consider specified factors in developing such rules; requiring that such prescriptions and procedures for patients older than 18 years of age be prescribed, administered, or performed only with the voluntary and informed consent of the patient; providing criteria for what constitutes voluntary and informed consent; providing that only a physician may prescribe, administer, or perform such prescriptions and procedures; defining the term “physician”; providing applicability; providing for disciplinary action; providing criminal penalties; requiring the Board of Medicine and the Board of Osteopathic Medicine to adopt certain emergency rules; providing that such emergency rules remain in effect until they are replaced by nonemergency rules; amending s. 456.074, F.S.; requiring the department to immediately suspend the license of a health care practitioner who is arrested for committing or attempting, soliciting, or conspiring to commit specified violations related to sex-reassignment prescriptions or procedures for a patient younger than 18 years of age; creating s. 766.318, F.S.; creating a cause of action to recover damages for personal injury or death resulting from the provision of sex-reassignment prescriptions or procedures to a minor; providing that certain limitations on punitive damages do not apply to such actions; specifying the timeframe within which such actions may be commenced; providing construction and applicability; providing severability; providing a directive to the Division of Law Revision; providing an effective date.

Be It Enacted by the Legislature of the State of Florida:

Section 1. Subsection (1) of section 61.517, Florida Statutes, is amended to read:

61.517 Temporary emergency jurisdiction.—

(1) A court of this state has temporary emergency jurisdiction if the child is present in this state and:

(a) The child has been abandoned; ~~or~~

(b) It is necessary in an emergency to protect the child because the child, or a sibling or parent of the child, is subjected to or threatened with mistreatment or abuse; or

(c) It is necessary in an emergency to protect the child because the child has been subjected to or is threatened with being subjected to sex-reassignment prescriptions or procedures, as defined in s. 456.001.

Section 2. Subsection (1) of section 61.534, Florida Statutes, is amended to read:

61.534 Warrant to take physical custody of child.—

(1) Upon the filing of a petition seeking enforcement of a child custody determination, the petitioner may file a verified application for the issuance of a warrant to take physical custody of the child if the child is likely to imminently suffer serious physical harm or removal from this state. Serious physical harm includes, but is not limited to, being subjected to sex-reassignment prescriptions or procedures as defined in s. 456.001.

Section 3. Section 286.31, Florida Statutes, is created to read:

286.31 Prohibited use of state funds.—

(1) As used in this section, the term “governmental entity” means the state or any political subdivision thereof, including the executive, legislative, and judicial branches of government; the independent establishments of the state, counties, municipalities, districts, authorities, boards, or commissions; and any agencies that are subject to chapter 286.

(2) A governmental entity, a public postsecondary educational institution as described in s. 1000.04, the state group health insurance program, a managing entity as defined in s. 394.9082, or a managed care plan providing services under part IV of chapter 409 may not expend state funds as described in s. 215.31 for sex-reassignment prescriptions or procedures as defined in s. 456.001.

Section 4. Subsections (8) and (9) are added to section 456.001, Florida Statutes, to read:

456.001 Definitions.—As used in this chapter, the term:

(8) “Sex” means the classification of a person as either male or female based on the organization of the human body of such person for a specific reproductive role, as indicated by the person’s sex chromosomes, naturally

occurring sex hormones, and internal and external genitalia present at birth.

(9)(a) “Sex-reassignment prescriptions or procedures” means:

1. The prescription or administration of puberty blockers for the purpose of attempting to stop or delay normal puberty in order to affirm a person’s perception of his or her sex if that perception is inconsistent with the person’s sex as defined in subsection (8).

2. The prescription or administration of hormones or hormone antagonists to affirm a person’s perception of his or her sex if that perception is inconsistent with the person’s sex as defined in subsection (8).

3. Any medical procedure, including a surgical procedure, to affirm a person’s perception of his or her sex if that perception is inconsistent with the person’s sex as defined in subsection (8).

(b) The term does not include:

1. Treatment provided by a physician who, in his or her good faith clinical judgment, performs procedures upon or provides therapies to a minor born with a medically verifiable genetic disorder of sexual development, including any of the following:

a. External biological sex characteristics that are unresolvably ambiguous.

b. A disorder of sexual development in which the physician has determined through genetic or biochemical testing that the patient does not have a normal sex chromosome structure, sex steroid hormone production, or sex steroid hormone action for a male or female, as applicable.

2. Prescriptions or procedures to treat an infection, an injury, a disease, or a disorder that has been caused or exacerbated by the performance of any sex-reassignment prescription or procedure, regardless of whether such prescription or procedure was performed in accordance with state or federal law.

3. Prescriptions or procedures provided to a patient for the treatment of a physical disorder, physical injury, or physical illness that would, as certified by a physician licensed under chapter 458 or chapter 459, place the individual in imminent danger of death or impairment of a major bodily function without the prescription or procedure.

Section 5. Section 456.52, Florida Statutes, is created to read:

456.52 Sex-reassignment prescriptions and procedures; prohibitions; informed consent.—

(1) Sex-reassignment prescriptions and procedures are prohibited for patients younger than 18 years of age, except that:

(a) The Board of Medicine and the Board of Osteopathic Medicine shall, within 60 days after the effective date of this act, adopt emergency rules pertaining to standards of practice under which a patient younger than 18 years of age may continue to be treated with a prescription consistent with those referenced under s. 456.001(9)(a)1. or 2. if such treatment for sex reassignment was commenced before, and is still active on, the effective date of this act. In developing rules under this paragraph, the boards shall consider requirements for physicians to obtain informed consent from such patient's parent or legal guardian, consistent with the parameters of informed consent under subsections (2) and (4), for such prescription treatment, and shall consider the provision of professional counseling services for such patient by a board-certified psychiatrist licensed under chapter 458 or chapter 459 or a psychologist licensed under chapter 490 in conjunction with such prescription treatment.

(b) A patient meeting the criteria of paragraph (a) may continue to be treated by a physician with such prescriptions according to rules adopted under paragraph (a) or nonemergency rules adopted under paragraph (6)(b).

(2) If sex-reassignment prescriptions or procedures are prescribed for or administered or performed on patients 18 years of age or older, consent must be voluntary, informed, and in writing on forms adopted in rule by the Board of Medicine and the Board of Osteopathic Medicine. Consent to sex-reassignment prescriptions or procedures is voluntary and informed only if the physician who is to prescribe or administer the pharmaceutical product or perform the procedure has, at a minimum, while physically present in the same room:

(a) Informed the patient of the nature and risks of the prescription or procedure in order for the patient to make a prudent decision;

(b) Provided the informed consent form, as adopted in rule by the Board of Medicine and the Board of Osteopathic Medicine, to the patient; and

(c) Received the patient's written acknowledgment, before the prescription or procedure is prescribed, administered, or performed, that the information required to be provided under this subsection has been provided.

(3) Sex-reassignment prescriptions or procedures may not be prescribed, administered, or performed except by a physician. For the purposes of this section, the term "physician" is defined as a physician licensed under chapter 458 or chapter 459 or a physician practicing medicine or osteopathic medicine in the employment of the Federal Government.

(4) Consent required under subsection (2) does not apply to renewals of prescriptions consistent with those referenced under s. 456.001(9)(a)1. and

2. if a physician and his or her patient have met the requirements for consent for the initial prescription or renewal. However, separate consent is required for any new prescription for a pharmaceutical product not previously prescribed to the patient.

(5)(a) Violation of this section constitutes grounds for disciplinary action under this chapter and chapter 458 or chapter 459, as applicable.

(b) Any health care practitioner who willfully or actively participates in a violation of subsection (1) commits a felony of the third degree, punishable as provided in s. 775.082, s. 775.083, or s. 775.084.

(c) Any health care practitioner who violates subsection (2), subsection (3), or subsection (4) commits a misdemeanor of the first degree, punishable as provided in s. 775.082 or s. 775.083.

(6)(a) The Board of Medicine and the Board of Osteopathic Medicine shall adopt emergency rules to implement this section.

(b) Any emergency rules adopted under this section are exempt from s. 120.54(4)(c) and shall remain in effect until replaced by rules adopted under the nonemergency rulemaking procedures of the Administrative Procedure Act.

Section 6. Present paragraphs (c) through (gg) of subsection (5) of section 456.074, Florida Statutes, are redesignated as paragraphs (d) through (hh), respectively, and a new paragraph (c) is added to that subsection, to read:

456.074 Certain health care practitioners; immediate suspension of license.—

(5) The department shall issue an emergency order suspending the license of any health care practitioner who is arrested for committing or attempting, soliciting, or conspiring to commit any act that would constitute a violation of any of the following criminal offenses in this state or similar offenses in another jurisdiction:

(c) Section 456.52(5)(b), relating to prescribing, administering, or performing sex-reassignment prescriptions or procedures for a patient younger than 18 years of age.

Section 7. Section 766.318, Florida Statutes, is created to read:

766.318 Civil liability for provision of sex-reassignment prescriptions or procedures to minors.—

(1) A cause of action exists to recover damages for personal injury or death resulting from the provision of sex-reassignment prescriptions or procedures, as defined in s. 456.001, to a person younger than 18 years of age which are prohibited by s. 456.52(1).

(2) The limitations on punitive damages in s. 768.73(1) do not apply to actions brought under this section.

(3) An action brought under this section:

(a) May be commenced within 20 years after the cessation or completion of the sex-reassignment prescription or procedure.

(b) Is in addition to any other remedy authorized by law.

(4) The cause of action created by this section does not apply to:

(a) Treatment with sex-reassignment prescriptions if such treatment is consistent with s. 456.001(9)(a)1. or 2. and was commenced on or before, and is still active on, the effective date of this act.

(b) Sex-reassignment prescriptions or procedures that were ceased or completed on or before the effective date of this act.

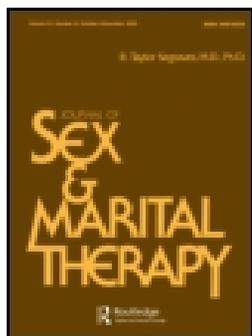
Section 8. If any provision of this act or its application to any person or circumstance is held invalid, the invalidity does not affect other provisions or applications of this act which can be given effect without the invalid provision or application, and to this end the provisions of this act are severable.

Section 9. The Division of Law Revision is directed to replace the phrase “the effective date of this act” wherever it occurs in this act with the date this act becomes a law.

Section 10. This act shall take effect upon becoming a law.

Approved by the Governor May 17, 2023.

Filed in Office Secretary of State May 17, 2023.



Journal of Sex & Marital Therapy

ISSN: (Print) (Online) Journal homepage: <https://www.tandfonline.com/loi/usmt20>

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To cite this article: E. Abbruzzese, Stephen B. Levine & Julia W. Mason (2023): The Myth of “Reliable Research” in Pediatric Gender Medicine: A critical evaluation of the Dutch Studies—and research that has followed, *Journal of Sex & Marital Therapy*, DOI: [10.1080/0092623X.2022.2150346](https://doi.org/10.1080/0092623X.2022.2150346)

To link to this article: <https://doi.org/10.1080/0092623X.2022.2150346>



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Published online: 02 Jan 2023.



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The Myth of “Reliable Research” in Pediatric Gender Medicine: A critical evaluation of the Dutch Studies—and research that has followed

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ABSTRACT

Two Dutch studies formed the foundation and the best available evidence for the practice of youth medical gender transition. We demonstrate that this work is methodologically flawed and should have never been used in medical settings as justification to scale this “innovative clinical practice.” Three methodological biases undermine the research: (1) subject selection assured that only the most successful cases were included in the results; (2) the finding that “resolution of gender dysphoria” was due to the reversal of the questionnaire employed; (3) concomitant psychotherapy made it impossible to separate the effects of this intervention from those of hormones and surgery. We discuss the significant risk of harm that the Dutch research exposed, as well as the lack of applicability of the Dutch protocol to the currently escalating incidence of adolescent-onset, non-binary, psychiatrically challenged youth, who are preponderantly natal females. “Spin” problems—the tendency to present weak or negative results as certain and positive—continue to plague reports that originate from clinics that are actively administering hormonal and surgical interventions to youth. It is time for gender medicine to pay attention to the published objective systematic reviews and to the outcome uncertainties and definable potential harms to these vulnerable youth.

Introduction

In our recent paper on informed consent for youth gender transition, we recognized a serious problem: the field has a penchant for exaggerating what is known about the benefits of the practice, while downplaying the serious health risks and uncertainties (Levine et al., 2022a). As a result, a false narrative has taken root. It is that “gender-affirming” medical and surgical interventions for youth are as benign as aspirin, as well-studied as penicillin and statins, and as essential to survival as insulin for childhood diabetes—and that the vigorous scientific debate currently underway is merely “science denialism” motivated by ignorance, religious zeal, and transphobia (Drescher et al., 2022; McNamara et al., 2022; Turban, 2022). This highly politicized and fallacious narrative, crafted and promoted by clinician-advocates, has failed to withstand scientific scrutiny internationally, with public health authorities in Sweden, Finland, and most recently England doing a U-turn on pediatric gender transitions in the last 24 months (COHERE

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This article has been corrected with minor changes. These changes do not impact the academic content of the article.

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(Council for Choices in Health Care), 2020; Socialstyrelsen [National Board of Health and Welfare], 2022; National Health Service (NHS), 2022a). In the U.S., however, medical organizations so far have chosen to use their eminence to shield the practice of pediatric “gender affirmation” from scrutiny. In response to mounting legal challenges, these organizations have been exerting their considerable influence to insist the science is settled (American Medical Association (AMA), 2022). We argued that this stance stifles scientific debate, threatens the integrity and validity of the informed consent process—and ultimately, hurts the very patients it aims to protect.

To demonstrate problems in existing research, we discussed two seminal studies that gave rise to the now-common practice of performing gender transitions on young people by giving them puberty blockers, cross-sex hormones, and “gender-affirming” surgery (de Vries et al., 2011; de Vries et al., 2014). We argued that these Dutch studies suffer from such profound limitations that they should never have been used as justification for propelling these interventions into general medical practice. We called for rigorous clinical research into the interventions known as “gender-affirming” care before these interventions are further scaled. Until such research is available, we urged clinicians to disclose the profound uncertainties regarding the outcomes of this treatment pathway to enable patients and families to make better-informed decisions about their care.

Our assertions drew a response from the first author of these Dutch studies (de Vries, 2022).¹ de Vries dismissed much of our criticism as a mere “misunderstanding” of their gender clinic’s process. While de Vries acknowledged some of the limitations in the Dutch research, she asserted that these gaps have since been sufficiently remedied by subsequent research from others in the field, rendering the practice of pediatric gender transition as proven beneficial, and ready to be widely scaled in general medical practice.

Having carefully examined de Vries’ counterarguments, we failed to find a single instance where our “misunderstanding” could explain away the significant problems that we pointed out. In this article, we justify our position that neither the Dutch research, nor the research that followed, is fit for shaping policy or treatment decisions regarding gender dysphoric youth at the population level. We present our response to de Vries in three sections. *First*, we provide a more complete justification for our assertions of the significant flaws in the foundational Dutch research. *Second*, we demonstrate that the claims that subsequent research remedied the deficiencies in the prior research are untrue. *Third*, we provide recommendations for research structure to yield reliable, trustworthy information. We conclude with a sense of urgency to avoid future harms by reminding readers of the intrinsic value of high-quality science.

Before we embark on outlining the critical methodological limitations of the Dutch research, we would like to make it clear that it is not our intention to discredit the Dutch clinicians’ past work. The quality of the Dutch studies, while unacceptably low by today’s standards, is commensurate with clinical and research practices in the 1990s. The key problem in pediatric gender medicine is not the lack of research rigor in the *past*—it is the field’s *present-day* denial of the profound problems in the existing research, and an unwillingness to engage in high quality research requisite in evidence-based medicine.

Evidence-based medicine vs empirical-based medicine

When the Dutch clinicians launched the practice of pediatric gender transition, it was not uncommon for medical professionals to practice medicine based on “empirical evidence,” relying on expert opinion and often backed by only minimal research (Drisko & Friedman, 2019). The term “evidence-based medicine” and its focus on quality comparative clinical research to determine optimal treatment only emerged in the 1990s (Guyatt, 1993). The Dutch researchers began to medically transition gender dysphoric adolescents in the late 1980s–early 1990s—just as medicine was starting to undergo this major paradigm shift.

Examining the Dutch research from today’s vantage point, their gender-transitioning of youth is most consistent with the “innovative practice” framework. This framework allows clinicians

to implement untested but promising interventions for a condition which, if left untreated, might have dire outcomes; when existing treatment options seem ineffective; and when the number of affected patients is small (Brierley & Larcher, 2009; Earl, 2019). The number of adolescents suffering from gender dysphoria in the 1990s was exceedingly small. Evidence was starting to demonstrate that gender reassignment undertaken in adulthood failed to resolve trans people's mental health problems (Cohen-Kettenis & Van Goozen, 1997). The Dutch clinicians hoped that the "less positive results among adults" (p. 266) would be remedied with early adolescent gender transition. In this context, the methodological deficiencies in the foundational Dutch research ought not to be viewed as a *failure*. It was never their goal to generate *reliable reproducible research*. In fact, the many irregularities, which we elucidate below, reflect the Dutch *success* at rapidly evolving their approaches to reach a point of *technical excellence*: convincing physical transformations of adolescent bodies that satisfied the young patients (Biggs, 2022). These clinicians were "flying the plane while building the plane," and their published research merely reflects this messy clinical reality.

The "innovative practice" model of care is a double-edged sword. On the one hand, it rapidly advances the medical field. On the other hand, it is capable of hurting individuals and societies by promoting a nonbeneficial or harmful intervention. For these reasons, it is an ethical requirement that as soon as viability of a new intervention is demonstrated under the "innovative practice" framework, the research must move into high-quality clinical research settings capable of demonstrating that the benefits outweigh the risks. This step is imperative because it prevents "runaway diffusion"—the phenomenon whereby the medical community mistakes a small innovative experiment as a proven practice, and a potentially nonbeneficial or harmful practice "escapes the lab," rapidly spreading into general clinical settings (Earl, 2019).

"Runaway diffusion" is exactly what has happened in pediatric gender medicine. "Affirmative treatment" with hormones and surgery rapidly entered general clinical practice worldwide, without the necessary rigorous clinical research to confirm the hypothesized robust and lasting psychological benefits of the practice. Nor was it ever demonstrated that the benefits were substantial enough to outweigh the burden of lifelong dependence on medical interventions, infertility and sterility, and various physical health risks. The studies also failed to quantify the risk to "false positives"—that is, those gender dysphoric youth whose distress would have remitted with time without resorting to irreversible medical and surgical interventions.

The speed of the "runaway diffusion" accelerated exponentially when pediatric gender dysphoria/transgender identity went from a relatively rare phenomenon before 2015, to one that impacts as many as 1 in 10–20 young people in the Western world (American College Health Association [ACHA], 2022; Johns et al., 2019; Kidd et al. 2021). The current politicization of transgender healthcare has provided further fuel to the rapid proliferation of youth gender reassignment. A proposal by the U.S. government to mandate healthcare entities to provide "gender-affirming" interventions to minors, or risk claims of "discrimination" and loss of federal healthcare funding is yet another example of "runaway diffusion" (Health and Human Services [HHS], 2022; Keith, 2022).

The difficult task of reversing runaway diffusion begins with a systematic review of evidence, follows with updating treatment guidelines, and culminates with de-implementation of unproven or harmful practices, known as "practice reversals" (Herrera-Perez et al., 2019; Prasad, 2011; Prasad & Ioannidis, 2014). *Systematic reviews of evidence* play a uniquely important role in this process. Rather than arbitrarily selecting studies and simply restating their results and conclusions, systematic reviews of evidence analyze *all of the available evidence* meeting pre-specified criteria and *scrutinize the studies* for methodological bias and errors, issuing an overarching conclusion about what's known about the effects of an intervention based on the totality of the evidence (Higgins et al., 2022). A "practice reversal" of pediatric gender transitions has already begun. Several recent international systematic reviews of evidence have concluded that the practice of pediatric gender transition rests on *low to very low quality evidence*—meaning that the benefits reported by the existing studies are unlikely to be true due to profound problems in the study designs (National

Institute for Health and Care Excellence (NICE), 2020a, 2020b; Pasternack et al., 2019; SBU (Swedish Agency for Health Technology Assessment and Assessment of Social Services), 2022). Following these systematic reviews of evidence, three European countries—Sweden, Finland and England—have begun to articulate new and much more cautious treatment guidelines for gender dysphoric youth, which prioritize noninvasive psychosocial interventions while sharply restricting the provision of hormones and surgery (COHERE (Council for Choices in Health Care), 2020; Socialstyrelsen [National Board of Health and Welfare], 2022; NHS, 2022a).

Paradoxically, this international reckoning has had almost no influence on the U.S. gender medicine establishment. When Florida’s Medical Board, following an overview of existing systematic reviews (Brignardello-Peterson & Wiercioch, 2022), took on the question of regulating pediatric gender medicine and invited the proponents of pediatric gender transitions to reconcile their stance with the recent European developments, these clinician advocates were either unaware of the European changes, or minimized their extent and significance (Janssen, 2022 00:46:43; McNamara, 2022 01:45:27). More generally, when faced with questions about the rapidly growing numbers of youth subjected to highly invasive and often irreversible interventions based on *low to very low quality evidence*, the field of U.S. pediatric gender medicine has chosen to throw its weight behind two indefensible and contradictory claims: (1) that “low quality evidence” is a misleading technical term which actually describes high quality reliable research; and (2) that true high quality research can only come from randomized placebo-controlled trials, which are unattainable and unethical (Drescher, 2022; McNamara et al., 2022). We refuted these misleading claims in our recent publication (Levine et al., 2022b).

As we begin our discussion of the profound limitations in the two foundational Dutch studies that have propelled the practice of pediatric gender transition into mainstream clinical practice worldwide, we are aware that we are mounting a serious challenge to the research that has been viewed by many as the “gold standard” in the field. Questioning this assumption, we welcome further debate. A quote from philosopher Karl Popper, perceptively invoked by Balon (2022), is particularly apt: “the growth of knowledge depends entirely on disagreement.”

I. The “Dutch studies” are deeply flawed

There is no argument that the Dutch experience, and in particular two Dutch studies—de Vries et al. (2011), and de Vries et al. (2014)—forms the foundation of the practice of youth gender transition. It is evident when examining prevailing treatment guidelines. The Endocrine Society’s statements regarding the potential benefits of puberty blockers and cross-sex hormones in gender dysphoric adolescents are supported only by references to these two studies (Hembree et al., 2017, p. 12, p. 16). Similarly, the World Professional Association for Transgender Health (WPATH) “Standards of Care” guidelines version 7 (SOC 7)—the version under which the practice of medicalization of gender dysphoric youth became widespread—only references the Dutch experience (Coleman et al., 2012). Despite several newer studies available, the proponents of gender affirmation still correctly emphasize that “the best longitudinal data we have on transgender youth comes primarily out of the Dutch clinic...the Dutch studies in the Dutch model of care. That’s the prevailing model that most of the American clinics have based their care upon” (Janssen, 2022, 00:47:42). de Vries in her response to us, also agrees with this: “...indeed, as of today, the Dutch papers, and especially the de Vries et al., 2014 study, are still used as main evidence for provision of early medical intervention including puberty blockers in transgender youth (de Vries et al., 2014)” (de Vries, 2022, p. 2).

The two main Dutch studies in question, de Vries et al., 2011, and de Vries et al., 2014 (from here on, “the Dutch studies”) convincingly demonstrated that hormonal and surgical interventions can successfully change the phenotypical appearance of secondary sex characteristics of adolescents and young adults. What the studies *failed* to show, however, is that these physical changes resulted in meaningful psychological improvements significant enough to justify the adverse effects of the treatment—including the *certainty* of sterility.

Besides the lack of a control group and a small final sample of 55 cases, with key outcomes available for as few as 32 individuals, there are *three major areas of concern* that render these studies unfit for clinical or policy decision-making.

- A. **High risk of bias:** The Dutch studies suffer from multiple sources of bias which undermine confidence into the reported “benefits.” The subject selection assured that only the most successful cases at each treatment stage were included in reported results. The linchpin finding of “resolution of gender dysphoria” is entirely invalid, since the home-grown gender dysphoria scale and its scoring mechanism were reversed after treatment, essentially guaranteeing a significant post-surgical drop in “gender dysphoria” scores. The finding of modest psychological benefits was compromised by the conflation of medical interventions with psychotherapy, making it impossible to determine whether gender reassignment, therapy, or the psychological maturation that occurs with the passage of time led to these few modest “improvements.”
- B. **Incompleteness of evidence regarding physical health risks:** The Dutch studies did not evaluate *physical health* outcomes of “gender-affirmative” treatments, even though adverse effects of hormonal interventions on bone and brain had been hypothesized from the start (and were confirmed by subsequent research). Even without setting out to assess the risks, the Dutch research inadvertently revealed that the rate of short-term morbidity and mortality associated with “gender-affirming” interventions may be as high as 6%-7%.
- C. **Poor generalizability/applicability to current cases:** Today, most youth suffer from post-pubertal onset of gender dysphoria and significant mental illness—two clinical presentations the Dutch *explicitly disqualified* from their studies. As such, none of the Dutch findings are applicable to most of the youth seeking treatment today.

de Vries (2022) disputed only our assertion that the studies suffer from *high risk of bias* and therefore their findings of benefits are unreliable. She did not comment on our arguments that the research *failed to assess physical health risks* and *were not generalizable* to the majority of currently presenting cases. It is unclear if this silence indicates agreement or disagreement. Below, we address each of our points in greater detail, concluding with an additional observation about the overall lack of equipoise—genuine uncertainty about which treatment options are superior (London, 2017), which limits the utility of the Dutch research beyond describing a small-scale “innovative practice.”

A. High risk of bias in the Dutch research

de Vries rejected our assertion that the Dutch findings suffer from a high risk of bias and insisted that we mistook the study protocol’s careful process of establishing study eligibility for “bias.” To clarify, we use the term “risk of bias” in a strict methodological sense. It refers to a systematic error, or deviation from the “truth” in study results (Boutron et al., 2022; Socialstyrelsen [National Board of Health and Welfare], 2022). Observational research conducted in the context of ongoing clinical care is often subject to risk of bias (Nguyen et al., 2021), which is one of the main reasons why rigorous clinical research using robust research designs must follow. In the case of the Dutch studies, we identified three major sources of bias, or systematic error, involving: (1) case selection; (2) measurement of outcomes; and (3) confounding.

1. Bias in case selection: Only the “best-case scenario” cases made it into the Dutch studies’ “completers”

Because of an unusual case selection and reporting methodology, the Dutch studies inadvertently reported on only their best-case outcomes at each of the three phases of treatment (puberty blockers, cross-sex hormones, and surgery)—while failing to report the outcomes of the less positively affected, or even harmed, cases. de Vries disagreed with this assertion, continuing to insist that “participation was based on consecutive referral” (de Vries, 2022, p. 4).

Below, we present evidence that the claim of consecutive referral-based *prospective case selection* is not technically accurate. The actual case selection for the original sample of 70 puberty-blocked cases (de Vries et al., 2011) was *retrospective* and inadvertently biased toward including cases with favorable outcomes. The outcome reporting methodology in the second and final Dutch study (de Vries et al., 2014), which evaluated the final outcomes post-surgery, further biased the results toward reporting on the most favorable cases.

de Vries et al., 2011 (“puberty blocker” study). The 70 cases comprising the entire sample for the “puberty blocker” study (de Vries et al., 2011) were *retrospectively, non-randomly selected* from a larger group of consecutively referred 111 cases. According to both the original study, and de Vries’ response to us, to participate in the “puberty blocker” study, a study subject already had to be starting the *next phase* of treatment with cross-sex hormones:

Of the 196 consecutively referred adolescents...111 (those below age 16) had started puberty suppression... In the 2011 study we evaluated the first 70 of those 111 who were about to start with the next step of their treatment, affirming hormones, around the age of 16 years. (de Vries, 2022, p. 4)²

Using the start date of the *next phase* of treatment (cross-sex hormones) as the defining inclusion criterion for the study of the *prior phase* of the treatment (puberty blockers) introduced serious bias.

First, had any of the original 111 study subjects been harmed by puberty blockers or chosen to stop the treatment, they would never have advanced to the next phase, and thus, they had no chance of being included in the puberty blocker study, skewing the sample. *Second*, since the Dutch considered the puberty suppression phase both a treatment and a *diagnostic phase* (Cohen-Kettenis & van Goozen, 1998), the more complex cases may have remained in the puberty blocked phase longer. As de Vries’ predecessors explained, subjects for whom the psychotherapist or parents had doubts, or where “the personal situation of the youngster” was more complicated, were delayed from starting cross-sex hormone treatment, which was the first stage the Dutch researchers considered to have an “irreversible” effect (Gooren & Delemarre-van de Waal, 1996, p. 11). This would further skew “the first 70 of those 111 who were about to start with the next step of their treatment, affirming hormones” (de Vries, 2022, p. 4)—the entire puberty blocker study sample—toward the most clinically straightforward and stable cases.

Third, such an unusual case selection methodology may have skewed the sample toward an older age than was stipulated by the protocol. Since to be eligible for the “puberty blocker” study, a subject had to have been deemed ready to start the next phase of cross-sex hormones, which *required a minimum age of 16* (according to the Dutch protocol version published in 2012, de Vries, 2012), all else being equal, older subjects had a greater chance of being included than younger ones. This may explain why the sample of 70 selected subjects was on average, age 15 when started on puberty blockers rather than age 12 as outlined by the protocol, which introduced another source of systematic error, by biasing the sample toward subjects with greater physical and cognitive maturity.

Given that the 2011 Dutch study’s main goal was to evaluate the novel use of *puberty blockers* for gender dysphoria in a prospective cohort study (de Vries et al., 2011), the study should have enrolled, and reported the outcomes of, *all of the intent to treat* cases based on the date of eligibility to start *puberty suppression*—not cross-sex hormones.

It is notable that the only attempt to replicate the 2011 Dutch study results with more than a handful of cases took place in the UK but failed (Carmichael et al., 2021), with the conclusion of “no changes in psychological function” (p. 1). We suspect the key reason for this failure was the fact that the UK researchers truly *prospectively* selected “sequentially eligible” cases for treatment (Carmichael et al., 2021, p. 4) and as a result, ended with a diverse range of outcomes, including worsening of problems among female subjects during puberty blockade (Biggs, 2020). In contrast, the Dutch *retrospective* case selection methodology (misunderstood as prospective) inadvertently resulted in skewing the sample toward the best-case-scenario puberty-blocked cases. In our view, such case selection methodology invalidates the 2011 study conclusions of

psychological benefits of puberty suppression—or, as research methodologists would say, puts this finding at a “critical risk of bias.”

de Vries et al, 2014 (post-surgery study). Skewing the sample toward the best-case scenario cases is even more apparent in the 2014 study, which reported on post-surgical outcomes and assessed the entire “gender-affirmative” treatment pathway (de Vries et al., 2014). The 70 participants who began the 2014 study, already biased toward more positive outcomes, shrank to 55. Fifteen subjects were dropped from the study and relabeled “nonparticipants.” This subset, however, was not random, but instead heavily skewed toward subjects who experienced serious problems, including 3 who developed severe diabetes and obesity and 1 death following surgical complications. There is also considerable uncertainty about the outcomes of the 5 of 70 subjects (refusal, failure to return questionnaire, and dropping out of care) who, after several years of close contact with the research team, were unwilling to engage further:

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 (e.g., *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* [emphasis added]. (de Vries et al., 2014, p. 697)

In her response, de Vries repeated the assertion that because a statistical comparison of the 15 “nonparticipants” to the 55 “participants” revealed no significant difference in their *pretreatment* baseline characteristics, “the results of the 2014 study can be generalized with substantial trust to the complete group of 70” (de Vries, 2022, pp. 4–5). We strongly disagree. The “participant” and “nonparticipant” cohorts are demonstrably different: while 100% of the 55 “participants” had successful gender reassignment according to the study reporting, at least 27% of the “nonparticipant” group (4/15: 1 death and 3 cases of diabetes) did not. Not only is a statistical analysis of such small subgroups massively underpowered to detect differences, **no** statistical analysis of *pretreatment* data suggesting “similarity” can negate the reality of the markedly different *post-treatment* outcomes in two groups. Nor is it clear why the research team made the unusual decision to stop the study early, before the remaining 6 participants had a chance to complete the 1-year post-surgical follow-up.

The “missing” Dutch study on the effect of cross-sex hormones. The second and final Dutch study (de Vries et al., 2014) combined the cross-sex hormone and post-surgical treatment results into a single set of outcomes. This conflation may have made some sense at the time, as all the hormonally-treated patients were *required* to undergo surgery (removal of breasts, ovaries, uterus, penis, testes, and construction of a neovagina) by the protocol. When surgery is not required, only 25–35% of transgender-identified adults appear to seek “gender-affirming” surgical procedures (Nolan et al., 2019). According to recently published data, this number is even smaller for youth: for every teen treated surgically, there are 15 treated *only* with cross-sex hormones (Respaut & Terhune, 2022). The inability of the Dutch research to elucidate the outcomes of cross-sex hormone treatments (separate from surgery) has been noted by NICE, which appropriately excluded the 2014 Dutch study from its systematic review of evidence (NICE, 2020b).

It is unknown whether the 4.3% of the sample (n=3) that experienced obesity and diabetes sometime before the surgery was a result of the hormonal treatment; this rate appears to be double the expected rate for pediatric populations in the Netherlands at the time (Rotteveel et al., 2007; Schönbeck et al., 2011). Nor is it known if the cross-sex hormones contributed to the one subject who discontinued treatment due to other medical or psychological problems. Other research suggest that testosterone may actually *increase* dysphoria in female gender-dysphoric individuals (Olson-Kennedy, Warus, et al., 2018).

2. Bias in measurement of outcomes: The finding of “resolution of gender dysphoria” is invalid

The linchpin result of the Dutch studies is the reported *resolution of gender dysphoria*, as measured by the Utrecht Gender Dysphoria Scale (UGDS) (Steensma, Kreukels, et al., 2013). de

Vries agreed with us on this point: “the main finding remains the resolution of gender dysphoria” (de Vries, 2022, p. 3). According to the final Dutch study, the UGDS *gender dysphoria* scores plummeted, from a near-maximum score of 54 (maximum of 60) at baseline, to the near-minimum score of 16 (minimum of 12) after the final surgery (de Vries et al., 2014).

Rather than a true “resolution” of *gender dysphoria*, however, this spectacular drop was an artifact of switching the scale from “female” to “male” versions (and vice versa) before and after treatment, prompting a problematic *reversal* in the scoring. We argued that this fact alone invalidates the study’s main conclusion of the resolution of gender dysphoria (Levine et al., 2022a). While de Vries conceded the use of the UGDS scale post-treatment was “not ideal” because “the UGDS was not...designed to be used after treatment,” she asserted that it “does not imply that UGDS ‘falsely’ measured the improvement in GD [gender dysphoria]” (de Vries, 2022, p. 4). We think it is vitally important for the scientific community to recognize that the UGDS scale use was not merely “not ideal”—but that it *entirely invalidated* the Dutch study’s main finding.

The following hypothetical scenario clearly demonstrates the problem. A severely gender dysphoric, cross-sex identified female patient is asked to answer two of the UGDS questions: “Every time someone treats me like a girl I feel hurt” and “Every time someone treats me like a boy I feel hurt” (Items 2 on the “female” and the “male” versions of the UGDS scale, respectively). It is likely that the patient would *strongly agree* with the first statement, and *strongly disagree* with the second. The first answer would lead to the score of “5” on the UGDS gender dysphoria scale, indicating the highest possible level of gender dysphoria. The second answer—which is effectively the same answer—would result in the score of “1” indicating the lowest possible gender dysphoria. This is because unlike the first question, which belongs to the “female” battery of questions, the second question belongs to the “male” battery of questions and effectively assumes the subject to be male—hence, the lack of distress of being associated with “maleness” receives the minimum “gender dysphoria” score.

If we now consider that only the “female” scale was used for gender dysphoric females at baseline but was then switched to the “male” scale after the final surgery (and vice-versa for male subjects), it becomes clear that the remarkable drop in “gender dysphoria” the UGDS scale registered after surgery entirely results from switching the scale. The *same* gender dysphoric individual, effectively answering the *same* question (albeit linguistically inverted), in the *same* way results in either the maximum or the minimum “gender dysphoria” score—depending on which sexed version of the scale was used. We reproduced both the “male” and the “female” versions of the UGDS scale in Table 1 so that others can easily observe how switching the scale “sex” version consistently leads to a “drop” of the gender dysphoria score, regardless of any treatment effect.

When defending the choice to reverse the UGDS scale (de Vries, 2022), de Vries pointed out—and we agree—that it would make no sense to ask postoperative natal males to rate a statement such as “I dislike having erections” (Table 1, UGDS-M, item 11), since they no longer have penises. We empathize with the Dutch researchers’ plight, as they found themselves without a valid tool to measure the construct of “gender dysphoria” after treatment. It is equally nonsensical, however, to ask natal males to rate statements such as, “I hate menstruating because it makes me feel like a girl” (Table 1, UGDS-F, item 10)—and it makes even less sense to report “resolution of gender dysphoria” because they don’t “hate menstruating.”

In her response, de Vries pointed to the validation research of the UGDS dysphoria scale (de Vries, 2022; Steensma, Kreukels, et al., 2013). To the best of our knowledge, this work has never appeared in a peer-reviewed publication. In our opinion, this UGDS validation research missed a key opportunity to identify the threat to validity of using the UGDS scale in post-gender reassignment context, which should have become apparent to the Dutch research team by 2013 when the validation paper was published. The greater community of international gender clinicians relying on the Dutch pioneering experience was not alerted to the need to find another instrument that can provide a valid pre-post “gender dysphoria” measure. Instead, the validation

Table 1. Utrecht Gender Dysphoria Scale, Adolescent Version (de Vries, Cohen-Kettenis, & Delemarre-van de Waal, 2006). Response categories are *agree completely, agree somewhat, neutral, disagree somewhat, disagree completely*.

UGDS-F (female)	UGDS-M (male)
Response categories are: agree completely, agree somewhat, neutral, disagree somewhat, disagree completely. Items 1, 2, 4–6 and 10–12 are scored from 5 to 1; items 3 and 7–9 are scored from 1 to 5.	Response categories are: agree completely, agree somewhat, neutral, disagree somewhat, disagree completely. Items are all scored from 5 to 1.
1. I prefer to behave like a boy.	1. My life would be meaningless if I would have to live as a boy.
2. Every time someone treats me like a girl I feel hurt.	2. Every time someone treats me like a boy I feel hurt.
3. I love to live as a girl.	3. I feel unhappy if someone calls me a boy.
4. I continuously want to be treated like a boy.	4. I feel unhappy because I have a male body.
5. A boy's life is more attractive for me than a girl's life.	5. The idea that I will always be a boy gives me a sinking feeling.
6. I feel unhappy because I have to behave like a girl.	6. I hate myself because I'm a boy.
7. Living as a girl is something positive for me.	7. I feel uncomfortable behaving like a boy, always and everywhere.
8. I enjoy seeing my naked body in the mirror.	8. Only as a girl my life would be worth living.
9. I like to behave sexually as a girl.	9. I dislike urinating in a standing position.
10. I hate menstruating because it makes me feel like a girl.	10. I am dissatisfied with my beard growth because it makes me look like a boy.
11. I hate having breasts.	11. I dislike having erections.
12. I wish I had been born as a boy.	12. It would be better not to live than to live as a boy.

research buttressed the problematic practice of using UGDS to measure the level of gender dysphoria after gender reassignment by stating: “From follow-up studies it was already known that gender dysphoria, as measured by the UGDS, disappeared post gender reassignment. These qualities make the instrument useful for clinical and research purposes” (Steensma, Kreukels, et al., 2013, p. 56). This statement is misleading, as the finding of the “disappearance” of gender dysphoria post-gender reassignment in the past “follow-up” research came from studies that also switched the sexed scale versions post-treatment, as Dr. de Vries pointed out in her response to us (de Vries, 2022).

Thus, in a spectacular display of circular reasoning, the scale validation research claimed that the follow-up research endorsed the use of the inverted UGDS scale version post gender reassignment, while the follow-up research defended this unusual practice by pointing to the validation research. de Vries doubled down on this circular reasoning in her response to our critique (de Vries, 2022):

Levine et al. (2022) questions whether the improvement in gender dysphoria does then not stem from this switching, and not from the treatment? However, this seems turning the matter around. What the measure shows, the disappearance or resolution of gender dysphoria, is what the gender affirming treatment is aimed to resolve. (pp. 3–4)

At least three research groups noted the critical threat to the validity of the finding of “resolution of gender dysphoria” due to the switching of the scale (Biggs, 2022; McGuire et al., 2020; van de Grift et al., 2017). McGuire et al. (2020) explicitly stated, “Because the original UGDS is composed of two scales, it is impossible to determine if this is a real difference in gender dysphoria between groups or if this is an artifact of measurement error (p. 195).

The likely meaning of the “plummeting” gender dysphoria scores. What, if anything, did the “plummeting” gender dysphoria scores post scale-flipping signal, if not the “disappearance of gender dysphoria” claimed by the Dutch researchers? We posit that the UGDS scale can only measure the construct which it was originally designed and validated to measure—the level of incongruence between natal sex and gender identity leading to the provision of the DSM diagnosis (Cohen-Kettenis & van Goozen, 1997; Iliadis et al., 2020; Steensma, Kreukels, et al., 2013). This is true whether the scale is used before or after treatment, and whether the “treatment” in question is “gender-affirmation” with hormones and surgeries, psychotherapy, or mere “watchful waiting,” with the scale administered at various time points.

The fact that after gender reassignment, the UGDS scores were low on the opposite-sex scale indicates that the subjects would have scored high on the natal sex scale, which corresponds to a *persistence in transgender identity*. This is the only plausible interpretation of the “plummeting” UGDS scores that survives in the context of the scale questions and the linguistic and numerical gymnastics the scale underwent in the post-gender-reassignment context. The finding of persistence of transgender identity is not unexpected, especially since the Dutch researchers selected subjects with lifelong extreme cross-sex identification and follow-up was only 1.5 years post-surgery. What it does *not* mean is that the feeling of “incongruence” resolved. This point is underscored by the long-term follow-up data on male-to-female Dutch transitioners, presented at the WPATH 2022 Symposium by Dr. van der Meulen (Steensma et al., 2022). Nearly a quarter of the participants have felt that their bodies were still too masculine, and over half have experienced shame for the “operated vagina” and fearful their partner will find out their post-surgical status—despite registering low “gender dysphoria” UGDS scores (Steensma et al., 2022).

3. Bias from confounding: Psychotherapy was comingled with medical interventions

Although the Dutch research is frequently commended for having demonstrated “psychological improvements,” an examination of the outcomes reveals that standard measures of psychological functioning such as anxiety, depression, anger, and global function showed very little clinically significant change after treatment (Levine et al., 2022a). de Vries acknowledged that a number of psychological measures showed no meaningful change, but insisted that the “more robust” measures, such as Child Behavior Check List (CBCL) and Youth Self Report (YSR), *did* show clinically relevant changes (de Vries, 2022, p. 3). She also noted that post-intervention, the sample of gender dysphoric youth in the Dutch research functioned at a similarly high level as their non-dysphoric peers, which was also an indicator of success. We have three observations about this response.

First, the impressive drop in the percentage of cases in the “clinical” range for CBCL and YSR (de Vries et al., 2014) was only apparent after *dichotomizing* these scales into the “clinical” (problematic) versus “non-clinical” ranges. In comparison, the sample’s *average* post-intervention score changes on these scales were much more modest. For example, while the 2014 Dutch study points out that the “percent in the clinical range dropped from 30% to 7% on the YSR/ASR,” which looks like an impressive reduction, the *average* t-scores had a modest drop of from 54.72 before treatment, to 48.53 after surgery (de Vries et al., 2014, p. 702). Further, both before and after t-scores were less than 60—typically interpreted as having no clinically significant symptoms (Achenbach & Rescorla, 2001). This suggests the reported improvements in CBCL and YSR came from relatively small score changes, which are of limited clinical significance, even if in the process the clinical threshold is crossed for some cases.

Second, while de Vries points to the *post-treatment* similarity in function of the gender-dysphoric group to the general population as evidence of treatment success, it is not known how different the groups were from the general population *pretreatment*. According to earlier research by Cohen-Kettenis and van Goozen (1997), which presumably utilized similar selection criteria, “when both pre- and posttest group means were compared with Dutch normative data, *all scores turned out to be within the average range* [emphasis added]” (p. 269). Smith et al. (2001) confirm this and explicitly state that both pretreatment and post-treatment, the group of gender dysphoric youth selected for the interventions were “normal functioning” as compared to their age peers in the Netherlands (Smith et al., 2001, p. 477). If the sample used in the two Dutch studies, which was recruited several years later but used the same careful case selection criteria, bears resemblance to the sample described by this earlier Dutch research, then the reported post-treatment similarities in psychological function between the “treated” group and the general population of peers should not be attributed to gender reassignment.

Third, and perhaps most relevant to this discussion, is the question of whether *any* of the reported changes in post-treatment psychological function scores, clinically significant or not, can be reasonably attributed to gender reassignment—or if these changes were influenced by confounding factors not accounted for in the research design. As noted by the authors of the

CBCL and YSR scales that de Vries says she favors, “improvement in scores from before to after services does not prove that the services were responsible for improvement. Other explanations are possible, such as (a) children’s problems tend to decrease as they get older; (b) the people providing the data may report improvements because they believe that the services helped, and (c) the test-retest attenuation effect (a general tendency for people to report fewer problems at a second assessment)” (Achenbach & Rescorla, 2001, p. 183).

In addition to the general sources of confounding in uncontrolled studies relying on “before and after” measures, a vital source of confounding in the Dutch studies has been hiding in plain sight: All the subjects received psychotherapy at the same time they were undergoing gender reassignment. This comingling of interventions makes it impossible to determine which of the interventions “worked.”

Psychotherapy was a key element in the Dutch protocol. Contrary to the now-common but erroneous assertion by the U.S. gender medicine establishment that psychotherapy for gender dysphoria is akin to “conversion” and should be avoided or even banned (Cantor, 2020), the Dutch studies reveal that psychotherapy was a key element of the protocol. According to the Dutch protocol, “[i]n cases involving confusion about gender feelings, psychotherapy and peer support can be helpful in *resolving the confusion and coming to self-acceptance* [emphasis added]” (de Vries, Cohen-Kettenis & Delemarre-van de Waal, 2006, p. 87). Not only was psychotherapy thought to be beneficial, but apparently it was a core part of the intervention: “...the adolescents were all regularly seen by one of the clinic’s psychologists or psychiatrists. Psychological or social problems could thus be timely addressed” (de Vries et al., 2011, p. 2281). The researchers acknowledge that psychotherapy “...may have contributed to the psychological well-being of these gender dysphoric adolescents” (de Vries et al., 2011, p. 2281).

A discussion of the utility of psychotherapy to ameliorate gender dysphoria and related psychological distress is outside the scope of this article, other than to point out that the results of at least two studies suggest that psychological interventions are associated with improvements in two of the outcome domains—*gender dysphoria* (van de Grift et al., 2017) and *global function* (Costa et al., 2015)—absent any medical interventions.

B. Incompleteness of evidence regarding risks

Failure to consider the physical health risks of “gender-affirming” endocrine and surgical interventions is another methodological weakness of the Dutch studies. This omission is surprising since the Dutch team hypothesized that hormonal interventions might adversely impact bone and brain development several years before their seminal studies commenced (Delemarre-van de Waal & Cohen-Kettenis, 2006, p. 134). As discussed earlier, the Dutch studies did, however, report on the cases that were reclassified from “participants” to “non-participants,” and listed the reasons for the nonparticipation, which revealed a possible 6–7% rate of associated adverse events.

Several studies since have confirmed likely adverse health effects of hormonal interventions, although their long-term impact on future health is not yet known. Research suggests that youth treated with puberty blockers develop problems with bone density accrual (Biggs, 2021; Nokoff et al., 2022) and that bone density may be impaired even after treatment with cross-sex hormones is initiated (Klink et al., 2015). Other research suggests heightened insulin resistance (Nokoff et al., 2021), elevated blood pressure, elevated triglycerides, and impaired liver function (Olson-Kennedy, Okonta, et al., 2018). Cross-sex hormone administration places adolescents in the medical category of early life indicators of future cardiovascular disease (Jacobs et al., 2022).

These adverse changes, already evident after a relatively short period of hormonal interventions, do not bode well for long-term health, since “gender-affirming” hormones are prescribed with the presumption of ongoing, lifelong treatment essential for maintaining a masculinized or feminized appearance. It is likely that other medical risks will emerge in the future. Patients and their families cannot make informed decisions about a treatment when the physical health

risks are assumed to be minimal and not reported, and only the potential psychological benefits are considered.

C. Poor generalizability/applicability to currently presenting cases

Given the dramatic change in the epidemiology of youth gender dysphoria which occurred after the studies were published (Levine et al., 2022a), the question of the applicability of the Dutch research to the current clinical dilemmas is one of the most important questions to interrogate in the field of pediatric gender medicine today.

Generalizability/applicability questions whether “available research evidence can be directly used to answer the health and healthcare question at hand” (Schünemann et al., 2022). We asserted and continue to assert that the Dutch studies are not applicable/generalizable to most gender dysphoric youth presenting today. This is evidenced by two facts: (1) the most common profile of youth seeking gender transition today is an adolescent with postpubertal emergence of a transgender identity and significant uncontrolled mental health comorbidities; (2) the Dutch researchers explicitly disqualified such patients from their studies because of their concern that the risks of early gender transition might outweigh the benefits.

1. Most of today’s adolescents have postpubertal onset of trans identity and comorbid mental illness

Until about a decade ago, most patients seen by gender clinics were very young boys who wished to be girls and most of these children subsequently lost their cross-sex identification before reaching adulthood (Hembree et al., 2017; Ristori & Steensma, 2016; Singh et al., 2021). Today, the majority are female adolescents (de Graaf et al., 2018; Kaltiala-Heino et al., 2018; Zhang et al., 2021) with previously gender-normative childhoods whose trans identity emerged around or after puberty (Hutchinson et al., 2020; Zucker, 2019). Many suffer from significant preexisting mental illness such as depression and anxiety or neurocognitive challenges such as autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD) (Becerra-Culqui et al., 2018; de Graaf et al., 2021; Kaltiala-Heino et al., 2015; Kozłowska et al., 2021; Strang et al., 2018; Thrower et al., 2020).

The presentation of adolescent-onset gender dysphoria is not entirely new—what’s new is its scale. As with many trends, the change occurred “gradually, then suddenly.” While there was evidence of it in the mid-2000s, around 2014–2015 the presentation of pediatric gender dysphoria in the Western world sharply shifted, from childhood-onset that skewed toward males, to adolescent-onset with a preponderance of females with mental health problems (Aitken et al., 2015; de Graaf et al., 2018). The Dutch researchers began their experiments with pediatric gender transition well before this demographic shift began to dominate clinical presentations of youth gender dysphoria.

Finland’s national pediatric gender program was among the first to sound the alarm regarding the changing epidemiology of gender dysphoria presentation in youth. In 2015, they began observing that the youth presenting for treatment were primarily females who “do not fit the commonly accepted image of a gender dysphoric minor” (Kaltiala-Heino et al., 2015). The Finnish researchers saw a new pattern of “severe psychopathology preceding onset of gender dysphoria,” with 75% already in treatment for other psychiatric issues when their gender dysphoria emerged. By 2019, the Finnish gender program was in full-alarm mode: “Research on adolescent onset gender dysphoria is scarce, and optimal treatment options have not been established... The reasons for the sudden increase in treatment-seeking due to adolescent onset gender dysphoria/transgender identification are not known” (Kaltiala-Heino & Lindberg, 2019, p. 62). This changing epidemiology was noted by other Nordic countries as well (Kaltiala, Bergman, et al., 2020).

The novel presentation of youth gender dysphoria was also reported by the largest pediatric gender clinic in the world at the time, the UK’s GIDS/Tavistock (de Graaf et al., 2018). The now-famous graph of the GIDS data shows a trickle of gender dysphoric youth in years past

turning into a tidal wave by 2015, with a significant overrepresentation of teen girls. Between 2009 and 2016, the number of gender dysphoric females increased more than 70 times (de Graaf et al., 2018). The UK researchers concluded:

The steep increase in birth-assigned females seeking help from gender services across the age range highlights an emerging phenomenon. It is important to follow birth-assigned females' trajectories, to better understand the changing clinical presentations in gender-diverse children and adolescents and to monitor the influence of social and cultural factors that impact on their psychological well-being. (de Graaf et al., 2018, p. 4)

The number of gender dysphoric youth referrals in the UK doubled again between 2020–2021 and 2021–2022 (NHS, 2022b).

While U.S. population-level data are hard to come by due to the country's decentralized and highly fragmented health care system, recent research shows that the number of gender dysphoric teens has also sharply risen in recent years, with a nearly 70% increase just between 2020 and 2021 (Respaut & Terhune, 2022). Combined with U.S. medical chart data samples, which show that the composition of the population changed “from predominantly transfeminine to...predominantly transmasculine in children and adolescents” (Zhang et al., 2021, p. 390) and that over 70% of gender dysphoric youth had been diagnosed with ASD, ADHD and other mental health problems *before* their diagnosis of gender dysphoria (Becerra-Culqui et al., 2018), it is apparent that the U.S. has not been immune to this remarkable epidemiologic trend that has engulfed youth in the Western world.

This now-ubiquitous presentation of gender dysphoria in troubled adolescents with previously gender-normative childhoods lacks a DSM-5-TR descriptor (American Psychiatric Association [APA], 2022), leaving clinicians to refer to it by many names, including *adolescent-onset gender dysphoria*; *postpuberty adolescent-onset transgender history*; and *rapid-onset gender dysphoria (ROGD)*. The latter term was introduced by a U.S. researcher (Littman, 2018). Despite the controversy that Littman's hypotheses generated in the gender medicine establishment (Marchiano, 2018), her research withstood a second round of rigorous peer review (Littman, 2020). Subsequent detransitioner research lent further support to the ROGD hypothesis, with patients themselves reporting “that their gender dysphoria began during or after puberty and that mental health issues, trauma, peers, social media, online communities, and difficulty accepting themselves as lesbian, gay, or bisexual were related to their gender dysphoria and desire to transition” (Littman, 2021, p. 15). Even WPATH, which in 2018 strongly objected to Littman's research (WPATH, 2018), conceded in its 2022 “Standards of Care 8” that while no one has attempted to replicate Littman's research, it is apparent that “[f]or a select subgroup of young people, susceptibility to social influence impacting gender may be an important differential to consider” (Coleman et al., 2022, p. S45).

The novel phenomenon of high numbers of young people declaring a transgender identity for the first time in adolescence, often in the context of preexisting mental illness and/or trauma and social difficulties, has been described by several other mental health clinicians (Hutchinson et al., 2020; Schwartz, 2021; Zucker 2019). The only exception to the trend of mentally struggling adolescents presenting with gender dysphoria is the Amsterdam gender clinic itself, which has also seen an influx of teens and the preponderance of girls, but apparently without the mental health problems (Arnoldussen et al., 2020). Nonetheless, writing for the American journal *Pediatrics*, de Vries recognized the emergence of this new clinical phenomenon, noting that “gender identity development is diverse, and a new developmental pathway is proposed involving youth with postpuberty adolescent-onset transgender histories” (de Vries, 2020, p. 1) and noting that “some case histories illustrate the complexities that may be associated with later-presenting transgender adolescents and describe that some eventually detransition (de Vries, 2020, p. 2).

2. The Dutch studies disqualified cases most commonly presenting today: Adolescents with recent-onset gender dysphoria, nonbinary identities, or mental illness

From the outset in the late 1990s when the Dutch researchers first began to report on the results of youth gender transitions, they made it clear that their focus was exclusively on youth with

complete cross-sex identification “from toddlerhood onwards” (Cohen-Kettenis & van Goozen, 1998, p. 1). Furthermore, there was a strict requirement of psychological stability:

First, they must have shown a *lifelong extreme and complete crossgender identity/role* [emphasis added]. Around puberty these feelings and behaviors must have become more rather than less pronounced. Second, they must be *psychologically stable* [emphasis added] (with the exception of depressed feelings, which often are a consequence of their living in the unwanted gender role) and function socially without problems (e.g., have a supportive family, do well at school). (Cohen-Kettenis & van Goozen, 1997, p. 265)

Of note, youth with non-binary identities, common today (Green et al., 2022), were *ineligible* for medical interventions according to the Dutch protocol, and instead needed psychotherapy: “adolescents... whose wish for sex reassignment seems to originate from factors other than a genuine and complete cross-gender identity are *served best by psychological interventions* [emphasis added] (de Vries et al., 2006, pp. 87–88).

Thus, the Dutch protocol explicitly *excluded* the characteristics of adolescents presenting to clinics in recent years—those whose trans-identities emerged around puberty; non-binary presentations without the wish for a complete cross-sex reassignment; or cases of gender dysphoria accompanied by significant uncontrolled mental illness. The high level of psychological functioning of the Dutch cohort *at baseline* serves as evidence that these selection criteria were indeed followed at the time (de Vries et al., 2011). The fact that “gender-affirming” interventions are now provided to the very segment that was explicitly excluded from the eligibility in the foundational studies is alarming.

D. Failure to consider alternatives (lack of research equipoise)

The Dutch researchers began their research into treatments of gender-dysphoric adolescents with the *foregone conclusion* that children who had life-long gender dysphoria and who continue to be cross-sex identified as adolescents would inevitably grow up to be transgender-identified adults. This assumption, based on “expert observations” from a handful of cases (O’Malley & Ayad, 2022; Cohen-Kettenis & van Goozen, 1997), has never been tested in rigorous comparative research. Further, the research team assumed that the only feasible treatment for these adolescents is early gender transition, and that psychotherapy alone is ineffective—also without testing this assumption through research. This violates the key requirement of equipoise in research—the principle that clinical investigators must approach research with genuine uncertainty regarding diagnostic, prevention, and treatment options—and allocate individuals to interventions in a manner that allows for generation of new knowledge (Freedman, 1987; London, 2017).

In fact, as de Vries’ response to us emphasizes, the Dutch researchers continue to hold such firm belief into the beneficial nature of gender reassignment for youth, that they are far more concerned with the risk of “nontreatment” with hormones and surgery than they are with the possibility that the youth undergoing transition may not have needed such drastic interventions (de Vries, 2022, p. 3). However, some of the earlier research on the “non-treated” gender-variant and gender dysphoric adolescents challenges the assumptions of the permanence of trans identity in teens.

1. Non-treatment of “referred” adolescents with significant mental illness

Because of the careful case selection, the Dutch protocol rejected some youth from eligibility for gender reassignment due to serious “psychological or environmental problems” (Smith et al., 2001, p. 473). According to the study that followed the trajectories of these youth, the majority no longer wished to undergo gender transition once they reached *adulthood*.

Smith et al. (2001) reported that individuals rejected from gender reassignment in adolescence found noninvasive ways to deal with their gender dysphoria, and gender dysphoria significantly diminished. Upon follow-up 1–7 years later, only 22% of the rejected subjects (6/27) underwent gender reassignment as adults, while 78% refrained from it. Among those who remained medically untreated and participated in follow-up research, a remarkable 79% (11/14) “*did not feel*

any regrets about having refrained from SR [sex reassignment] or being rejected....” Only 7% (1 of 14) expressed strong regret (Smith et al., 2001, p. 477).

Data from the study by Smith et al. (2001) raise the possibility that the majority of those rejected from hormonal interventions not only were unharmed by waiting but benefited from “nontreatment” with gender reassignment in adolescence. Unlike the medically and surgically treated subjects, the “rejects” completed uninterrupted physical and psychological development, avoided sterility, maintained their sexual function, eliminated their risk of iatrogenic harm from surgery, and avoided the need for decades of dependence on cross-sex hormones. These cases also demonstrate that the assumption that “adolescents do not desist” was not true even at the time the Dutch team first introduced gender transitions of youth. It is even less true now, with research showing 10-30% rates of medical detransition among those who were trans-identified in adolescence and young adulthood (Boyd et al., 2022; Hall et al., 2021; Roberts et al., 2022). The long-term follow-up data on the Dutch adolescent transitioner cohort recently presented at the WPATH 2022 Symposium (Steensma et al., 2022) also suggest that the rate of cross-sex identification was not as stable as originally expected, with a sizable percentage reporting one or more instances of identity changes after treatment completion, especially among the individuals on the autistic spectrum (Steensma et al., 2022).

2. Non-treatment of “gender variant” youth in a community sample

Another study, also from the Netherlands, that took place before the practice of pediatric gender transition became widespread (Steensma, van der Ende, et al., 2013), also sheds light on what happens when childhood and adolescent gender-variance remains medically untreated. This large prospective longitudinal study based on a community sample (n=879) found that about 6% of children (n=51) ages 7–8 in a community sample were identified as “gender variant.” At follow-up 24 years later, when the subjects were on average in their early 30s, *not a single individual* from the previously “gender-variant” subgroup of 51 children sought to undergo gender reassignment, despite the availability of these services.

There are three noteworthy observations in this study. *First*, the rate of “gender variance” of 6% reported in the community sample is remarkably similar to the current rate of transgender identification in U.S. youth of 2–9% (Johns et al., 2019; Kidd et al. 2021). *Second*, the gender-variant children were roughly 8–15 times more likely to grow up to be gay, lesbian, or bisexual adults compared to gender-normative youth. Gender variance is a common precursor to future homosexuality (Korte et al., 2008) and in fact in the Dutch studies, 97% of youth were gay, lesbian, or bisexual relative to their natal sex (de Vries et al., 2011). *Third*, only *one* of the 879 individuals in the sample underwent a male-to-female gender reassignment as an adult—and the individual had *not* been deemed “gender-variant” as a child (Steensma, van der Ende, et al., 2013, p. 2729). This challenges the current focus on medical interventions at increasingly younger ages.

The fact that none of the “gender variant” children in the sample sought gender reassignment as adults, when the study was published in 2013, merits scrutiny. These children would have been coming “of age” just a few years before the Dutch researchers conceived of the notion of *juvenile transsexual* and began to offer gender reassignment to adolescents. Thus, these children just missed the clinical shift in the Dutch practice—and perhaps not coincidentally, apparently all avoided the lifelong medical burden of living as a gender-reassigned individual.

The title of de Vries’ commentary, *Ensuring Care for Transgender Adolescents Who Need It* (de Vries, 2022) prompts us to pose two questions. First, has the availability of the Dutch protocol itself created the “need?” Second, absent clear criteria to separate a young person’s “wish” from a “need,” will research rigor be required to demonstrate that the benefits outweigh the risks?

II. Newer research claiming benefits of youth gender transition is even more flawed

de Vries acknowledged that the Dutch research suffers from some limitations but insisted that newer research has sufficiently addressed these problems. She criticized us for not including a

review of newer studies that “consistently demonstrate improved or stable psychological functioning, body image, or treatment satisfaction varying from three months to up to two years from the initiation of treatment” (de Vries, 2022, p. 5). We are familiar with the seven studies de Vries mentions—as well as a number of other recent studies. What these studies “consistently demonstrate” is the art of *spin*—a well-documented problem in biomedical research where researchers “distort the interpretation of results and mislead readers so that results are viewed in a more favorable light” (Chiu et al., 2017). Due to length concerns, we discuss only three examples—Carmichael et al. (2021), Costa et al. (2015), and Tordoff et al. (2022). Most of the current research on the purported benefits of “gender-affirming care” suffers from similar limitations.

The UK study of puberty blockers by Carmichael et al. (2021), which attempted to replicate the Dutch puberty blocker study’s findings of psychological improvements (de Vries et al., 2011), *failed to demonstrate psychological improvements*, conceding that its results are “in contrast to the Dutch study” (Carmichael et al., 2021, p. 19). The study found problems in bone mass density accrual among puberty-blocked youth. These problematic findings take on a decisively positive spin in the study conclusions, which refocus the reader on the positive “overall patient experience of changes on GnRHa treatment”; dismiss bone density problems as merely “consistent with suppression of growth”; and camouflage the failure to replicate the psychological benefits of puberty suppression by simply stating, “we identified no changes in psychological function” (Carmichael et al., 2021, p. 2). de Vries aided in the positive interpretation of the results by recasting the lack of improvement in psychological function following puberty suppression, as a *positive* finding of “stable psychological function” (de Vries 2022, p. 5)—yet it has never been demonstrated that psychological function of gender dysphoric adolescents with high baseline mental health function, as was required by the study criteria, would be expected to deteriorate absent intervention.

Spin also characterizes Costa et al. (2015), which compared psychosocial functioning of gender dysphoric youth who were puberty-suppressed to those who were delayed for medical treatment and received only psychotherapy. By the end of the 18-month study period, both groups ended up in the same psychosocial functional range using the Children’s Global Assessment Scale (CGAS): 61–70 (out of 100 points), corresponding to “[s]ome difficulty in a single area, but generally functioning pretty well” (Shaffer, 1983). This study can hardly be cited as evidence of the superiority of the medical approach and in fact points to the viability of providing noninvasive therapy as an alternative to puberty suppression. Yet, the authors focus their abstract on the fact that the puberty-blocked group had higher function after puberty suppression than before, ignoring the fact that both the puberty-suppressed and the psychologically-treated only groups improved and there was no statistically-significant difference between the two by the end of the study period (Biggs, 2019). Questions regarding the extent to which improvements in self-reported psychological measures could be due to the placebo effect of puberty blockers have been recently raised (Clayton, 2022).

The spin of Tordoff et al. (2022) is dramatic. This study claimed that puberty blockers and “gender-affirming” hormones produced a 60% reduction in depression after only one year. However, this conclusion is in stark contrast to the raw data: at baseline, 59% of the yet-to-be treated patients had *moderate to severe depression*; by the end of the study at 12 months, 56% were still moderately to severely depressed, despite receiving hormone treatment (Supplementary material of eTable 3 Tordoff et al., 2022). This unchanged rate of depression became an “observed 60% lower odds of depression” via a methodology that *inferred* the “improvement” in the *treated cases* from the reported “worsening” in the *untreated cases*. Indeed, the untreated cases in the study had depression rates of 86% by the end of the study period ($n = 7$), compared to 56% of the treated cases ($n = 57$), seemingly supporting the conclusion that treatment with hormones alleviates depression.

However, by basing their conclusion about the relative success of the “treated” on the finding of lack of success among the “untreated” cases, the researchers failed to consider that

they lost an astounding 80% of their “untreated” cohort by the end of the study (28 of 35); in contrast, over 80% of the “treated” cohort (57 of 69) remained enrolled. The high dropout rate in “untreated” subjects makes intuitive sense: the study took place in a gender clinic setting, the primary purpose of which is provision of gender transition services. Youth whose distress was ameliorated without the use of hormones would have little reason to stay enrolled in the clinic and participate in the ongoing research. However, what this also suggests is that the highest functioning “untreated” youth dropped out of the study. Thus, the entire conclusion that because “untreated” cases fared so poorly on measures of depression, anxiety, or suicidality, it must be that hormones given to the “treated” cases “worked,” is invalid. There are other problems in the study, including the fact that the use of psychiatric medications was not accounted for in the analysis. The university was aware of the problems with this research but chose to remain silent because the study’s optimistic conclusions were so well received by national news media outlets (Rantz, 2022).

These examples demonstrate why we do not share de Vries’ optimism that the newer studies conducted since the publication of the two seminal Dutch studies provide any additional confidence in, or support for, the practice of youth gender transitions. Most of the current research into the practice of pediatric transition continues in the context of gender clinic settings, which are actively providing gender transition to willing youth. Such low-quality observational research not only lacks the ability to control for the multiple sources of bias due to limitations in research design, but also is often led by clinicians with vested intellectual, professional, and financial conflicts of interest (Prasad, 2013).

III. Suggestions for future research

We were pleased to learn that de Vries has been awarded a substantial research grant to continue to study the effects of the Dutch protocol (Amsterdam UMC, 2022a). We welcome her decision to study the effects of the Dutch protocol on the novel cohort of youth whose trans identity only emerged in adolescence, as we agree that it is important to know “whether medical treatment is ...useful for this group or whether there are too many risks... such as regret afterwards” (Amsterdam UMC, 2022b).

However, we think the time has come to reexamine the entire 25 years of Dutch experience using rigorous methodologies, to answer the critical questions about the full range of risks and benefits of the Dutch protocol. We offer five suggestions relating to both past and future research:

1. Conduct comprehensive retrospective research

There have been over 6600 referrals to the Amsterdam gender clinic alone between 2000 and 2019 (Steensma et al., 2022), with likely additional referrals to the other Dutch gender clinics over the same time period, as well as new referrals since 2019. A retrospective chart review of these referred patients, supplemented by the data from the Dutch health and civil records registries (Registers in The Netherlands 2022) could allow researchers to reexamine its quarter-century of experience of gender transition of youth and their outcomes in a way that is methodologically sound. The analysis should include outcomes of *all* patients diagnosed with gender dysphoria as children, adolescents, or young adults, rather than focusing only on those who chose to pursue medical interventions and explicitly agreed to participate in research. This retrospective review should seek to examine the outcomes of medical transition, psychotherapy, and no intervention. The effects of each step of the Dutch protocol should be disaggregated to gain a better understanding of the benefits and risks at each stage, and the results should be analyzed by natal sex and the age of gender dysphoria onset as validated by medical records.

2. Focus on comparative outcomes

The importance of *comparative* research to determine optimal treatments has been known since the 1990s (Guyatt, 1993). Comparing “before” and “after” psychological outcomes tends to overstate benefits due to number of factors, including “regression to the mean” (Knapp, 2016). Gender dysphoric youth often seek help at the peak of their distress. That many such “extreme” situations tend to naturally revert to a milder state even without an intervention is a well-recognized clinical and statistical phenomenon. While randomization is still the gold standard to reliably estimate treatment effects, when it is not possible (as is the case with retrospective research), researchers should consider utilizing quasi-experimental research designs (Harris et al., 2006). Recent post-hoc analysis of the effects of “gender-affirming” surgery, which utilized propensity-score matching to construct comparator groups, is an example of such analysis (Bränström & Pachankis, 2020c).

3. Track a full range of health outcomes utilizing objective measures whenever possible

The current exclusive focus on psychological and sexual functioning and self-reports is insufficient. Research should include a more objective evaluation of the effects of gender reassignment interventions on bone, brain, cardiovascular health, malignancies, and overall morbidity and all-cause mortality. As mentioned earlier, retrospective chart reviews of the referred patient cohorts, supplemented with relevant data from the Dutch health and civil records registries, should provide sufficient information to estimate the longer-term impact of hormonal and surgical interventions on morbidity and mortality, while also documenting the incidence of osteoporosis, cardiovascular disease, and cancer, as well as rates of mental illness and suicidality/suicide.

4. Pre-specify primary and secondary outcome measures and consistently track them

The primary outcomes of pediatric gender reassignment have been a moving target. In 1997, the Dutch researchers stated that the decision to start gender transition had as its goal to improve the “psychological problems of untreated adolescents” (Delemarre-van de Waal & Cohen-Kettenis, 2006, p. 132), since transitions undertaken in adulthood were already adequately relieving the feeling of gender incongruence itself. In her commentary, however, de Vries stated that psychological function may not be the “best indicator for the benefits of such treatment” and that “measures that assess what makes life most worth living...” are most appropriate (de Vries, 2022, p. 3). Yet in a recent interview, she stated that the best indicator of treatment benefits is “satisfaction with care” (O’Malley & Ayad, 2022, 54:36). Primary outcome measures that serve as the rationale for the intervention must be clearly stated, justified, and consistently tracked.

If relief of “gender dysphoria” is still considered a primary outcome by the Dutch research team, a new measure of gender dysphoria that can be validated in both the pre- and the post-treatment settings is urgently needed, as the UGDS scale’s use post-treatment is invalid. The updated UGDS-GS scale (McGuire et al., 2020) currently favored by de Vries (de Vries, 2022), appears to be a derivative of the earlier UGDS scale, and therefore may suffer from similar limitations when used in post-gender-reassignment settings.

5. Focus on long-term outcomes

Until recently, the long-term outcomes on the cohort of 70/55 cases have been an unanswered question. It was partially answered in a recent WPATH Symposium presentation by the Dutch team, comprised of presentations by Drs. de Rooy, Asseler, van der Meulen, van der Miesen, and Steensma (Steensma et al., 2022). As we look forward to seeing these preliminary findings elucidated in the upcoming peer-reviewed publications, we note several concerns.

First, it appears that the follow-up research combined the earlier-treated cohorts with the later-treated ones. We hope to see the outcomes of the 70/55 cases reported separately from other cases, so that the original cohort's outcomes can be quantified. *Second*, only half of the treated cases engaged in follow-up research (Bazelon, 2022; Steensma et al., 2022). This can bias the results, as individuals who experience more difficulties with their gender transition are less likely to engage with the physicians who treated them (Vandenbussche, 2022). Much follow-up research that reports positive outcomes relies on self-reported data compromised by high dropout rates (D'Angelo, 2018). In contrast, research that utilizes medical records and objective outcome measures shows much less optimistic outcomes (Dhejne et al., 2011; Bränström & Pachankis, 2020a, 2020b, 2020c). To mitigate the non-response bias, the Dutch research team should leverage chart data for all the referred patients, and report objective health outcomes for the *entire cohort* that was treated.

Third, we are concerned by the apparent dismissal of reproductive regret, which affected more than a quarter of the patients (according to the data presented by Asseler), as merely a problem of the past when sterilizing surgery was a requirement (Steensma et al., 2022). The current treatment protocol of blocking puberty at Tanner stage 2 followed by cross-sex hormones, endorsed by the Endocrine Society (Hembree et al., 2017) and WPATH (Coleman et al., 2022), will most likely lead to chemical sterility, just as the prior surgical protocol led to permanent surgically-induced sterility. There are currently no effective, established methods to preserve fertility of individuals whose gametes have not matured (Rosenthal, 2021).

Fourth, the reported relationship difficulties reported by Asseler, with over 60% of individuals in their early to mid-30's still single, also deserve serious consideration. The apparent sexual difficulties reported by male-to-female transitioners by van der Meulen (around 70% have problems with libido, have pain during sex, or have problems with achieving orgasm), combined with reproductive challenges, may be contributing to this outcome. *Fifth*, the team's preliminary optimistic conclusions that early puberty blockade did not worsen sexual function appears to be based on a problematic combining Tanner stages 2 and 3. The development of sexual organs and fertility is significantly more advanced in Tanner stage 3, compared to stage 2. Whether or not the high rate of sexual problems found in the transitioned population may be related to blocking puberty at Tanner stage 2 needs to be investigated.

These newly reported data underscore an urgent need to determine whether the benefits of medical interventions outweigh the now much better understood risks.

Concluding thoughts

The question, "Just because we can, should we?" is not unique to pediatric gender medicine. What makes this arena exceptional is the radical, irreversible nature of "gender-affirming" medical and surgical interventions desired by the exponentially growing numbers of youth in the Western world. The recent changes announced by WPATH SOC 8—specifically the removal of minimum age limits for medical and surgical treatments, and the elimination of the "distress" requirement by switching from DSM-5-TR to ICD-11 diagnostic criteria (Coleman et al., 2022; Robles García & Ayuso-Mateos, 2019; World Health Organization, 2019)—takes the field further in a truly extraordinary direction whereby *any desired body modification* desired by a child or a young person becomes automatically "medically necessary."

Another unique aspect of the gender medicine field is that a number of clinicians tasked with caring for gender-distressed have taken on the role of political campaigners—and in doing so, have traded wisdom and nuance for blunt activism (Kuper et al., 2022; McNamara et al., 2022). Their insistence that today's gender-dysphoric teens are tomorrow's transgender adults, and that their future happiness and mere survival hinges on early access to gender reassignment, is demonstrably false. While still reported as "rare" by the gender medicine establishment (Coleman et al., 2022; McNamara et al., 2022), the rate of medical detransition is already 10%-30% just a few years following transition (Boyd et al., 2022; Hall et al., 2021; Roberts et al., 2022). These

numbers are likely to rise in the future as regret historically has taken over a decade to materialize (Dhejne et al., 2014). Not all of those who detransitioned will consider themselves harmed, but many will—and a number already have (Vandenbussche, 2022; Littman, 2021).

When clinician-activists misuse the eminence of their institutions and medical societies to deny or obfuscate important facts about pediatric gender transition—that puberty blockers are prescribed to peri-pubertal children as young as 8–9; that mastectomies are commonly provided to teens; that the wave of detransition is rising and already far exceeds what’s been historically recorded; and that no other pediatric intervention of similarly drastic nature has ever been delivered at scale based such low quality of evidence (McNamara et al., 2022)—they may succeed in scoring a political or legal “victory” in the short-term, but they also contribute to the longer-term erosion of public trust in the medical profession. They also inadvertently contribute to medical harm.

The scale of the potential harm can be fully appreciated if one considers that an astounding 1 in 10–20 middle school, high school, and college students in the West currently claim a transgender identity (ACHA, 2022; Johns et al., 2019; Kidd et al. 2021). Adolescent mental health in general is at an all-time low (Centers for Disease Control and Prevention [CDC], 2022). Lesbian, gay and bisexual youth and those on the autism spectrum (Bradley, 2022) are at particularly high risk of refracting their gender-non-conformity through the prism of transgender identity. Youth referrals for gender reassignment have risen already several thousand percent in the last decade, and nearly doubled between 2020/2021 and 2021/2022 (NHS, 2022b; Respaut & Terhune, 2022). If these young patients’ sense of urgency is confused with certainty about their future happiness, while a flawed evidence base is mistaken for proven safety and effectiveness of youth gender reassignment, harm at scale will ensue.

As physicians are increasingly instructed to widely adopt “gender identity screening” of adolescents to “facilitate and increase...the delivery of gender-affirming” interventions (Lau et al., 2021, p. 1) and are misled about the (very low) quality of research, an analogy of the opioid epidemic powerfully emerges. The gender medicine field must reflect on the parallels between the pain as the “fifth vital sign,” the misuse of research (Porter & Jick, 1980; Zhang, 2017), the pressure to meet patient demands, and the role of powerful special interests during the height of the opioid epidemic—and the trends in pediatric gender medicine today.

The field of gender medicine has a short time to self-correct before a growing number of authorities step in and impose guardrails to safeguard youth. Public health authorities in Finland, Sweden, and most recently England have already done just that, sharply deviating from the WPATH’s poorly evidenced recommendations in “SOC 7” (Dahlen et al., 2021), with no apparent intention to follow the updated “SOC 8” either (COHERE (Council for Choices in Health Care), 2020; Socialstyrelsen [National Board of Health and Welfare], 2022; NHS, 2022a). NHS England’s decision to close GIDS/Tavistock—the world’s biggest pediatric gender clinic—and to place the care of gender-distressed youth in established clinical settings that “maintain a broad clinical perspective,” provide “strong links to mental health services,” and do not “exceptionalise gender identity issues,” (Cass, 2022; NHS, 2022b) is a vote of no-confidence in the WPATH-endorsed “gender-affirming” approach that dominates the “gender clinic” model of care.

The American medical establishment appears to be taking a different approach. Rather than acknowledging the problems with the gender-affirmation model of care, there is an apparent effort underway to retrospectively redefine what “gender-affirmation” is. Originally defined as comprised of the provision of hormones and surgery to youth (Table 2, Rafferty, 2018), more recently gender affirmation has been positioned as merely “holistic care.” The American Academy of Pediatrics recently made a surprising and welcome statement that hormones and surgery are not the preferred treatment for gender dysphoric youth, and that in fact “for the vast majority of children, it recommends the opposite” (Szilagyi, 2022). Whether this statement will be followed by earnest efforts to restrict the provision of highly invasive interventions to exceptional situations and to endorse non-invasive psychosocial interventions as first line of treatment—instead of inappropriately conflating psychotherapy for gender dysphoria with “conversion”—remains to be seen.

The former era of eminence-based, expert-opinion-led medicine, under which the innovative clinical practice of pediatric gender transition proliferated, has been replaced by a new standard, *evidence-based medicine*, which demands rigor in the research that underpins population-level treatment recommendations (Sackett et al., 1996; Zimmerman, 2013). Our analysis of the Dutch protocol has been written with three goals in mind. *First*, we wanted to definitively refute the claims that the foundational Dutch research represents “solid prospective research” that provides reliable evidence of net benefits of youth gender transition. In fact, it is much better described as case series—one of the lowest levels of evidence available (Dekkers et al., 2012, Mathes & Pieper, 2017). *Second*, we aimed to demonstrate that the type of non-comparative, short-term research that the gender medicine establishment continues to pursue is incapable of generating reliable information. And *third and most importantly*, we wanted to remind the medical community that medicine is a double-edged sword capable of both much good and much harm. The burden of proof—demonstrating that a treatment does more good than harm—is *on those promoting the intervention*, not on those concerned about the harms. Until gender medicine commits to conducting high quality research capable of reliably demonstrating the preponderance of benefits over harms of these invasive interventions, we must be skeptical of the enthusiasm generated by headlines claiming that yet another “gender study” proved benefits of transitioning youth. This time-honored concern about risk/benefit ratio is a sobering reminder that the history of medicine is replete with examples of “cures” which turned out to far more harmful than the “disease.”

Notes

1. de Vries also served as a peer-reviewer of our original paper, Levine et al. (2022a).
2. While not central to our argument, de Vries’ claim that the selection of the 111 participants from the original 196 was based only on the researchers’ interest in those age 16 and under is contradicted by the data. According to Table 1 in de Vries et al. (2011), there was at least one natal female participant who was 18.6 years old when the puberty blockers were initiated. Although selection criteria of the 111 from 196 may have introduced additional bias, we are most concerned with bias in the subsequent selection of 70 from the 111.

Acknowledgements

The Society for Evidence-Based Gender Medicine (SEGM) paid for this publication to have Open Access.

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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ORIGINAL ARTICLE

Transgender-based disparities in suicidality: A population-based study of key predictions from four theoretical models

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Funding information

Forskningsrådet om Hälsa, Arbetsliv och Välfärd, Grant/Award Number: 2018-01628; Vetenskapsrådet, Grant/Award Number: 2016-01707 and 2018-01876

Abstract

Introduction: Numerous studies have reported a high prevalence of suicidality among transgender individuals. Yet few studies have reported results from population-based samples, leaving open questions about the generalizability of existing findings. Factors proposed to explain transgender individuals' elevated risk of suicidality derive from several theoretical models (i.e., clinical model, interpersonal model, minority stress model, and societal integration model). These models identify both general risk factors (e.g., mental health risks and interpersonal risks) assumed to be elevated among transgender individuals because of transgender individuals' exposure to stigma-related disadvantage and the stigma-specific risks themselves (e.g., minority stressors such as discrimination). This is one of the first population-based studies to examine differences in suicidality between transgender and cisgender individuals and theoretically derived factors potentially explaining such differences.

Methods: A sample of 533 transgender and 104,757 cisgender individuals (age 16–84) was analyzed.

Results: Compared to cisgender individuals, transgender individuals were at a substantially higher risk of reporting both lifetime and past 12-month suicidality. Several factors partially mediated the increased risk of suicidality among transgender compared to cisgender individuals, including depressive symptoms, lack of social support, and exposure to discrimination.

Conclusions: This study suggests that transgender people experience multiple psychosocial health threats and calls for interventions to reduce these threats.

KEYWORDS

LGBTQ, minority stress, suicidality, transgender

INTRODUCTION

Results from many studies have suggested that suicidality is more common among transgender people (i.e.,

individuals who experience incongruity between their sex assigned at birth and current gender identity), compared to the general, presumably cisgender, population (Bränström & Pachankis, 2020; Connolly et al., 2016; Dhejne et al.,

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2016; Haas et al., 2010; Winter et al., 2016). Yet, despite a recent increase in studies focusing on the mental health of transgender individuals, most have been conducted in small non-representative samples (Reisner et al., 2016). Therefore, reported rates of suicidal ideation and suicide attempts vary considerably between studies. As an illustration, one systematic review of suicidality among transgender people reported that rates of suicidal ideation ranged from 37% to 83% across studies, whereas rates of suicide attempt ranged from 9.8% to 44% (McNeil et al., 2017). Such wide discrepancies suggest that included studies might be reflecting the experiences of quite different samples of transgender individuals. Population-based sampling can overcome this limitation while also providing comparisons to the prevalence of suicidality among cisgender individuals and examining psychosocial determinants as predictors of the disparities in suicidality between transgender and cisgender individuals (White Hughto et al., 2015).

Multiple factors have been suggested to explain the higher risk for suicidality among transgender people. First, transgender people's higher exposure to well-established mental health precursors to suicidality, including depressive symptoms and substance abuse, is believed to at least partially explain the increased risk of suicidality within this group (Dhejne et al., 2016; Keuroghlian et al., 2015; Reisner et al., 2016; White Hughto et al., 2015). According to the *clinical model of suicidality*, psychiatric illness and impulsivity together determine risk for suicidal behavior, in particular among individuals with a lifetime history of aggressive behavior, substance abuse, and childhood experience of abuse (Mann et al., 1999). While psychiatric illness increases risk for suicidal ideation, impulsivity and a predisposition for aggressive behavior increases the likelihood of acting on that ideation. As an externalizing mental health problem, substance abuse can be conceptualized as emerging in part from an underlying tendency toward disinhibition and impulsivity (Krueger et al., 2005; Mann et al., 1999), and thus, according to the clinical model of suicidality can serve as a robust predictor of suicidality, especially in combination with other psychiatric illness such as depression.

Second, according to the *interpersonal theory of suicide* (Van Orden et al., 2010), suicidal ideation is caused by thwarted belongingness and perceived burdensomeness, which are conceptualized as feelings of being socially isolated, lacking social support, and a perception of being a burden to others. This theoretical model has recently been used in one study to explain the increased risk of suicidality among transgender individuals (Testa et al., 2017). However, because that study used a non-probability sample without a cisgender comparison group, differences in these interpersonal predictors between transgender and cisgender individuals and their role in explaining the disparities in suicidality between these two populations were not possible.

Third, transgender individuals are exposed to stigma-related stress not experienced by the general population (Hatzenbuehler & Pachankis, 2016; White Hughto et al., 2015). The *minority stress model*, originally developed to explain differences in mental health based on sexual orientation (Meyer, 2003), has in recent years expanded to facilitate understanding of the increased risk of mental health problems based on transgender status as well (Hendricks & Testa, 2012; Operario et al., 2014; Testa et al., 2015; White Hughto et al., 2015). According to the gender minority stress model, stressors related to the stigma associated with belonging to a minority group negatively affects the mental health of transgender individuals and can at least partially explain the elevated risk of suicidality experienced by transgender people (Hatzenbuehler & Pachankis, 2016; Hendricks & Testa, 2012; Testa et al., 2017). One study assessing both internal and external minority stress factors in a non-probability sample of transgender individuals showed that stigma-based internal stressors, such as internalized transphobia and anxious anticipation of being exposed to negative events, were particularly strongly related to suicidality in this group (Testa et al., 2017). Also congruent with the minority stress model, external stigma-based stressors including exposure to stigma-based discrimination and violence, have also been linked to suicidality among transgender people (Clements-Nolle et al., 2006; Nuttbrock et al., 2010; Testa et al., 2017).

Fourth, studies in support of the *societal integration model* (Durkheim, 1897) find that sociological risks reflecting one's lack of attachment to society as a whole explain elevations in suicidal ideation and suicide attempts among other minority populations (e.g., sexual minorities; Bränström et al., 2020). In that study, more frequent suicidal ideation and suicide attempts among sexual minority individuals compared with heterosexual individuals were partially explained by barriers to societal integration, including not being married or living with a partner, not living with children, lacking societal trust, and being unemployed. These barriers to societal integration explained the sexual orientation disparity even over-and-above the effect of the clinical, interpersonal, and minority stress-related risk factors reviewed above (Bränström et al., 2020). Whether such barriers might similarly function as predictors of transgender individuals' increased risk of suicidality remains yet unknown.

This study aimed to investigate the prevalence of suicidality among transgender individuals, and differences in suicidality between transgender and cisgender individuals, using a population-based probability sample in Sweden. The study also examined several key components of each of the four models of suicidality described above: clinical model (i.e., depression and substance abuse),

interpersonal model (i.e., lack of social support), minority stress model (i.e., discrimination and threat of violence), and societal integration model (i.e., not being married, in a registered partnership or living with a partner, not living with children, lack of societal trust, and being unemployed) as potential explanatory factors of any observed disparities in suicidality.

This study possesses several methodological strengths capable of advancing knowledge of the transgender-cisgender disparity in suicidality. First, this study represents one of the few population-based examinations of the mental health of transgender individuals, with a comparison group of cisgender participants and a large-enough sample of transgender individuals to enable an exploration of multiple factors contributing to the increased risk of suicidality within this group. Second, this study assessed a comprehensive set of risk factors for suicidality, thereby permitting a simultaneous test of key components of four theories of suicidality: the clinical model (Mann et al., 1999), interpersonal model (Van Orden et al., 2010), minority stress model (Meyer, 2003), and societal integration model (Durkheim, 1897). Previous studies have only either tested one of these models (Clements-Nolle et al., 2006; Perez-Brumer et al., 2015) or two of these models in combination (Testa et al., 2017), but never the integration of models examined here. Further, none have tested any combination of these models using a population-based sample of transgender individuals.

Taking advantage of these combined methodological strengths, we tested the hypotheses that (1) transgender individuals are at greater risk of suicidality than cisgender individuals, and (2) the increased risk of suicidality among transgender individuals can be partially explained by: (a) more depressive symptoms and substance abuse, (b) lack of social support, (c) greater exposure to discrimination and threat of violence, and (d) barriers to societal integration, drawing upon key predictions of prominent models of suicidality in the general (Durkheim, 1897; Mann et al., 1999; Van Orden et al., 2010) and transgender (Hendricks & Testa, 2012; Testa et al., 2017) population.

METHODS

Participants

This study takes advantage of data from the Swedish National Public Health Survey collected in 2018 by the Public Health Agency of Sweden. Invitations to participate in the survey were sent to a random sample of 282,086 people (age 16–84); 117,178 (41.5%) individuals successfully responded. The participants could answer the survey via paper-and-pencil or online. The survey collected

information about the health and life experiences of the Swedish population and responses were complemented with data about legal gender, age, marital and partnership status, level of education, and income drawn from national registers. Data were weighted to reflect the total population in Sweden in 2018.

Materials

Transgender status

Participants' transgender status was classified as either transgender or cisgender based on responses to the question "Are you or have you been a trans person?" with a definition: "Trans person is a collective term that usually concerns individuals whose gender identity and/or gender expression sometimes or always deviates from the norm of the gender they were assigned at birth." The question could be answered with "yes," "no," or "I don't know." Of all participants in this study, 533 (0.5%) responded "yes" and were categorized as transgender, and 104,757 (99.5%) responded "no" and were categorized as cisgender. Individuals who did not answer the question (1.7%) and individuals who answered "I don't know" (0.8%) were not included in further analyses due to unknown transgender status.

Suicidality

Four measures of suicidality were used in the current study: lifetime suicidal ideation and suicide attempt and past 12-month suicidal ideation and suicide attempt. Suicidal ideation was identified using the question: "Have you ever been in a situation where you seriously considered taking your own life?" Suicide attempts were identified using the question: "Have you ever tried taking your own life?" Both questions had the response alternatives "no, never," "yes, more than 12 months ago" and "yes, during the last 12 months." From this, four dichotomous variables were created: (1) lifetime suicidal ideation (i.e., having considered suicide more than 12 months ago or during the past 12 months) or not, (2) lifetime suicide attempt (i.e., having attempted suicide more than 12 months ago or during the past 12 months) or not, (3) past 12-month suicidal ideation or not, and (4) past 12-month suicide attempt or not.

Mental health risks

Mental health risk factors for suicidality included depressive symptoms and substance abuse. Depressive symptoms were measured with a five-item version of the General Health

Questionnaire (GHQ-5), a frequently used measure of current depression. The GHQ-5 focuses on two major types of symptoms: the inability to carry out normal functions (e.g., “Over the past few weeks, have you been able to enjoy your normal day-to-day activities?” with response alternatives: “more so than usual,” “same as usual,” “less so than usual,” and “much less than usual”) and the presence of distressing experiences (e.g., “Over the past few weeks, have you been feeling unhappy and depressed?” with response alternatives: “not at all,” “no more than usual,” “rather more than usual,” and “much more than usual”). Responses to each item were first coded as indicating the presence of the symptom or absence of the symptom, and the responses to all five items were summed into a total score (range: 0–5). Consistent with prior literature and recommended scoring [23], we created a dichotomous variable categorizing participants into groups with “no elevated depression symptoms (i.e., less than two symptoms)” and “current elevated depression symptoms (i.e., two symptoms or more).” The GHQ has shown adequate validity in general population samples and has demonstrated satisfactory sensitivity and specificity for predicting current major depressive disorder diagnosis [22–24].

Substance abuse was measured as high-risk alcohol consumption and/or any use of cannabis and/or any use of other narcotics during the past 12 months, creating a dichotomous variable. High-risk alcohol consumption was measured as drinking at least six units of alcohol during one occasion at least once per month during the past 12 months.

Interpersonal risks

Interpersonal risks were operationalized as lack of social support, measured with two questions: “Do you have someone you can share your innermost feelings with and entrust?” with the response alternatives “yes” and “no,” and “Can you get help from any person or people if you have practical problems or are ill?” with the response alternatives “yes, always,” “yes, most of the time,” “no, most of the time not,” and “no, never.” The answers involving “no” were coded as lacking this type of social support. Participants were classified as lacking social support if they had answered “no” to one or both of the social support questions.

Minority stress risks

Two items assessed minority stress risks. Exposure to discrimination was measured with the question “In the past 3 months, have you been treated in a way that made you

feel discriminated against?” with the response alternatives “no,” “yes, one time,” and “yes, many times,” with the last two answers being categorized as having been exposed to discrimination, creating a dichotomous variable. Exposure to threats of violence was measured with the question “In the past 12 months, have you been subjected to threats of violence so that you were frightened?”, with the response alternatives “yes” and “no.”

Societal integration risks

Four variables were used to operationalize barriers to societal integration: (1) not being married, in a registered partnership, or living with a partner, (2) not living with children, (3) lack of societal trust, and (4) being unemployed. Information on marital and partnership status was collected from national registers. Self-reported household composition was used to categorize participants as living with a partner or not, and as living with children or not. Lack of societal trust was assessed with the question “Do you think one can generally rely on most people?” with the response alternatives “yes” and “no,” with participants answering “no” being categorized as lacking societal trust. Being unemployed was assessed using the question “What is your current occupation?” with “unemployed” being one of the response alternatives.

Sociodemographic factors

Age, annual disposable income, level of education (i.e., having a university degree or not), ethnicity (i.e., born in Sweden, born in another European country, or born outside of Europe), urbanicity (i.e., living in a larger city, living in a smaller city, or living in a rural community), and sexual orientation (i.e., heterosexual, bisexual, homosexual, “I don’t know,” “other,” and non-response) were used as covariates in the analyses. Information about legal gender was collected from national registers. Gender identity was assessed using the question: “How do you define your gender identity?” with the response alternatives “woman,” “man,” “other,” and “I don’t know.” In a report by the Public Health Agency of Sweden (Public Health Agency of Sweden, 2015), 14% of the respondents included in a targeted non-probability sample of transgender individuals reported having changed their legal gender, and more than a third of the participants reported that they wanted to change their legal gender. Since we did not have access to information regarding change of legal gender in the current study, this variable was not used as a covariate; some

participants may have changed legal gender, while others may not have done so. We did not use gender identity as a covariate given its potential association with transgender status.

Statistical analyses

Descriptive statistics were used to examine sociodemographic differences between transgender and cisgender participants. Unadjusted and adjusted logistic regression analyses were then used to estimate differences between transgender and cisgender participants in terms of suicidality and the proposed risk factors. Next, we examined whether mental health, interpersonal, minority stress, and societal integration risks explained or partially explained disparities in suicidality between transgender and cisgender participants using multiple mediation analyses. For the multiple mediation analyses, all nine proposed mediating variables drawn from the theoretical models were included: mental health risks (i.e., depression, substance abuse), interpersonal risks (i.e., lack of social support), minority stress risks (i.e., discrimination, victimization/threats), and societal integration risks (i.e., not married/living with a partner, not living with a child, lack of societal trust, and unemployment). To statistically test mediation, we calculated the indirect effects of each variable as a mediator of the association between transgender status and past 12-month suicidality. Analyses were performed using MPlus using maximum likelihood parameter estimates with robust standard errors (MLR) to calculate direct and indirect effects with 95% confidence intervals. A significant indirect effect ($p < 0.05$) was interpreted as evidence of mediation. To provide information regarding the relative explanatory potential of our variables, we performed stepwise multiple mediation models to calculate the unique proportion of the disparity that was explained by each block of proposed mediators: the mental health risks, interpersonal risks, minority stress risks, and societal integration risks.

There was a total non-response rate of 0.0%–3.5% across the variables used in this study, with the highest non-response rates on the questions concerning sexual orientation (3.5%), depressive symptoms (1.7%), and substance abuse (1.8%). Only respondents with complete data on all outcome and predictor variables were included in analyses. All statistical analyses were performed using post-stratification weights to adjust for selection probabilities and non-response. Analyses were performed using SPSS version 24 and Mplus Version 8.5.

RESULTS

Descriptive statistics

Sociodemographic descriptives of the sample and differences between transgender and cisgender individuals are presented in Table 1. Transgender individuals were younger (range: 16–84; median = 40.0; mean = 43.0 [SD = 18.8], $t = 6.75$, $p < 0.001$) compared with cisgender individuals' (range: 16–84; median = 48.0; mean = 47.8 [SD = 18.5]). Transgender participants were less likely to have been born in Sweden ($X^2 = 70.28$, $p < 0.001$); more likely to be born outside of Europe ($X^2 = 136.36$, $p < 0.001$); and more likely to have a female legal gender, report not knowing their gender identity ($X^2 = 321.91$, $p < 0.001$), and report another gender identity than woman or man ($X^2 = 8442.82$, $p < 0.001$), and therefore also less likely to report man ($X^2 = 32.73$, $p < 0.001$) or woman ($X^2 = 6.99$, $p = 0.008$) as their gender identity, compared with cisgender participants. Moreover, compared with cisgender participants, transgender participants were more likely to report being bisexual, being homosexual, or being uncertain of their sexual orientation, to report “other” as their sexual orientation, and to not respond to the question about sexual orientation (*all* $p < 0.001$). Additionally, transgender individuals had a lower annual income and level of education than cisgender individuals. Urbanicity did not differ significantly between groups.

Differences in suicidality and risk factors between transgender and cisgender participants

Transgender individuals were significantly more likely to report both lifetime suicidality (suicidal ideation: 36.1%; suicide attempt: 15.5%) and 12-month suicidality (suicidal ideation: 13.3%; suicide attempt: 1.9%) compared with cisgender individuals (lifetime suicide ideation: 12.5%; lifetime suicide attempt: 3.6%; 12-month suicidal ideation: 3.2%; 12-month suicide attempt: 0.4%; Table 2). Mental health risks (i.e., depressive symptoms), interpersonal risks (i.e., lack of social support), minority stress risks (i.e., exposure to discrimination and threat of violence), and societal integration risks (i.e., not being married/partnered and not living with children) were more common among transgender individuals than cisgender individuals. However, no significant difference between the groups was found for lack of societal trust and unemployment in adjusted analyses. Further, in adjusted analyses, transgender individuals were less likely to report substance abuse compared with cisgender individuals.

TABLE 1 Sample characteristics by transgender status

	Cisgender <i>n</i> = 104,757	Transgender <i>n</i> = 533	
Age, years	<i>n</i> (% ^a)	<i>n</i> (% ^a)	<i>t</i> = 6.75***
16–25	9330 (14.6)	98 (26.1)	
26–35	11,460 (15.9)	82 (18.5)	
36–45	13,525 (16.8)	49 (9.4)	
46–55	17,008 (15.8)	75 (15.8)	
56–65	19,159 (16.5)	94 (17.6)	
66–75	23,498 (13.7)	88 (7.6)	
76–84	10,777 (6.6)	47 (4.9)	
Individual income	mean (SD) ^b	mean (SD) ^b	
Mean annual income in SEK	257,998 (387 735)	200,094 (262 501)	<i>t</i> = 3.86***
Education	<i>n</i> (% ^a)	<i>n</i> (% ^a)	<i>X</i> ² = 17.03***
University degree	28,477 (25.1)	112 (18.2)	
Country of birth	<i>n</i> (% ^a)	<i>n</i> (% ^a)	<i>X</i> ² = 136.59***
Sweden	92,860 (81.7)	403 (69.2)	
Other European country	7229 (9.3)	52 (8.9)	
Non-European country	4668 (9.0)	78 (21.9)	
Legal gender	<i>n</i> (% ^a)	<i>n</i> (% ^a)	<i>X</i> ² = 5.02*
Woman	56,839 (49.6)	291 (53.9)	
Man	47,918 (50.4)	242 (46.1)	
Gender identity	<i>n</i> (% ^a)	<i>n</i> (% ^a)	<i>X</i> ² = 8764.33***
Woman	56,613 (49.6)	227 (44.4)	
Man	47,523 (50.2)	223 (39.0)	
Other	55 (0.1)	64 (13.8)	
Do not know	104 (0.1)	17 (2.8)	
Sexual orientation	<i>n</i> (% ^a)	<i>n</i> (% ^a)	<i>X</i> ² = 1369.05***
Heterosexual	97,273 (91.6)	335 (57.6)	
Bisexual	1898 (2.5)	55 (12.7)	
Homosexual	802 (1.0)	30 (9.3)	
Uncertain	1972 (2.2)	33 (6.3)	
Other	500 (0.6)	43 (7.5)	
No answer	2312 (2.1)	37 (6.7)	
Urbanicity	<i>n</i> (% ^a)	<i>n</i> (% ^a)	<i>X</i> ² = 3.17
Larger city	34,083 (34.5)	195 (37.0)	
Smaller city	26,966 (33.8)	128 (30.7)	
Rural community	43,708 (31.7)	210 (32.3)	

*Significant at $p < 0.05$; **significant at $p < 0.01$; ***significant at $p < 0.001$.

^aWeighted percentages.

^bStandard deviation.

Psychosocial determinants as mediators of the difference in suicidality between transgender and cisgender people

Results from the multiple mediation analysis showed that most of the examined risks including mental health, interpersonal, minority stress, and societal integration,

were significantly associated with past 12-month suicidality (Figure 1). The only non-significant associations were between suicidality (both suicide ideation and attempts) and not living with children, and between 12-month suicide attempt and discrimination and violence. Depressive symptoms and lack of social support showed the strongest indirect effect of the association between

TABLE 2 Logistic regressions with associations between transgender status and suicidal ideation and suicide attempts and clinical, interpersonal, minority stress, and societal integration factors

	Logistic regression results				
	Cisgender	Transgender	Cisgender	Transgender	
	<i>n</i> (%) ^a	<i>n</i> (%) ^a	Reference	OR (CI 95%)	AOR ^b (CI 95%)
Lifetime suicidal ideation	10,934 (12.5)	135 (36.1)	1	3.97*** (3.38, 4.65)	3.66*** (2.59, 5.17)
Lifetime suicide attempt	3183 (3.6)	60 (15.5)	1	4.86*** (3.93, 6.00)	4.04*** (2.37, 6.88)
Suicidal ideation past 12 months	2522 (3.2)	56 (13.3)	1	4.68*** (3.73, 5.86)	3.86*** (2.47, 6.04)
Suicide attempt past 12 months	267 (0.4)	10 (1.9)	1	5.39*** (3.07, 9.47)	3.45** (1.40, 8.50)
Depressive symptoms	14,506 (16.2)	137 (30.6)	1	2.277*** (1.93, 2.69)	1.99*** (1.40, 2.82)
Substance abuse past 12 months	14,249 (16.3)	66 (11.5)	1	0.67** (0.53, 0.85)	0.65* (0.43, 0.98)
Lack of social support	12,455 (13.2)	100 (24.0)	1	2.08*** (1.74, 2.48)	1.77** (1.17, 2.68)
Exposure to discrimination	20,145 (22.2)	151 (37.5)	1	2.10*** (1.80, 2.46)	1.89*** (1.37, 2.61)
Exposure to victimization or threat of violence	4235 (5.2)	60 (10.0)	1	2.01*** (1.56, 2.59)	1.72* (1.06, 2.80)
Not married, in partnership or living with a partner	30,500 (35.3)	217 (48.8)	1	1.74*** (1.50, 2.03)	1.52* (1.04, 2.23)
Not living with children	61,641 (59.9)	367 (75.9)	1	2.10*** (1.76, 2.51)	2.04*** (1.48, 2.80)
Lack of societal trust	22,698 (26.2)	150 (27.6)	1	1.07 (0.90, 1.27)	0.82 (0.58, 1.18)
Unemployed	2439 (3.6)	29 (6.1)	1	1.76*** (1.28, 2.42)	1.21 (0.70, 2.11)

*Significant at $p < 0.05$; **significant at $p < 0.01$; ***significant at $p < 0.001$.

^aWeighted percentages.

^bOdds ratios adjusted for age, level of education, country of birth, annual income, and urbanicity.

transgender status and both past 12-month suicidal ideation and suicide attempts. For both outcomes, the direct effect of transgender status on suicidality was reduced by more than 25% in models adjusted for all mediators, suggesting that the mediators derived from our four different explanatory model explain just over one-fourth of the increased risk of suicidality among transgender participants.

To explore the relative importance of the risk factors based on our four proposed theoretical models of suicidality, we calculated the change in direct effect between transgender status and suicidality when our different groups of mediators (i.e., clinical, interpersonal, minority stress, and societal integration) were added. We report the explained variance for each group of mediators (see Figure 1). For suicidal ideation, the largest explained variance was found when the clinical mental health factors (16.3%) and the interpersonal factor (15.6%) were entered as mediators. For suicide attempts, the largest explained variance was found when the interpersonal factor (15.4%) and the minority stress factors (13.0%) were entered as mediators. Our results indicate that societal integration does not contribute to the explanation of the difference in suicidality based on transgender status.

DISCUSSION

This study provided the unique opportunity to investigate the prevalence of suicidality among transgender individuals compared with cisgender individuals using a population-representative sample and to explore the relevance of theoretically derived risks for suicidality as explanations of the suicidality disparity between these two groups. Our results showed that 35% and 13% transgender individuals reported lifetime and past 12-month suicidal ideation, respectively, and 16% and 2% reported lifetime and past 12-month suicide attempts, respectively. As hypothesized, and in line with prior research using non-probability samples (Connolly et al., 2016; Public Health Agency of Sweden, 2015; Winter et al., 2016), transgender individuals were at a substantially greater risk of having experienced both suicidal ideations and attempted suicide compared with cisgender individuals. Further, transgender people reported a higher prevalence of most of the risk factors of suicidality examined here, including those derived from theoretical models of clinical risk (i.e., depression), interpersonal risk (i.e., lack of social support), minority stress risk (i.e., discrimination, victimization/threats), and societal integration risk (i.e., not being partnered, and not living with children). These risks, together,

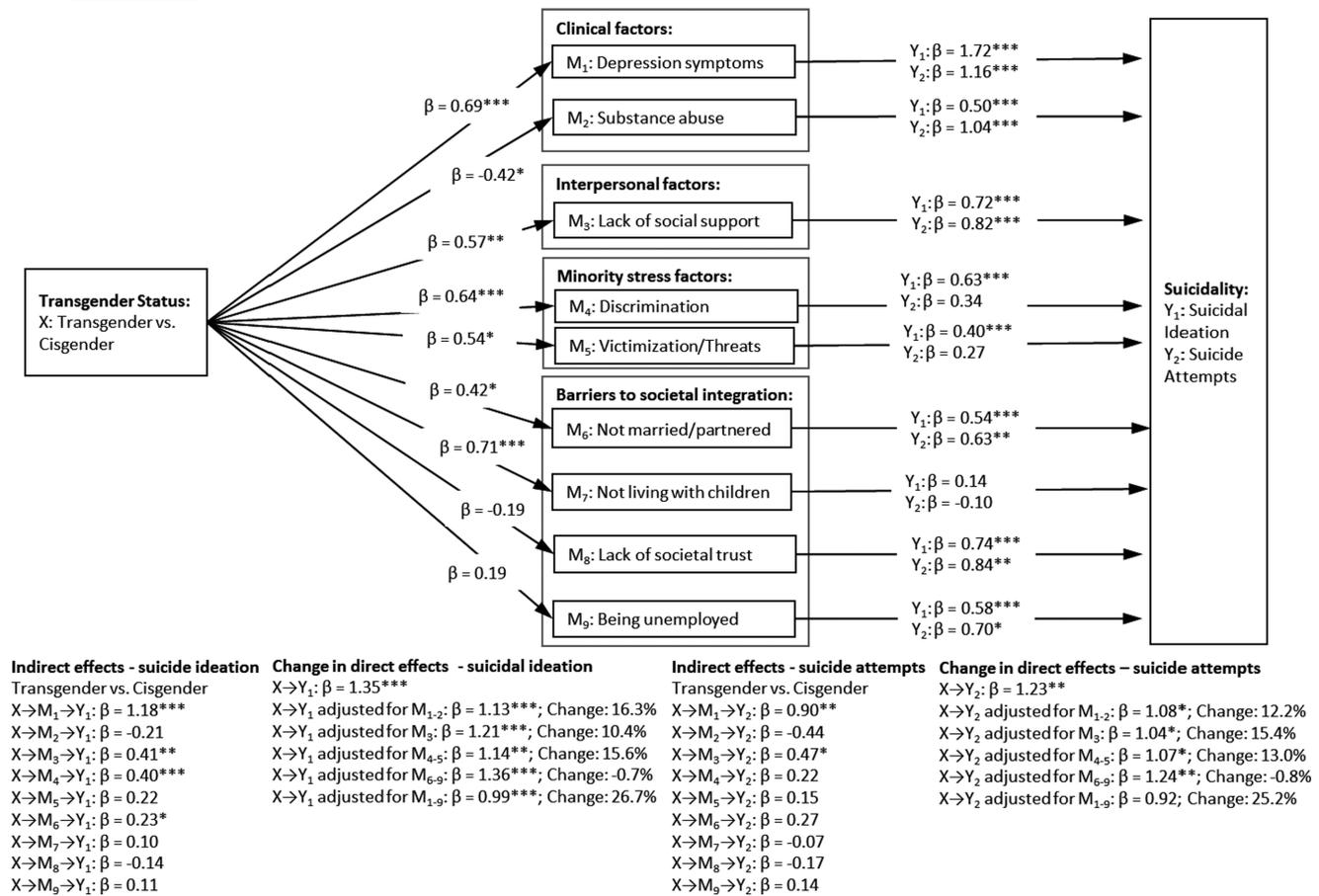


FIGURE 1 Indirect and direct effect of differences in past 12-month suicidality between transgender and cisgender participants mediated through clinical, interpersonal, minority stress, and societal integration variables

partially explained the increased risk of suicidality among transgender individuals compared with cisgender individuals. Although the increased risk of suicidality among transgender people and some of its explanatory factors have been proposed and partially been supported by previous smaller non-probability studies (Public Health Agency of Sweden, 2015; Reisner et al., 2016; White Hughto et al., 2015), this is, to our knowledge, the first study to report the increased population prevalence of suicidality among transgender people as compared with cisgender people and to demonstrate the explanatory value of a comprehensive set of theoretically derived risks in explaining this disparity.

Since few population-based studies exist of suicidality among transgender people, it is difficult to compare prevalence rates from our study with previous findings. Also, prevalence rates for suicidality among transgender people tend to vary greatly between studies, for instance, a systematic review of mostly non-probability studies showed that between 37% and 78% of transgender individuals report a history of suicidal ideation across different studies, and between 9.8% and 44% report a history of suicide attempts (McNeil et al., 2017). Although the prevalence of

lifetime suicidal ideation and suicide attempts found in this study falls within the range of these previous studies (i.e., 35% reported suicidal ideation and 16% reported suicide attempts), the prevalence of suicidality in this population-based sample was closer to the lower end of what is generally reported in studies using non-probability samples of transgender participants. This is consistent with reviews of the literature on sexual minorities' risk of suicidality, which find that non-probability community samples overrepresent individuals at risk for suicide-related outcomes (Salway et al., 2019).

Findings from this study lend support to three of the four theories of suicide that served as the basis for our exploration as applied to understanding the increased risk of suicidality among transgender people. For instance, the importance of elevated mental health concerns as a risk factor for suicidality, as suggested by the clinical model (Mann et al., 1999), is clearly supported by our findings showing a strong link between depression and both suicide ideation and attempts. The elevated prevalence of depression among transgender people also seemed to explain about 12%–16% of the increased risk of suicidality in this group as compared to cisgender people. In support of the

interpersonal model, our results showed that lack of social support, an important aspect of the construct *thwarted belongingness* (Van Orden et al., 2010), was strongly related to suicidality and also significantly mediated the increased risk among transgender people. The addition of social support in our mediation models explained 10.4% of the difference in suicidal ideation and 15.4% of suicide attempts based on transgender status. Further, our results support the minority stress model that describes stigma-based discrimination and victimization as important risk factors contributing to poor health and risk behaviors among transgender people (Testa et al., 2017). The addition of the minority stress risk factors in our mediation models explained 15.6% of the difference in suicidal ideation and 13.0% of the difference in suicide attempts between transgender and cisgender individuals. However, we did not find that the societal integration model (Durkheim, 1897), which has heretofore only been applied to understanding the elevated suicidality risk among sexual minorities (Bränström et al., 2020), seemed to contribute to transgender people's increased risk of suicidality. Future studies are needed to understand why barriers to societal integration explain sexual orientation differences in suicidality but do not contribute to the understanding of suicidality disparities based on transgender status.

While most of the present findings are consistent with those of previous non-probability studies (Connolly et al., 2016; Moody & Smith, 2013; Reisner et al., 2016; White Hughto et al., 2015) and existing theories of suicidality (Durkheim, 1897; Mann et al., 1999; Van Orden et al., 2010) as applied to transgender individuals, some of the findings were unexpected. For example, contrary to our hypothesis and findings of previous studies, substance abuse, which has been identified as a risk factor for both suicidal ideation and suicide attempt (Clements-Nolle et al., 2006; Keuroghlian et al., 2015; Reback & Fletcher, 2014; Reisner et al., 2014), was less common among transgender individuals than among cisgender individuals. This was true despite the fact that sexual minority status, which is known to be associated with higher levels of substance use (Bränström et al., 2020), was more common among transgender individuals. This unexpected finding could be due to the fact that most previous research finding elevated levels of alcohol and illicit drug consumption among transgender individuals has been conducted in the United States (Gilbert et al., 2018), whereas the present study took place in Sweden. Sweden contains a well-established social welfare system, universal health care, and legislation against workplace and school discrimination targeting one's gender minority status, whereas the United States contains more variable stigma and more variable access to resources depending on socioeconomic and geographic context (International

Lesbian Gay Bisexual Trans & Intersex Association, 2019; White Hughto et al., 2016). Another possible explanation for this result could be the fact that few other studies have investigated the prevalence of substance use problems in a representative sample of transgender individuals. Further, in contrast to our prediction, the addition of barriers to societal integration did not seem to contribute to explain the increased risk for suicidality among transgender individuals, but rather seemed to suggest that, given their lower degree of social integration, transgender individuals are somewhat more resilient to suicidality compared with cisgender people. While most barriers to societal integration were associated with suicidality, transgender individuals were only more likely to report not being partnered and not living with children, when controlling for other variables. Notably, when adjusting for sociodemographic factors, transgender individuals were not more likely to report lack of societal trust, a societal integration risk factor associated with both suicidal ideation and suicide attempt. So, while our results support Durkheim's (Durkheim, 1897) theory of societal integration—that being tethered to societal structures of meaning and purpose protect against suicidality risk—the theory did not seem to explain the observed disparities in suicidality between the transgender and cisgender population examined here. However, risks such as low income, depressive symptoms, and lack of social support could actually be consequences of facing barriers to societal integration, and examining barriers to societal integration alongside these factors might have diminished associations.

This study identifies several risk factors for suicidality that are more common among transgender than cisgender individuals, highlighting potential multilevel areas of intervention focus. At the individual level, psychotherapies adapted for transgender populations could address the psychological (i.e., depression) risks of suicidality identified here; some such treatments are currently being evaluated (Budge, 2020). Still, this type of individual-level intervention could be seen as a way to treat the symptoms rather than the underlying cause. The present findings also suggest that interpersonal interventions, for example, those that promote social inclusion and social support among transgender individuals could reduce transgender individuals' disproportionate risk of suicide. Such interventions might include mentoring, peer support, and family-focused interventions. Such interventions can be effectively embedded within existing LGBTQ community venues or delivered online (Hatzenbuehler & Pachankis, 2016), especially in places where access to brick-and-mortar resources might be limited. Providing cisgender family and friends psychoeducation and information on transgender-related supports and needs, and the significance of interpersonal acceptance and support, could be

other ways to support transgender individuals (Budge, 2020; Reisner et al., 2016).

In line with minority stress theory and extensions thereof for gender minority stress (Hendricks & Testa, 2012; Testa et al., 2017), interventions that reduce discrimination by challenging transphobic cultural norms, enacting protective legislation, and creating policies that reduce discrimination at the societal level, might also be reasonable candidates for reducing suicidality according to the present study. While Sweden has been shown to have lower levels of structural stigma (e.g., discriminatory legislation and negative attitudes in the general population) towards gender minority individuals than many other European countries (Bränström & Pachankis, 2021), the results from this study show that more effort is needed in order to improve the life chances of transgender individuals even in such a relatively accepting environment. Such efforts could include further de-pathologizing transgender individuals, for instance through the appropriate and affirmative provision of gender-related assessments and treatments (Budge, 2020), as well as actions to enable less rigid gender norms and strivings toward a more widespread acceptance of diverse gender expressions.

Limitations and future research

This study has several notable strengths including the use of population-based probability sampling and comprehensive assessments of key components of prominent theories of suicidality. Nonetheless, the study should be considered in light of several limitations. First, the cross-sectional design does not make it possible to determine directionality or causality. An age-period-cohort design could help better infer directional effects of the risk factors examined here. Such a design could also capture longitudinal changes in individuals' nationally registered or self-reported gender status and associated experiences potentially related to suicidality or protections thereagainst. Second, the data is mostly self-reported, introducing potential response bias. Using more objective measures of suicidality, for example, registry-based data, (Bränström & Pachankis, 2020), could possibly yield different results. Third, the assessments of study outcomes—suicidal ideation and attempt—were created for this study and, although they used wording similar to other suicidality assessments in national health surveys (Kessler et al., 1999), these exact items have not been validated against other indicators of suicidality (e.g., registry-based data regarding suicidality). Further, these two outcomes do not capture other indicators of suicide risk, including creation of a suicide plan, which can provide a more comprehensive assessment of risk (Kessler

et al., 1999). Fourth, the current study permitted limited information about transgender identity, gender expression, and gender-affirming health care. The measure of transgender status that we used in this study (i.e., one question about being or having been a transgender person) does not reflect the large heterogeneity within the transgender population. A more comprehensive set of specific questions on the transgender experience, gender identity, and gender expression should be included in future studies using probability samples, to extend this knowledge. Similarly, measures of risk factors for suicidality were limited to those that can be assessed of the general population often using single items, and measures of exposure to discrimination and violence were assessed in a way that did not make it possible to know if these experiences were linked specifically to transgender identity, a requirement for any indicator of minority stress. While the assessment approach of the current study allowed us to compare the prevalence of risks between transgender and cisgender individuals and to assess all risks as explanatory factors in the population disparity in suicidality, future research is needed that uses well-validated scales and to incorporate additional risk factors including those specific to transgender individuals. For instance, minority stress theory specifies identity concealment, anxious anticipation of stigma-based rejection, internalized bias, and lack of gender affirmation as risks (Hendricks & Testa, 2012). Additional variables for consideration in future studies not assessed in the present study include factors derived from the interpersonal model of suicide (e.g., markers of acquired capability including previous suicide attempts and habituation; Van Orden et al., 2010), and clinical model (e.g., generalized anxiety disorder and social anxiety, as well as impulsivity and lifetime aggressive behaviors; Mann et al., 1999). Future research is needed to incorporate these additional factors to more comprehensively evaluate and compare the four theories examined here. Finally, Sweden has been shown to have lower levels of structural stigma towards LGBTQ individuals compared with many other countries, and a lower degree of country-level structural stigma has been shown to be associated with higher life satisfaction among transgender individuals (Bränström & Pachankis, 2021). Therefore, results must be interpreted within the specific context of Sweden.

CONCLUSIONS

Whereas prior research stems mostly from smaller non-probability studies and has demonstrated a high, but widely varying, risk of suicidality among transgender

people, the present study, using a population-based sampling design and cisgender comparison, shows that transgender individuals are at an increased risk of experiencing suicidal ideation and suicide attempt. Drawing upon key components of four theoretical models of suicide, the present findings also provide insight into possible explanations for this increased risk, including derived from clinical, interpersonal, minority stress, and societal integration models of suicide. Overall, the present findings add to the growing number of studies showing that transgender people experience multiple threats to health (Reisner et al., 2016) and suggest future interventions that address these health threats across individual, interpersonal, and structural levels.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

Richard Bränström: Conceptualization (lead); Data curation (lead); Funding acquisition (lead); Investigation (equal); Methodology (lead). **Isabella Stormbom:** Investigation (equal). **Morgan Bergendal:** Investigation (equal). **John Pachankis:** Conceptualization (equal); Investigation (equal); Methodology (equal).

ETHICAL APPROVAL

This study has been approved by the Swedish Ethics Review Authority (registration number 2019-06335).

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