EXHIBIT 42

International Journal of Transgender Health

Taylor & Francis

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/wijt21

Ex. 26

Standards of Care for the Health of Transgender and Gender Diverse People, Version 8

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To cite this article: E. Coleman, A. E. Radix, W. P. Bouman, G. R. Brown, A. L. C. de Vries, M. B. Deutsch, R. Ettner, L. Fraser, M. Goodman, J. Green, A. B. Hancock, T. W. Johnson, D. H. Karasic, G. A. Knudson, S. F. Leibowitz, H. F. L. Meyer-Bahlburg, S. J. Monstrey, J. Motmans, L. Nahata, T. O. Nieder, S. L. Reisner, C. Richards, L. S. Schechter, V. Tangpricha, A. C. Tishelman, M. A. A. Van Trotsenburg, S. Winter, K. Ducheny, N. J. Adams, T. M. Adrián, L. R. Allen, D. Azul, H. Bagga, K. Başar, D. S. Bathory, J. J. Belinky, D. R. Berg, J. U. Berli, R. O. Bluebond-Langner, M.-B. Bouman, M. L. Bowers, P. J. Brassard, J. Byrne, L. Capitán, C. J. Cargill, J. M. Carswell, S. C. Chang, G. Chelvakumar, T. Corneil, K. B. Dalke, G. De Cuypere, E. de Vries, M. Den Heijer, A. H. Devor, C. Dhejne, A. D'Marco, E. K. Edmiston, L. Edwards-Leeper, R. Ehrbar, D. Ehrensaft, J. Eisfeld, E. Elaut, L. Erickson-Schroth, J. L. Feldman, A. D. Fisher, M. M. Garcia, L. Gijs, S. E. Green, B. P. Hall, T. L. D. Hardy, M. S. Irwig, L. A. Jacobs, A. C. Janssen, K. Johnson, D. T. Klink, B. P. C. Kreukels, L. E. Kuper, E. J. Kvach, M. A. Malouf, R. Massey, T. Mazur, C. McLachlan, S. D. Morrison, S. W. Mosser, P. M. Neira, U. Nygren, J. M. Oates, J. Obedin-Maliver, G. Pagkalos, J. Patton, N. Phanuphak, K. Rachlin, T. Reed, G. N. Rider, J. Ristori, S. Robbins-Cherry, S. A. Roberts, K. A. Rodriguez-Wallberg, S. M. Rosenthal, K. Sabir, J. D. Safer, A. I. Scheim, L. J. Seal, T. J. Sehoole, K. Spencer, C. St. Amand, T. D. Steensma, J. F. Strang, G. B. Taylor, K. Tilleman, G. G. T'Sjoen, L. N. Vala, N. M. Van Mello, J. F. Veale, J. A. Vencill, B. Vincent, L. M. Wesp, M. A. West & J. Arcelus (2022) Standards of Care for the Health of Transgender and Gender Diverse People, Version 8, International Journal of Transgender Health, 23:sup1, S1-S259, DOI: 10.1080/26895269.2022.2100644

Shumer
EXHIBIT NO. 26
FOR IDENTIFICATION
DATE: 4.2.24
Leisa Pastor, CSR, CRR

To link to this article: https://doi.org/10.1080/26895269.2022.2100644

INTERNATIONAL JOURNAL OF TRANSGENDER HEALTH
2022, VOL. 23, NO. S1, S1–S258
https://doi.org/10.1080/26895269.2022.2100644

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REPORT

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Standards of Care for the Health of Transgender and Gender Diverse People, Version 8

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ABSTRACT

Background: Transgender healthcare is a rapidly evolving interdisciplinary field. In the last decade, there has been an unprecedented increase in the number and visibility of transgender and gender diverse (TGD) people seeking support and gender-affirming medical treatment in parallel with a significant rise in the scientific literature in this area. The World Professional Association for Transgender Health (WPATH) is an international, multidisciplinary, professional association whose mission is to promote evidence-based care, education, research, public policy, and respect in transgender health. One of the main functions of WPATH is to promote the highest standards of health care for TGD people through the Standards of Care (SOC). The SOC was initially developed in 1979 and the last version (SOC-7) was published in 2012. In view of the increasing scientific evidence, WPATH commissioned a new version of the Standards of Care, the SOC-8.

Aim: The overall goal of SOC-8 is to provide health care professionals (HCPs) with clinical guidance to assist TGD people in accessing safe and effective pathways to achieving lasting personal comfort with their gendered selves with the aim of optimizing their overall physical health, psychological well-being, and self-fulfillment.

Methods: The SOC-8 is based on the best available science and expert professional consensus in transgender health. International professionals and stakeholders were selected to serve on the SOC-8 committee. Recommendation statements were developed based on data derived from independent systematic literature reviews, where available, background reviews and expert opinions. Grading of recommendations was based on the available evidence supporting interventions, a discussion of risks and harms, as well as the feasibility and acceptability within different contexts and country settings.

Results: A total of 18 chapters were developed as part of the SOC-8. They contain recommendations for health care professionals who provide care and treatment for TGD people. Each of the recommendations is followed by explanatory text with relevant references. General areas related to transgender health are covered in the chapters Terminology, Global Applicability, Population Estimates, and Education. The chapters developed for the diverse population of TGD people include Assessment of Adults, Adolescents, Children, Nonbinary, Eunuchs, and Intersex Individuals, and people living in Institutional Environments. Finally, the chapters related to gender-affirming treatment are Hormone Therapy, Surgery and Postoperative Care, Voice and Communication, Primary Care, Reproductive Health, Sexual Health, and Mental Health.

Conclusions: The SOC-8 guidelines are intended to be flexible to meet the diverse health care needs of TGD people globally. While adaptable, they offer standards for promoting optimal health care and guidance for the treatment of people experiencing gender incongruence. As in all previous versions of the SOC, the criteria set forth in this document for gender-affirming medical interventions are clinical guidelines; individual health care professionals and programs may modify these in consultation with the TGD person.

KEYWORDS

adolescents; assessment; children; communication; education; endocrinology; eunuch; gender diverse; health care professional; institutional settings; intersex; mental health; nonbinary; population; postoperative care; primary care; reproductive health; sexual health; SOC8; Standards of Care; surgery; terminology; transgender; voice

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INTRODUCTION

Purpose and use of the Standards of Care

The overall goal of the World Professional Association for Transgender Health's (WPATH) Standards of Care—Eighth Edition (SOC-8) is to provide clinical guidance to health care professionals to assist transgender and gender diverse (TGD) people in accessing safe and effective pathways to achieving lasting personal comfort with their gendered selves with the aim of optimizing their overall physical health, psychological well-being, and self-fulfillment. This assistance may include but is not limited to hormonal and surgical treatments, voice and communication therapy, primary care, hair removal, reproductive and sexual health, and mental health care. Healthcare systems should provide medically necessary gender-affirming health care for TGD people: See Chapter 2—Global Applicability, Statement 2.1.

WPATH is an international, multidisciplinary, professional association whose mission is to promote evidence-based care, education, research, public policy, and respect in transgender health. Founded in 1979, the organization currently has over 3,000 health care professionals, social scientists, and legal professionals, all of whom are engaged in clinical practice, research, education and advocacy that affects the lives of TGD people. WPATH envisions a world wherein people of all gender identities and gender expressions have access to evidence-based health care, social services, justice, and equality.

One of the main functions of WPATH is to promote the highest standards of health care for individuals through the Standards of Care (SOC) for the health of TGD people. The SOC-8 is based on the best available science and expert professional consensus. The SOC was initially developed in 1979, and the last version was published in 2012.

Most of the research and experience in this field comes from a North American and Western European perspective; thus, adaptations of the SOC-8 to other parts of the world are necessary. Suggestions for approaches to cultural relativity and cultural competence are included in this version of the SOC.

WPATH recognizes that health is not only dependent upon high-quality clinical care but also relies on social and political climates that ensure social tolerance, equality, and the full rights of citizenship. Health is promoted through public policies and legal reforms that advance tolerance and equity for gender diversity and that eliminate prejudice, discrimination, and stigma. WPATH is committed to advocacy for these policy and legal changes. Thus, health care professionals who provide care to TGD people are called upon to advocate for improved access to safe and licensed gender-affirming care while respecting the autonomy of individuals.

While this is primarily a document for health care professionals, individuals, their families, and social institutions may also use the SOC-8 to understand how it can assist with promoting optimal health for members of this diverse population.

The SOC-8 has 18 chapters containing recommendations for health care professionals working with TGD people. Each of the recommendations is followed by explanatory text with relevant references. The recommendations for the initiation of gender-affirming medical and/or surgical treatments (GAMSTs) for adults and adolescents are contained in their respective chapters (see Assessment for Adults and Adolescent chapters). A summary of the recommendations and criteria for GAMST can be found in Appendix D.

Populations included in the SOC-8

In this document, we use the phrase transgender and gender diverse (TGD) to be as broad and comprehensive as possible in describing members of the many varied communities that exist globally of people with gender identities or expressions that differ from the gender socially attributed to the sex assigned to them at birth. This includes people who have culturally specific and/or language-specific experiences, identities or expressions, which may or may not be based on or encompassed by Western conceptualizations of gender or the language used to describe it.

WPATH SOC-8 expands who is included under the TGD umbrella, and the settings in which these guidelines should be applied to promote equity and human rights.

CHAPTER 6 Adolescents

Historical context and changes since previous Standards of Care

Specialized health care for transgender adolescents began in the 1980s when a few specialized gender clinics for youth were developed around the world that served relatively small numbers of children and adolescents. In more recent years, there has been a sharp increase in the number of adolescents requesting gender care (Arnoldussen et al., 2019; Kaltiala, Bergman et al., 2020). Since then, new clinics have been founded, but clinical services in many places have not kept pace with the increasing number of youth seeking care. Hence, there are often long waitlists for services, and barriers to care exist for many transgender youth around the world (Tollit et al., 2018).

Until recently, there was limited information regarding the prevalence of gender diversity among adolescents. Studies from high school samples indicate much higher rates than earlier thought, with reports of up to 1.2% of participants identifying as transgender (Clark et al., 2014) and up to 2.7% or more (e.g., 7–9%) experiencing some level of self-reported gender diversity (Eisenberg et al., 2017; Kidd et al., 2021; Wang et al., 2020). These studies suggest gender diversity in youth should no longer be viewed as rare. Additionally, a pattern of uneven ratios by assigned sex has been reported in gender clinics, with adolescents assigned female at birth (AFAB) initiating care 2.5–7.1 times more frequently as compared to adolescents who are assigned male at birth (AMAB) (Aitken et al., 2015; Arnoldussen et al., 2019; Bauer et al., 2021; de Graaf, Carmichael et al., 2018; Kaltiala et al., 2015; Kaltiala, Bergman et al., 2020).

A specific World Professional Association for Transgender Health's (WPATH) Standards of Care section dedicated to the needs of children and adolescents was first included in the 1998 WPATH Standards of Care, 5th version (Levine et al., 1998). Youth aged 16 or older were deemed potentially eligible for gender-affirming medical care, but only in select cases. The subsequent 6th (Meyer et al., 2005) and 7th (Coleman et al., 2012) versions divided medical-affirming treatment for adolescents into three categories and presented eligibility criteria regarding age/puberty stage—namely fully reversible puberty delaying blockers as soon as puberty had started; partially reversible hormone therapy (testosterone, estrogen) for adolescents at the age of majority, which was age 16 in certain European countries; and irreversible surgeries at age 18 or older, except for chest "masculinizing" mastectomy, which had an age minimum of 16 years. Additional eligibility criteria for gender-related medical care included a persistent, long (childhood) history of gender "non-conformity"/dysphoria, emerging or intensifying at the onset of puberty; absence or management of psychological, medical, or social problems that interfere with treatment; provision of support for commencing the intervention by the parents/caregivers; and provision of informed consent. A chapter dedicated to transgender and gender diverse (TGD) adolescents, distinct from the child chapter, has been created for this 8th edition of the Standards of Care given 1) the exponential growth in adolescent referral rates; 2) the increased number of studies specific to adolescent gender diversity-related care; and 3) the unique developmental and gender-affirming care issues of this age group.

Non-specific terms for gender-related care are avoided (e.g., gender-affirming model, gender exploratory model) as these terms do not represent unified practices, but instead heterogenous care practices that are defined differently in various settings.

Adolescence overview

Adolescence is a developmental period characterized by relatively rapid physical and psychological maturation, bridging childhood and adulthood (Sanders, 2013). Multiple developmental processes occur simultaneously, including pubertal-signaled changes. Cognitive, emotional, and social systems mature, and physical changes associated with puberty progress. These processes do not all begin and end at the same time for a given individual, nor do they occur at the same age for all persons. Therefore, the lower and upper borders of adolescence are imprecise and cannot be defined exclusively by age. For example, physical pubertal changes may

begin in late childhood and executive control neural systems continue to develop well into the mid-20s (Ferguson et al., 2021). There is a lack of uniformity in how countries and governments define the age of majority (i.e., legal decision-making status; Dick et al., 2014). While many specify the age of majority as 18 years of age, in some countries it is as young as 15 years (e.g., Indonesia and Myanmar), and in others as high as 21 years (e.g., the U.S. state of Mississippi and Singapore).

For clarity, this chapter applies to adolescents from the start of puberty until the legal age of majority (in most cases 18 years), however there are developmental elements of this chapter, including the importance of parental/caregiver involvement, that are often relevant for the care of transitional-aged young adults and should be considered appropriately.

Cognitive development in adolescence is often characterized by gains in abstract thinking, complex reasoning, and metacognition (i.e., a young person's ability to think about their own feelings in relation to how others perceive them; Sanders, 2013). The ability to reason hypothetical situations enables a young person to conceptualize implications regarding a particular decision. However, adolescence is also often associated with increased risk-taking behaviors. Along with these notable changes, adolescence is often characterized by individuation from parents and the development of increased personal autonomy. There is often a heightened focus on peer relationships, which can be both positive and detrimental (Gardner & Steinberg, 2005). Adolescents often experience a sense of urgency that stems from hypersensitivity to reward, and their sense of timing has been shown to be different from that of older individuals (Van Leijenhorst et al., 2010). Social-emotional development typically advances during adolescence, although there is a great variability among young people in terms of the level of maturity applied to inter- and intra-personal communication and insight (Grootens-Wiegers et al., 2017). For TGD adolescents making decisions about gender-affirming treatments—decisions that may have lifelong consequences—it is critical to understand how all these aspects of development may impact decision-making for a given young person within their specific cultural context.

Gender identity development in adolescence

Our understanding of gender identity development in adolescence is continuing to evolve. When providing clinical care to gender diverse young people and their families, it is important to know what is and is not known about gender identity during development (Berenbaum, 2018). When considering treatments, families may have questions regarding the development of their adolescent's gender identity, and whether or not their adolescent's declared gender will remain the same over time. For some adolescents, a declared gender identity that differs from the assigned sex at birth comes as no surprise to their parents/caregivers as their history of gender diverse expression dates back to childhood (Leibowitz & de Vries, 2016). For others, the declaration does not happen until the emergence of pubertal changes or even well into adolescence (McCallion et al., 2021; Sorbara et al., 2020).

Historically, social learning and cognitive developmental research on gender development was conducted primarily with youth who were not gender diverse in identity or expression and was carried out under the assumption that sex correlated with a specific gender; therefore, little attention was given to gender identity development. In addition to biological factors influencing gender development, this research demonstrated psychological and social factors also play a role (Perry & Pauletti, 2011). While there has been less focus on gender identity development in TGD youth, there is ample reason to suppose, apart from biological factors, psychosocial factors are also involved (Steensma, Kreukels et al., 2013). For some youth, gender identity development appears fixed and is often expressed from a young age, while for others there may be a developmental process that contributes to gender identity development over time.

Neuroimaging studies, genetic studies, and other hormone studies in intersex individuals demonstrate a biological contribution to the development of gender identity for some

individuals whose gender identity does not match their assigned sex at birth (Steensma, Kreukels et al., 2013). As families often have questions about this very issue, it is important to note it is not possible to distinguish between those for whom gender identity may seem fixed from birth and those for whom gender identity development appears to be a developmental process. Since it is impossible to definitively delineate the contribution of various factors contributing to gender identity development for any given young person, a comprehensive clinical approach is important and necessary (see Statement 3). Future research would shed more light on gender identity development if conducted over long periods of time with diverse cohort groups. Conceptualization of gender identity by shifting from dichotomous (e.g., binary) categorization of male and female to a dimensional gender spectrum along a continuum (APA, 2013) would also be necessary.

Adolescence may be a critical period for the development of gender identity for gender diverse young people (Steensma, Kreukels et al., 2013). Dutch longitudinal clinical follow-up studies of adolescents with childhood gender dysphoria who received puberty suppression, gender-affirming hormones, or both, found that none of the youth in adulthood regretted the decisions they had taken in adolescence (Cohen-Kettenis & van Goozen, 1997; de Vries et al., 2014). These findings suggest adolescents who were comprehensively assessed and determined emotionally mature enough to make treatment decisions regarding gender- affirming medical care presented with stability of gender identity over the time period when the studies were conducted.

When extrapolating findings from the longer-term longitudinal Dutch cohort studies to present-day gender diverse adolescents seeking care, it is critical to consider the societal changes that have occurred over time in relation to TGD people. Given the increase in visibility of TGD identities, it is important to understand how increased awareness may impact gender development in different ways (Kornienko et al., 2016). One trend identified is that more young people are presenting to gender clinics with nonbinary identities (Twist & de Graaf, 2019). Another phenomenon occurring in clinical practice is the increased number of adolescents seeking care who have not seemingly experienced, expressed (or experienced and expressed) gender diversity during their childhood years. One researcher attempted to study and describe a specific form of later-presenting gender diversity experience (Littman, 2018). However, the findings of the study must be considered within the context of significant methodological challenges, including 1) the study surveyed parents and not youth perspectives; and 2) recruitment included parents from community settings in which treatments for gender dysphoria are viewed with scepticism and are criticized. However, these findings have not been replicated. For a select subgroup of young people, susceptibility to social influence impacting gender may be an important differential to consider (Kornienko et al., 2016). However, caution must be taken to avoid assuming these phenomena occur prematurely in an individual adolescent while relying on information from datasets that may have been ascertained with potential sampling bias (Bauer et al., 2022; WPATH, 2018). It is important to consider the benefits that social connectedness may have for youth who are linked with supportive people (Tuzun et al., 2022)(see Statement 4).

Given the emerging nature of knowledge regarding adolescent gender identity development, an individualized approach to clinical care is considered both ethical and necessary. As is the case in all areas of medicine, each study has methodological limitations, and conclusions drawn from research cannot and should not be universally applied to all adolescents. This is also true when grappling with common parental questions regarding the stability versus instability of a particular young person's gender identity development. While future research will help advance scientific understanding of gender identity development, there may always be some gaps. Furthermore, given the ethics of self-determination in care, these gaps should not leave the TGD adolescent without important and necessary care.

Research evidence of gender-affirming medical treatment for transgender adolescents

A key challenge in adolescent transgender care is the quality of evidence evaluating the effectiveness of medically necessary gender-affirming medical

and surgical treatments (GAMSTs) (see medically necessary statement in the Global chapter, Statement 2.1), over time. Given the lifelong implications of medical treatment and the young age at which treatments may be started, adolescents, their parents, and care providers should be informed about the nature of the evidence base. It seems reasonable that decisions to move forward with medical and surgical treatments should be made carefully. Despite the slowly growing body of evidence supporting the effectiveness of early medical intervention, the number of studies is still low, and there are few outcome studies that follow youth into adulthood. Therefore, a systematic review regarding outcomes of treatment in adolescents is not possible. A short narrative review is provided instead.

At the time of this chapter's writing, there were several longer-term longitudinal cohort follow-up studies reporting positive results of early (i.e., adolescent) medical treatment; for a significant period of time, many of these studies were conducted through one Dutch clinic (e.g., Cohen-Kettenis & van Goozen, 1997; de Vries, Steensma et al., 2011; de Vries et al., 2014; Smith et al., 2001, 2005). The findings demonstrated the resolution of gender dysphoria is associated with improved psychological functioning and body image satisfaction. Most of these studies followed a pre-post methodological design and compared baseline psychological functioning with outcomes after the provision of medical gender-affirming treatments. Different studies evaluated individual aspects or combinations of treatment interventions and included 1) gender-affirming hormones and surgeries (Cohen-Kettenis & van Goozen, 1997; Smith et al., 2001, 2005); 2) puberty suppression (de Vries, Steensma et al., 2011); and 3) puberty suppression, affirming hormones, and surgeries (de Vries et al., 2014). The 2014 long-term follow-up study is the only study that followed youth from early adolescence (pretreatment, mean age of 13.6) through young adulthood (posttreatment, mean age of 20.7). This was the first study to show gender-affirming treatment enabled transgender adolescents to make age-appropriate developmental transitions while living as their affirmed gender with satisfactory objective and subjective outcomes in adulthood (de Vries et al., 2014). While the study employed a small (n = 55), select, and socially supported sample, the results were convincing. Of note, the participants were part of the Dutch clinic known for employing a multidisciplinary approach, including provision of comprehensive, ongoing assessment and management of gender dysphoria, and support aimed at emotional well-being.

Several more recently published longitudinal studies followed and evaluated participants at different stages of their gender-affirming treatments. In these studies, some participants may not have started gender-affirming medical treatments, some had been treated with puberty suppression, while still others had started gender-affirming hormones or had even undergone gender-affirming surgery (GAS) (Achille et al., 2020; Allen et al., 2019; Becker-Hebly et al., 2021; Carmichael et al., 2021; Costa et al., 2015; Kuper et al., 2020, Tordoff et al., 2022). Given the heterogeneity of treatments and methods, this type of design makes interpreting outcomes more challenging. Nonetheless, when compared with baseline assessments, the data consistently demonstrate improved or stable psychological functioning, body image, and treatment satisfaction varying from three months to up to two years from the initiation of treatment.

Cross-sectional studies provide another design for evaluating the effects of gender-affirming treatments. One such study compared psychological functioning in transgender adolescents at baseline and while undergoing puberty suppression with that of cisgender high school peers at two different time points. At baseline, the transgender youth demonstrated lower psychological functioning compared with cisgender peers, whereas when undergoing puberty suppression, they demonstrated better functioning than their peers (van der Miesen et al., 2020). Grannis et al. (2021) demonstrated transgender males who started testosterone had lower internalizing mental health symptoms (depression and anxiety) compared with those who had not started testosterone treatment.

Four additional studies followed different outcome designs. In a retrospective chart study, Kaltiala, Heino et al. (2020) reported transgender

adolescents with few or no mental health challenges prior to commencing gender-affirming hormones generally did well during the treatment. However, adolescents with more mental health challenges at baseline continued to experience the manifestations of those mental health challenges over the course of gender-affirming medical treatment. Nieder et al. (2021) studied satisfaction with care as an outcome measure and demonstrated transgender adolescents were more satisfied the further they progressed with the treatments they initially started. Hisle-Gorman et al. (2021) compared health care utilization pre- and post-initiation of gender-affirming pharmaceuticals as indicators of the severity of mental health conditions among 3,754 TGD adolescents in a large health care data set. Somewhat contrary to the authors' hypothesis of improved mental health, mental health care use did not significantly change, and psychotropic medication prescriptions increased. In a large non-probability sample of transgender-identified adults, Turban et al. (2022) found those who reported access to gender-affirming hormones in adolescence had lower odds of past-year suicidality compared with transgender people accessing gender- affirming hormones in adulthood.

Providers may consider the possibility an adolescent may regret gender-affirming decisions made during adolescence, and a young person will want to stop treatment and return to living in the birth-assigned gender role in the future. Two Dutch studies report low rates of adolescents (1.9% and 3.5%) choosing to stop puberty suppression (Brik et al., 2019; Wiepjes et al., 2018). Again, these studies were conducted in clinics that follow a protocol that includes a comprehensive assessment before the gender-affirming medical treatment is started. At present, no clinical cohort studies have reported on profiles of adolescents who regret their initial decision or detransition after irreversible affirming treatment. Recent research indicate there are adolescents who detransition, but do not regret initiating treatment as they experienced the start of treatment as a part of understanding their gender-related care needs (Turban, 2018). However, this may not be the predominant perspective of people who detransition (Littman, 2021; Vandenbussche, 2021). Some adolescents may regret the steps they have taken (Dyer, 2020). Therefore, it is important to present the full range of possible outcomes when assisting transgender adolescents. Providers may discuss this topic in a collaborative and trusting manner (i.e., as a "potential future experience and consideration") with the adolescent and their parents/caregivers before gender-affirming medical treatments are started. Also, providers should be prepared to support adolescents who detransition. In an internet convenience sample survey of 237 self-identified detransitioners with a mean age of 25.02 years, which consisted of over 90% of birth assigned females, 25% had medically transitioned before age 18 and 14% detransitioned before age 18 (Vandenbussche, 2021). Although an internet convenience sample is subject to selection of respondents, this study suggests detransitioning may occur in young transgender adolescents and health care professionals should be aware of this. Many of them expressed difficulties finding help during their detransition process and reported their detransition was an isolating experience during which they did not receive either sufficient or appropriate support (Vandenbussche, 2021).

To conclude, although the existing samples reported on relatively small groups of youth (e.g., n = 22-101 per study) and the time to follow-up varied across studies (6 months–7 years), this emerging evidence base indicates a general improvement in the lives of transgender adolescents who, following careful assessment, receive medically necessary gender-affirming medical treatment. Further, rates of reported regret during the study monitoring periods are low. Taken as a whole, the data show early medical intervention—as part of broader combined assessment and treatment approaches focused on gender dysphoria and general well-being—can be effective and helpful for many transgender adolescents seeking these treatments.

Ethical and human rights perspectives

Medical ethics and human rights perspectives were also considered while formulating the

Statements of Recommendations

6.1- We recommend health care professionals working with gender diverse adolescents:
6.1.a- Are licensed by their statutory body and hold a postgraduate degree or its equivalent in a clinical field relevant to this role granted by a nationally accredited statutory institution.
6.1.b- Receive theoretical and evidenced-based training and develop expertise in general child, adolescent, and family mental health across the developmental spectrum.
6.1.c- Receive training and have expertise in gender identity development, gender diversity in children and adolescents, have the ability to assess capacity to assent/consent, and possess general knowledge of gender diversity across the life span.
6.1.d- Receive training and develop expertise in autism spectrum disorders and other neurodevelopmental presentations or collaborate with a developmental disability expert when working with autistic/neurodivergent gender diverse adolescents.
6.1.e- Continue engaging in professional development in all areas relevant to gender diverse children, adolescents, and families.
6.2- We recommend health care professionals working with gender diverse adolescents facilitate the exploration and expression of gender openly and respectfully so that no one particular identity is favored.
6.3- We recommend health care professionals working with gender diverse adolescents undertake a comprehensive biopsychosocial assessment of adolescents who present with gender identity-related concerns and seek medical/surgical transition-related care, and that this be accomplished in a collaborative and supportive manner.
6.4- We recommend health care professionals work with families, schools, and other relevant settings to promote acceptance of gender diverse expressions of behavior and identities of the adolescent.
6.5- We recommend against offering reparative and conversion therapy aimed at trying to change a person's gender and lived gender expression to become more congruent with the sex assigned at birth.
6.6- We suggest health care professionals provide transgender and gender diverse adolescents with health education on chest binding and genital tucking, including a review of the benefits and risks.
6.7- We recommend providers consider prescribing menstrual suppression agents for adolescents experiencing gender incongruence who may not desire testosterone therapy, who desire but have not yet begun testosterone therapy, or in conjunction with testosterone therapy for breakthrough bleeding.
6.8- We recommend health care professionals maintain an ongoing relationship with the gender diverse and transgender adolescent and any relevant caregivers to support the adolescent in their decision-making throughout the duration of puberty suppression treatment, hormonal treatment, and gender- related surgery until the transition is made to adult care.
6.9- We recommend health care professionals involve relevant disciplines, including mental health and medical professionals, to reach a decision about whether puberty suppression, hormone initiation, or gender-related surgery for gender diverse and transgender adolescents are appropriate and remain indicated throughout the course of treatment until the transition is made to adult care.
6.10- We recommend health care professionals working with transgender and gender diverse adolescents requesting gender-affirming medical or surgical treatments inform them, prior to initiating treatment, of the reproductive effects including the potential loss of fertility and available options to preserve fertility within the context of the youth's stage of pubertal development.
6.11- We recommend when gender-affirming medical or surgical treatments are indicated for adolescents, health care professionals working with transgender and gender diverse adolescents involve parent(s)/guardian(s) in the assessment and treatment process, unless their involvement is determined to be harmful to the adolescent or not feasible.

The following recommendations are made regarding the requirements for gender-affirming medical and surgical treatment (All of them must be met):
6.12- We recommend health care professionals assessing transgender and gender diverse adolescents only recommend gender-affirming medical or surgical treatments requested by the patient when:
6.12.a- The adolescent meets the diagnostic criteria of gender incongruence as per the ICD-11 in situations where a diagnosis is necessary to access health care. In countries that have not implemented the latest ICD, other taxonomies may be used although efforts should be undertaken to utilize the latest ICD as soon as practicable.
6.12.b- The experience of gender diversity/incongruence is marked and sustained over time.
6.12.c- The adolescent demonstrates the emotional and cognitive maturity required to provide informed consent/assent for the treatment.
6.12.d- The adolescent's mental health concerns (if any) that may interfere with diagnostic clarity, capacity to consent, and gender-affirming medical treatments have been addressed.
6.12.e- The adolescent has been informed of the reproductive effects, including the potential loss of fertility and the available options to preserve fertility, and these have been discussed in the context of the adolescent's stage of pubertal development.
6.12.f- The adolescent has reached Tanner stage 2 of puberty for pubertal suppression to be initiated.
6.12.g- The adolescent had 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.

adolescent SOC statements. For example, allowing irreversible puberty to progress in adolescents who experience gender incongruence is not a neutral act given that it may have immediate and lifelong harmful effects for the transgender young person (Giordano, 2009; Giordano & Holm, 2020; Kreukels & Cohen-Kettenis, 2011). From a human rights perspective, considering gender diversity as a normal and expected variation within the broader diversity of the human experience, it is an adolescent's right to participate in their own decision-making

process about their health and lives, including access to gender health services (Amnesty International, 2020).

Short summary of statements and unique issues in adolescence

These guidelines are designed to account for what is known and what is not known about gender identity development in adolescence, the evidence for gender-affirming care in adolescence, and the unique aspects that distinguish adolescence from other developmental stages.

Identity exploration: A defining feature of adolescence is the solidifying of aspects of identity, including gender identity. Statement 6.2 addresses identity exploration in the context of gender identity development. Statement 6.12.b accounts for the length of time needed for a young person to experience a gender diverse identity, express a gender diverse identity, or both, so as to make a meaningful decision regarding gender-affirming care.

Consent and decision-making: In adolescence, consent and decision-making require assessment of the individual's emotional, cognitive, and psychosocial development. Statement 6.12.c directly addresses emotional and cognitive maturity and describes the necessary components of the evaluation process used to assess decision-making capacity.

Caregivers/parent involvement: Adolescents are typically dependent on their caregivers/parents for guidance in numerous ways. This is also true as the young person navigates through the process of deciding about treatment options. Statement 6.11 addresses the importance of involving caregivers/parents and discusses the role they play in the assessment and treatment. No set of guidelines can account for every set of individual circumstances on a global scale.

Statement 6.1

We recommend health care professionals working with gender diverse adolescents:

a. **Are licensed by their statutory body and hold a postgraduate degree or its equivalent in a clinical field relevant to this role granted by a nationally accredited statutory institution.**
b. **Receive theoretical and evidenced-based training and develop expertise in general child, adolescent, and family mental health across the developmental spectrum.**
c. **Receive training and have expertise in gender identity development, gender diversity in children and adolescents, have the ability to assess capacity to assent/consent, and possess general knowledge of gender diversity across the life span.**
d. **Receive training and develop expertise in autism spectrum disorders and other neurodevelopmental presentations or collaborate with a developmental disability expert when working with autistic/neurodivergent gender diverse adolescents.**
e. **Continue engaging in professional development in all areas relevant to gender diverse children, adolescents, and families.**

When assessing and supporting TGD adolescents and their families, care providers/health care professionals (HCPs) need both general as well as gender-specific knowledge and training. Providers who are trained to work with adolescents and families play an important role in navigating aspects of adolescent development and family dynamics when caring for youth and families (Adelson et al., 2012; American Psychological Association, 2015; Hembree et al., 2017). Other chapters in these standards of care describe these criteria for professionals who provide gender care in more detail (see Chapter 5—Assessment for Adults; Chapter 7—Children; or Chapter 13—Surgery and Postoperative Care). Professionals working with adolescents should understand what is and is not known regarding adolescent gender identity development, and how this knowledge base differs from what applies to adults and prepubertal children. Among HCPs, the mental health professional (MHP) has the most appropriate training and dedicated clinical time to conduct an assessment and elucidate treatment priorities and goals when working with transgender youth, including those seeking gender-affirming medical/surgical care. Understanding and managing the dynamics of family members who may share differing perspectives regarding the history and needs of the

young person is an important competency that MHPs are often most prepared to address.

When access to professionals trained in child and adolescent development is not possible, HCPs should make a commitment to obtain training in the areas of family dynamics and adolescent development, including gender identity development. Similarly, considering autistic/neurodivergent transgender youth represent a substantial minority subpopulation of youth served in gender clinics globally, it is important HCPs seek additional training in the field of autism and understand the unique elements of care autistic gender diverse youth may require (Strang, Meagher et al., 2018). If these qualifications are not possible, then consultation and collaboration with a provider who specializes in autism and neurodiversity is advised.

Statement 6.2

We recommend health care professionals working with gender diverse adolescents facilitate the exploration and expression of gender openly and respectfully so that no one particular identity is favored.

Adolescence is a developmental period that involves physical and psychological changes characterized by individuation and the transition to independence from caregivers (Berenbaum et al., 2015; Steinberg, 2009). It is a period during which young people may explore different aspects of identity, including gender identity.

Adolescents differ regarding the degree to which they explore and commit to aspects of their identity (Meeus et al., 2012). For some adolescents, the pace to achieving consolidation of identity is fast, while for others it is slower. For some adolescents, physical, emotional, and psychological development occur over the same general timeline, while for others, there are certain gaps between these aspects of development. Similarly, there is variation in the timeline for gender identity development (Arnoldussen et al., 2020; Katz-Wise et al., 2017). For some young people, gender identity development is a clear process that starts in early childhood, while for others pubertal changes contribute to a person's experience of themselves as a particular gender (Steensma, Kreukels et al., 2013), and for many others a process may begin well after pubertal changes are completed. Given these variations, there is no one particular pace, process, or outcome that can be predicted for an individual adolescent seeking gender-affirming care.

Therefore, HCPs working with adolescents should promote supportive environments that simultaneously respect an adolescent's affirmed gender identity and also allows the adolescent to openly explore gender needs, including social, medical, and physical gender-affirming interventions should they change or evolve over time.

Statement 6.3

We recommend health care professionals working with gender diverse adolescents undertake a comprehensive biopsychosocial assessment of adolescents who present with gender identity-related concerns and seek medical/surgical transition-related care, and that this be accomplished in a collaborative and supportive manner.

Given the many ways identity may unfold during adolescence, we recommend using a comprehensive biopsychosocial assessment to guide treatment decisions and optimize outcomes. This assessment should aim to understand the adolescent's strengths, vulnerabilities, diagnostic profile, and unique needs to individualize their care. As mentioned in Statement 6.1, MHPs have the most appropriate training, experience, and dedicated clinical time required to obtain the information discussed here. The assessment process should be approached collaboratively with the adolescent and their caregiver(s), both separately and together, as described in more detail in Statement 6.11. An assessment should occur prior to any medically necessary medical or surgical intervention under consideration (e.g., puberty blocking medication, gender-affirming hormones, surgeries). See medically necessary statement in Chapter 2—Global Applicability, Statement 2.1; see also Chapter 12—Hormone Therapy and Chapter 13—Surgery and Postoperative Care.

Youth may experience many different gender identity trajectories. Sociocultural definitions and experiences of gender continue to evolve over time, and youth are increasingly presenting with a range of identities and ways of describing their experiences and gender-related needs (Twist & de

Graaf, 2019). For example, some youth will realize they are transgender or more broadly gender diverse and pursue steps to present accordingly. For some youth, obtaining gender-affirming medical treatment is important while for others these steps may not be necessary. For example, a process of exploration over time might not result in the young person self-affirming or embodying a different gender in relation to their assigned sex at birth and would not involve the use of medical interventions (Arnoldussen et al., 2019).

The most robust longitudinal evidence supporting the benefits of gender-affirming medical and surgical treatments in adolescence was obtained in a clinical setting that incorporated a detailed comprehensive diagnostic assessment process over time into its delivery of care protocol (de Vries & Cohen-Kettenis, 2012; de Vries et al., 2014). Given this research and the ongoing evolution of gender diverse experiences in society, a comprehensive diagnostic biopsychosocial assessment during adolescence is both evidence-based and preserves the integrity of the decision-making process. In the absence of a full diagnostic profile, other mental health entities that need to be prioritized and treated may not be detected. There are no studies of the long-term outcomes of gender-related medical treatments for youth who have not undergone a comprehensive assessment. Treatment in this context (e.g., with limited or no assessment) has no empirical support and therefore carries the risk that the decision to start gender-affirming medical interventions may not be in the long-term best interest of the young person at that time.

As delivery of health care and access to specialists varies globally, designing a particular assessment process to adapt existing resources is often necessary. In some cases, a more extended assessment process may be useful, such as for youth with more complex presentations (e.g., complicating mental health histories (Leibowitz & de Vries, 2016)), co-occurring autism spectrum characteristics (Strang, Powers et al., 2018), and/or an absence of experienced childhood gender incongruence (Ristori & Steensma, 2016). Given the unique cultural, financial, and geographical factors that exist for specific populations, providers should design assessment models that are flexible and allow for appropriately timed care for as many young people as possible, so long as the assessment effectively obtains information about the adolescent's strengths, vulnerabilities, diagnostic profile, and individual needs. Psychometrically validated psychosocial and gender measures can also be used to provide additional information.

The multidisciplinary assessment for youth seeking gender-affirming medical/surgical interventions includes the following domains that correspond to the relevant statements:

- **Gender Identity Development:** Statements 6.12.a and 6.12.b elaborate on the factors associated with gender identity development within the specific cultural context when assessing TGD adolescents.
- **Social Development and Support; Intersectionality:** Statements 6.4 and 6.11 elaborate on the importance of assessing gender minority stress, family dynamics, and other aspects contributing to social development and intersectionality.
- **Diagnostic Assessment of Possible Co-Occurring Mental Health and/or Developmental Concerns:** Statement 6.12.d elaborates on the importance of understanding the relationship that exists, if at all, between any co-occurring mental health or developmental concerns and the young person's gender identity/gender diverse expression.
- **Capacity for Decision-Making:** Statement 6.12.c elaborates on the assessment of a young person's emotional maturity and the relevance when an adolescent is considering gender affirming-medical/surgical treatments.

Statement 6.4

We recommend health care professionals work with families, schools, and other relevant settings to promote acceptance of gender diverse expressions of behavior and identities of the adolescent.

Multiple studies and related expert consensus support the implementation of approaches that promote acceptance and affirmation of gender diverse youth across all settings, including families, schools, health care facilities, and all other organizations and communities with which they

interact (e.g., Pariseau et al., 2019; Russell et al., 2018; Simons et al., 2013; Toomey et al., 2010; Travers et al., 2012). Acceptance and affirmation are accomplished through a range of approaches, actions, and policies we recommend be enacted across the various relationships and settings in which a young person exists and functions. It is important for the family members and community members involved in the adolescent's life to work collaboratively in these efforts unless their involvement is considered harmful to the adolescent. Examples proposed by Pariseau et al. (2019) and others of acceptance and affirmation of gender diversity and contemplation and expression of identity that can be implemented by family, staff, and organizations include:

1. Actions that are supportive of youth drawn to engaging in gender-expansive (e.g., nonconforming) activities and interests;
2. Communications that are supportive when youth express their experiences about their gender and gender exploration;
3. Use of the youth's asserted name/pronouns;
4. Support for youth wearing clothing/uniforms, hairstyles, and items (e.g., jewelry, makeup) they feel affirm their gender;
5. Positive and supportive communication with youth about their gender and gender concerns;
6. Education about gender diversity issues for people in the young person's life (e.g., family members, health care providers, social support networks), as needed, including information about how to advocate for gender diverse youth in community, school, health care, and other settings;
7. Support for gender diverse youth to connect with communities of support (e.g., LGBTQ groups, events, friends);
8. Provision of opportunities to discuss, consider, and explore medical treatment options when indicated;
9. Antibullying policies that are enforced;
10. Inclusion of nonbinary experiences in daily life, reading materials, and curricula (e.g., books, health, and sex education classes, assigned essay topics that move beyond the binary, LGBTQ, and ally groups);
11. Gender inclusive facilities that the youth can readily access without segregation from nongender diverse peers (e.g., bathrooms, locker rooms).

We recommend HCPs work with parents, schools, and other organizations/groups to promote acceptance and affirmation of TGD identities and expressions, whether social or medical interventions are implemented or not as acceptance and affirmation are associated with fewer negative mental health and behavioral symptoms and more positive mental health and behavioral functioning (Day et al., 2015; de Vries et al., 2016; Greytak et al., 2013; Pariseau et al., 2019; Peng et al., 2019; Russell et al., 2018; Simons et al., 2013; Taliaferro et al., 2019; Toomey et al., 2010; Travers et al., 2012). Russell et al. (2018) found mental health improvement increases with more acceptance and affirmation across more settings (e.g., home, school, work, and friends). Rejection by family, peers, and school staff (e.g., intentionally using the name and pronoun the youth does not identify with, not acknowledging affirmed gender identity, bullying, harassment, verbal and physical abuse, poor relationships, rejection for being TGD, eviction) was strongly linked to negative outcomes, such as anxiety, depression, suicidal ideation, suicide attempts, and substance use (Grossman et al., 2005; Klein & Golub; 2016; Pariseau et al., 2019; Peng et al., 2019; Reisner, Greytak et al., 2015; Roberts et al., 2013). It is important to be aware that negative symptoms increase with increased levels of rejection and continue into adulthood (Roberts et al., 2013).

Neutral or indifferent responses to a youth's gender diversity and exploration (e.g., letting a child tell others their chosen name but not using the name, not telling family or friends when the youth wants them to disclose, not advocating for the child about rejecting behavior from school staff or peers, not engaging or participating in other support mechanisms (e.g., with psychotherapists and support groups) have also been found to have negative consequences, such as increased depressive symptoms (Pariseau et al., 2019). For these reasons, it is important not to ignore a youth's gender questioning or delay consideration of the youth's gender-related

care needs. There is particular value in professionals recognizing youth need individualized approaches, support, and consideration of needs around gender expression, identity, and embodiment over time and across domains and relationships. Youth may need help coping with the tension of tolerating others' processing/adjusting to an adolescent's identity exploration and changes (e.g., Kuper, Lindley et al., 2019). It is important professionals collaborate with parents and others as they process their concerns and feelings and educate themselves about gender diversity because such processes may not necessarily reflect rejection or neutrality but may rather represent efforts to develop attitudes and gather information that foster acceptance (e.g., Katz-Wise et al., 2017).

Statement 6.5

We recommend against offering reparative and conversion therapy aimed at trying to change a person's gender and lived gender expression to become more congruent with the sex assigned at birth.

Some health care providers, secular or religious organizations, and rejecting families may undertake efforts to thwart an adolescent's expression of gender diversity or assertion of a gender identity other than the expression and behavior that conforms to the sex assigned at birth. Such efforts at blocking reversible social expression or transition may include choosing not to use the youth's identified name and pronouns or restricting self-expression in clothing and hairstyles (Craig et al., 2017; Green et al., 2020). These disaffirming behaviors typically aim to reinforce views that a young person's gender identity/expression must match the gender associated with the sex assigned at birth or expectations based on the sex assigned at birth. Activities and approaches (sometimes referred to as "treatments") aimed at trying to change a person's gender identity and expression to become more congruent with the sex assigned at birth have been attempted, but these approaches have not resulted in changes in gender identity (Craig et al., 2017; Green et al., 2020). We recommend against such efforts because they have been found to be ineffective and are associated with increases in mental illness and poorer psychological functioning (Craig et al., 2017; Green et al., 2020; Turban, Beckwith et al., 2020).

Much of the research evaluating "conversion therapy" and "reparative therapy" has investigated the impact of efforts to change gender expression (masculinity or femininity) and has conflated sexual orientation with gender identity (APA, 2009; Burnes et al., 2016; Craig et al., 2017). Some of these efforts have targeted both gender identity and expression (AACAP, 2018). Conversion/reparative therapy has been linked to increased anxiety, depression, suicidal ideation, suicide attempts, and health care avoidance (Craig et al., 2017; Green et al., 2020; Turban, Beckwith et al., 2020). Although some of these studies have been criticized for their methodologies and conclusions (e.g., D'Angelo et al., 2020), this should not detract from the importance of emphasizing efforts undertaken a priori to change a person's identity are clinically and ethically unsound. We recommend against any type of conversion or attempts to change a person's gender identity because 1) both secular and religion-based efforts to change gender identity/expression have been associated with negative psychological functioning that endures into adulthood (Turban, Beckwith et al., 2020); and 2) larger ethical reasons exist that should underscore respect for gender diverse identities.

It is important to note potential factors driving a young person's gender-related experience and report of gender incongruence, when carried out in the context of supporting an adolescent with self-discovery, is not considered reparative therapy as long as there is no a priori goal to change or promote one particular gender identity or expression (AACAP, 2018; see Statement 6.2). To ensure these explorations are therapeutic, we recommend employing affirmative consideration and supportive tone in discussing what steps have been tried, considered, and planned for a youth's gender expression. These discussion topics may include what felt helpful or affirming, what felt unhelpful or distressing and why. We recommend employing affirmative responses to these steps and discussions, such as those identified in SOC-8 Statement 6.4.

Statement 6.6

We suggest health care professionals provide transgender and gender diverse adolescents with health education on chest binding and genital tucking, including review of the benefits and risks.

TGD youth may experience distress related to chest and genital anatomy. Practices such as chest binding, chest padding, genital tucking, and genital packing are reversible, nonmedical interventions that may help alleviate this distress (Callen-Lorde, 2020a, 2020b; Deutsch, 2016a; Olson-Kennedy, Rosenthal et al., 2018; Transcare BC, 2020). It is important to assess the degree of distress related to physical development or anatomy, educate youth about potential nonmedical interventions to address this distress, and discuss the safe use of these interventions.

Chest binding involves compression of the breast tissue to create a flatter appearance of the chest. Studies suggest that up to 87% of trans masculine patients report a history of binding (Jones, 2015; Peitzmeier, 2017). Binding methods may include the use of commercial binders, sports bras, layering of shirts, layering of sports bras, or the use of elastics or other bandages (Peitzmeier, 2017). Currently, most youth report learning about binding practices from online communities composed of peers (Julian, 2019). Providers can play an important role in ensuring youth receive accurate and reliable information about the potential benefits and risks of chest binding. Additionally, providers can counsel patients about safe binding practices and monitor for potential negative health effects. While there are potential negative physical impacts of binding, youth who bind report many benefits, including increased comfort, improved safety, and lower rates of misgendering (Julian, 2019). Common negative health impacts of chest binding in youth include back/chest pain, shortness of breath, and overheating (Julian, 2019). More serious negative health impacts such as skin infections, respiratory infections, and rib fractures are uncommon and have been associated with chest binding in adults (Peitzmeier, 2017). If binding is employed, youth should be advised to use only those methods considered safe for binding—such as binders specifically designed for the gender diverse population—to reduce the risk of serious negative health effects. Methods that are considered unsafe for binding include the use of duct tape, ace wraps, and plastic wrap as these can restrict blood flow, damage skin, and restrict breathing. If youth report negative health impacts from chest binding, these should ideally be addressed by a gender-affirming medical provider with experience working with TGD youth.

Genital tucking is the practice of positioning the penis and testes to reduce the outward appearance of a genital bulge. Methods of tucking include tucking the penis and testes between the legs or tucking the testes inside the inguinal canal and pulling the penis back between the legs. Typically, genitals are held in place by underwear or a gaff, a garment that can be made or purchased. Limited studies are available on the specific risks and benefits of tucking in adults, and none have been carried out in youth. Previous studies have reported tight undergarments are associated with decreased sperm concentration and motility. In addition, elevated scrotal temperatures can be associated with poor sperm characteristics, and genital tucking could theoretically affect spermatogenesis and fertility (Marsh, 2019) although there are no definitive studies evaluating these adverse outcomes. Further research is needed to determine the specific benefits and risks of tucking in youth.

Statement 6.7

We recommend providers consider prescribing menstrual suppression agents for adolescents experiencing gender incongruence who may not desire testosterone therapy, who desire but have not yet begun testosterone therapy, or in conjunction with testosterone therapy for breakthrough bleeding.

When discussing the available options of menstrual-suppressing medications with gender diverse youth, providers should engage in shared decision-making, use gender-inclusive language (e.g., asking patients which terms they utilize to refer to their menses, reproductive organs, and genitalia) and perform physical exams in a sensitive, gender-affirmative manner (Bonnington et al., 2020; Krempasky et al., 2020). There is no formal research evaluating how menstrual

suppression may impact gender incongruence and/or dysphoria. However, the use of menstrual suppression can be an initial intervention that allows for further exploration of gender-related goals of care, prioritization of other mental health care, or both, especially for those who experience a worsening of gender dysphoria from unwanted uterine bleeding (see Statement 6.12d; Mehringer & Dowshen, 2019). When testosterone is not used, menstrual suppression can be achieved via a progestin. To exclude any underlying menstrual disorders, it is important to obtain a detailed menstrual history and evaluation prior to implementing menstrual-suppressing therapy (Carswell & Roberts, 2017). As part of the discussion about menstrual-suppressing medications, the need for contraception and information regarding the effectiveness of menstrual-suppressing medications as methods of contraception also need to be addressed (Bonnington et al., 2020). A variety of menstrual suppression options, such as combined estrogen-progestin medications, oral progestins, depot and subdermal progestin, and intrauterine devices (IUDs), should be offered to allow for individualized treatment plans while properly considering availability, cost and insurance coverage, as well as contraindications and side effects (Kanj et al., 2019).

Progestin-only hormonal medication are options, especially in trans masculine or nonbinary youth who are not interested in estrogen-containing medical therapies as well as those at risk for thromboembolic events or who have other contraindications to estrogen therapy (Carswell & Roberts, 2017). Progestin-only hormonal medications include oral progestins, depo-medroxyprogesterone injection, etonogestrel implant, and levonorgestrel IUD (Schwartz et al., 2019). Progestin-only hormonal options vary in terms of efficacy in achieving menstrual suppression and have lower rates of achieving amenorrhea than combined oral contraception (Pradhan & Gomez-Lobo, 2019). A more detailed description of the relevant clinical studies is presented in Chapter 12—Hormone Therapy. HCPs should not make assumptions regarding the individual's preferred method of administration as some trans masculine youth may prefer vaginal rings or IUD implants (Akgul et al., 2019). Although hormonal medications require monitoring for potential mood lability, depressive effects, or both, the benefits and risks of untreated menstrual suppression in the setting of gender dysphoria should be evaluated on an individual basis. Some patients may opt for combined oral contraception that includes different combinations of ethinyl estradiol, with ranging doses, and different generations of progestins (Pradhan & Gomez-Lobo, 2019). Lower dose ethinyl estradiol components of combined oral contraceptive pills are associated with increased breakthrough uterine bleeding. Continuous combined oral contraceptives may be used to allow for continuous menstrual suppression and can be delivered as transdermal or vaginal rings.

The use of gonadotropin releasing hormone (GnRH) analogues may also result in menstrual suppression. However, it is recommended gender diverse youth meet the eligibility criteria (as outlined in Statement 6.12) before this medication is considered solely for this purpose (Carswell & Roberts, 2017; Pradhan & Gomez-Lobo, 2019). Finally, menstrual-suppression medications may be indicated as an adjunctive therapy for breakthrough uterine bleeding that may occur while on exogenous testosterone or as a bridging medication while awaiting menstrual suppression with testosterone therapy. When exogenous testosterone is employed as a gender-affirming hormone, menstrual suppression is typically achieved in the first six months of therapy (Ahmad & Leinung, 2017). However, it is vital adolescents be counseled ovulation and pregnancy can still occur in the setting of amenorrhea (Gomez et al., 2020; Kanj et al., 2019).

Statement 6.8

We recommend health care professionals maintain an ongoing relationship with the gender diverse and transgender adolescent and any relevant caregivers to support the adolescent in their decision-making throughout the duration of puberty suppression treatment, hormonal treatment, and gender-related surgery until the transition is made to adult care.

HCPs with expertise in child and adolescent development, as described in Statement 6.1, play an important role in the continuity of care for

young people over the course of their gender-related treatment needs. Supporting adolescents and their families necessitates approaching care using a developmental lens through which understanding a young person's evolving emotional maturity and care needs can take place over time. As gender-affirming treatment pathways differ based on the needs and experiences of individual TGD adolescents, decision-making for these treatments (puberty suppression, estrogens/androgens, gender-affirmation surgeries) can occur at different points in time within a span of several years. Longitudinal research demonstrating the benefits of pubertal suppression and gender-affirming hormone treatment (GAHT) was carried out in a setting where an ongoing clinical relationship between the adolescents/families and the multidisciplinary team was maintained (de Vries et al., 2014).

Clinical settings that offer longer appointment times provide space for adolescents and caregivers to share important psychosocial aspects of emotional well-being (e.g., family dynamics, school, romantic, and sexual experiences) that contextualize individualized gender-affirming treatment needs and decisions as described elsewhere in the chapter. An ongoing clinical relationship can take place across settings, whether that be within a multidisciplinary team or with providers in different locations who collaborate with one another. Given the wide variability in the ability to obtain access to specialized gender care centers, particularly for marginalized groups who experience disparities with access, it is important for the HCP to appreciate the existence of any barriers to care while maintaining flexibility when defining how an ongoing clinical relationship can take place in that specific context.

An ongoing clinical relationship that increases resilience in the youth and provides support to parents/caregivers who may have their own treatment needs may ultimately lead to increased parental acceptance—when needed—which is associated with better mental health outcomes in youth (Ryan, Huebner et al., 2009).

Statement 6.9

We recommend health care professionals involve relevant disciplines, including mental health and medical professionals, to reach a decision about whether puberty suppression, hormone initiation, or gender-related surgery for gender diverse and transgender adolescents are appropriate and remain indicated throughout the course of treatment until the transition is made to adult care.

TGD adolescents with gender dysphoria/gender incongruence who seek gender-affirming medical and surgical treatments benefit from the involvement of health care professionals (HCPs) from different disciplines. Providing care to TGD adolescents includes addressing 1) diagnostic considerations (see Statements 6.3, 6.12a, and 6.12b) conducted by a specialized gender HCP (as defined in Statement 6.1) whenever possible and necessary; and 2) treatment considerations when prescribing, managing, and monitoring medications for gender-affirming medical and surgical care, requiring the training of the relevant medical/surgical professional. The list of key disciplines includes but is not limited to adolescent medicine/primary care, endocrinology, psychology, psychiatry, speech/language pathology, social work, support staff, and the surgical team.

The evolving evidence has shown a clinical benefit for transgender youth who receive their gender-affirming treatments in multidisciplinary gender clinics (de Vries et al., 2014; Kuper et al., 2020; Tollit et al., 2019). Finally, adolescents seeking gender-affirming care in multidisciplinary clinics are presenting with significant complexity necessitating close collaboration between mental health, medical, and/or surgical professionals (McCallion et al., 2021; Sorbara et al., 2020; Tishelman et al., 2015).

As not all patients and families are in the position or in a location to access multidisciplinary care, the lack of available disciplines should not preclude a young person from accessing needed care in a timely manner. When disciplines are available, particularly in centers with existing multidisciplinary teams, disciplines, or both, it is recommended efforts be made to include the relevant providers when developing a gender care team. However, this does not mean all disciplines are necessary to provide care to a particular youth and family.

If written documentation or a letter is required to recommend gender-affirming medical and surgical treatment (GAMST) for an adolescent, 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 HCPs and MHPs (American Psychological Association, 2015; Hembree et al., 2017; Telfer et al., 2018). Further assessment results and written opinions may be requested when there is a specific clinical need or when team members are in different locations or choose to write their own summaries. For further information see Chapter 5—Assessment for Adults, Statement 5.5.

Statement 6.10

We recommend health care professionals working with transgender and gender diverse adolescents requesting gender-affirming medical or surgical treatments inform them, prior to the initiation of treatment, of the reproductive effects, including the potential loss of fertility and available options to preserve fertility within the context of the youth's stage of pubertal development.

While assessing adolescents seeking gender-affirming medical or surgical treatments, HCPs should discuss the specific ways in which the required treatment may affect reproductive capacity. Fertility issues and the specific preservation options are more thoroughly discussed in Chapter 12—Hormone Therapy and Chapter 16—Reproductive Health.

It is important HCPs understand what fertility preservation options exist so they can relay the information to adolescents. Parents are advised to be involved in this process and should also understand the pros and cons of the different options. HCPs should acknowledge adolescents and parents may have different views around reproductive capacity and may therefore come to different decisions (Quain et al., 2020), which is why HCPs can be helpful in guiding this process.

HCPs should specifically pay attention to the developmental and psychological aspects of fertility preservation and decision-making competency for the individual adolescent. While adolescents may think they have made up their minds concerning their reproductive capacity, the possibility their opinions about having biologically related children in the future might change over time needs to be discussed with an HCP who has sufficient experience, is knowledgeable about adolescent development, and has experience working with parents.

Addressing the long-term consequences on fertility of gender-affirming medical treatments and ensuring transgender adolescents have realistic expectations concerning fertility preservation options or adoption cannot not be addressed with a one-time discussion but should be part of an ongoing conversation. This conversation should occur not only before initiating any medical intervention (puberty suppression, hormones, or surgeries), but also during further treatment and during transition.

Currently, there are only preliminary results from retrospective studies evaluating transgender adults and the decisions they made when they were young regarding the consequences of medical-affirming treatment on reproductive capacity. It is important not to make assumptions about what future adult goals an adolescent may have. Research in childhood cancer survivors found participants who acknowledged missed opportunities for fertility preservation reported distress and regret surrounding potential infertility (Armuand et al., 2014; Ellis et al., 2016; Lehmann et al., 2017). Furthermore, individuals with cancer who did not prioritize having biological children before treatment have reported "changing their minds" in survivorship (Armuand et al., 2014).

Given the complexities of the different fertility preservation options and the challenges HCPs may experience discussing fertility with the adolescent and the family (Tishelman et al., 2019), a fertility consultation is an important consideration for every transgender adolescent who pursues medical-affirming treatments unless the local situation is such that a fertility consultation is not covered by insurance or public health care plans, is not available locally, or the individual circumstances make this unpreferable.

Statement 6.11

We recommend when gender-affirming medical or surgical treatments are indicated for adolescents, health care professionals working with transgender and gender diverse adolescents

involve parent(s)/guardian(s) in the assessment and treatment process, unless their involvement is determined to be harmful to the adolescent or not feasible.

When there is an indication an adolescent might benefit from a gender-affirming medical or surgical treatment, involving the parent(s) or primary caregiver(s) in the assessment process is recommended in almost all situations (Edwards-Leeper & Spack, 2012; Rafferty et al., 2018). Exceptions to this might include situations in which an adolescent is in foster care, child protective services, or both, and custody and parent involvement would be impossible, inappropriate, or harmful. Parent and family support of TGD youth is a primary predictor of youth well-being and is protective of the mental health of TGD youth (Gower, Rider, Coleman et al., 2018; Grossman et al., 2019; Lefevor et al., 2019; McConnell et al., 2015; Pariseau et al., 2019; Ryan, 2009; Ryan et al., 2010; Simons et al., 2013; Wilson et al., 2016). Therefore, including parent(s)/caregiver(s) in the assessment process to encourage and facilitate increased parental understanding and support of the adolescent may be one of the most helpful practices available.

Parent(s)/caregiver(s) may provide key information for the clinical team, such as the young person's gender and overall developmental, medical, and mental health history as well as insights into the young person's level of current support, general functioning, and well-being. Concordance or divergence of reports given by the adolescent and their parent(s)/caregiver(s) may be important information for the assessment team and can aid in designing and shaping individualized youth and family supports (De Los Reyes et al., 2019; Katz-Wise et al., 2017). Knowledge of the family context, including resilience factors and challenges, can help providers know where special supports would be needed during the medical treatment process. Engagement of parent(s)/caregiver(s) is also important for educating families about various treatment approaches, ongoing follow-up and care needs, and potential treatment complications. Through psychoeducation regarding clinical gender care options and participation in the assessment process, which may unfold over time, parent(s)/caregiver(s) may better understand their adolescent child's gender-related experience and needs (Andrzejewski et al., 2020; Katz-Wise et al., 2017).

Parent/caregiver concerns or questions regarding the stability of gender-related needs over time and implications of various gender-affirming interventions are common and should not be dismissed. It is appropriate for parent(s)/caregiver(s) to ask these questions, and there are cases in which the parent(s)/caregiver(s)' questions or concerns are particularly helpful in informing treatment decisions and plans. For example, a parent/caregiver report may provide critical context in situations in which a young person experiences very recent or sudden self-awareness of gender diversity and a corresponding gender treatment request, or when there is concern for possible excessive peer and social media influence on a young person's current self-gender concept. Contextualization of the parent/caregiver report is also critical, as the report of a young person's gender history as provided by parent(s)/caregiver(s) may or may not align with the young person's self-report. Importantly, gender histories may be unknown to parent(s)/caregiver(s) because gender may be internal experience for youth, not known by others unless it is discussed. For this reason, an adolescent's report of their gender history and experience is central to the assessment process.

Some parents may present with unsupportive or antagonistic beliefs about TGD identities, clinical gender care, or both (Clark et al., 2020). Such unsupportive perspectives are an important therapeutic target for families. Although challenging parent perspectives may in some cases seem rigid, providers should not assume this is the case. There are many examples of parent(s)/caregiver(s) who, over time with support and psychoeducation, have become increasingly accepting of their TGD child's gender diversity and care needs.

Helping youth and parent(s)/caregiver(s) work together on important gender care decisions is a primary goal. However, in some cases, parent(s)/caregiver(s) may be too rejecting of their adolescent child and their child's gender needs to be part of the clinical evaluation process. In these situations, youth may require the engagement of larger systems of advocacy and support to move

forward with the necessary support and care (Dubin et al., 2020).

Statement 6.12

We recommend health care professionals assessing transgender and gender diverse adolescents only recommend gender-affirming medical or surgical treatments requested by the patient when:

Statement 6.12.a

The adolescent meets the diagnostic criteria of gender incongruence as per the ICD-11 in situations where a diagnosis is necessary to access health care. In countries that have not implemented the latest ICD, other taxonomies may be used although efforts should be undertaken to utilize the latest ICD as soon as practicable.

When working with TGD adolescents, HCPs should realize while a classification may give access to care, pathologizing transgender identities may be experienced as stigmatizing (Beek et al., 2016). Assessments related to gender health and gender diversity have been criticized, and controversies exist around diagnostic systems (Drescher, 2016).

HCPs should assess the overall gender-related history and gender care-related needs of youth. Through this assessment process, HCPs may provide a diagnosis when it is required to get access to transgender-related care.

Gender incongruence and gender dysphoria are the two diagnostic terms used in the World Health Organization's International Classification of Diseases (ICD) and the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM), respectively. Of these two widely used classification systems, the DSM is for psychiatric classifications only and the ICD contains all diseases and conditions related to physical as well as mental health. The most recent versions of these two systems, the DSM-5 and the ICD-11, reflect a long history of reconceptualizing and de-psychopathologizing gender-related diagnoses (American Psychiatric Association, 2013; World Health Organization, 2019a). Compared with the earlier version, the DSM-5 replaced gender identity disorder with gender dysphoria, acknowledging the distress experienced by some people stemming from the incongruence between experienced gender identity and the sex assigned at birth. In the most recent revision, the DSM-5-TR, no changes in the diagnostic criteria for gender dysphoria are made. However, terminology was adapted into the most appropriate current language (e.g., birth-assigned gender instead of natal-gender and gender-affirming treatment instead of gender reassignment (American Psychiatric Association, 2022). Compared with the ICD 10th edition, the gender incongruence classification was moved from the Mental Health chapter to the Conditions Related to Sexual Health chapter in the ICD-11. When compared with the DSM-5 classification of gender dysphoria, one important reconceptualization is distress is not a required indicator of the ICD-11 classification of gender incongruence (WHO, 2019a). After all, when growing up in a supporting and accepting environment, the distress and impairment criterion, an inherent part of every mental health condition, may not be applicable (Drescher, 2012). As such, the ICD-11 classification of gender incongruence may better capture the fullness of gender diversity experiences and related clinical gender needs.

Criteria for the ICD-11 classification gender incongruence of adolescence or adulthood require a marked and persistent incongruence between an individual's experienced gender and the assigned sex, which often leads to a need to "transition" to live and be accepted as a person of the experienced gender. For some, this includes hormonal treatment, surgery, or other health care services to enable the individual's body to align as much as required, and to the extent possible, with the person's experienced gender. Relevant for adolescents is the indicator that a classification cannot be assigned "prior to the onset of puberty." Finally, it is noted "that gender variant behaviour and preferences alone are not a basis for assigning the classification" (WHO, ICD-11, 2019a).

Criteria for the DSM-5 and DSM-5-TR classification of gender dysphoria in adolescence and adulthood denote "a marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration' (criterion A, fulfilled when 2 of 6 subcriteria are manifest; DSM-5, APA, 2013; DSM 5-TR, APA, 2022).

Of note, although a gender-related classification is one of the requirements for receiving medical gender-affirming care, such a classification alone does not indicate a person needs medical-affirming care. The range of youth experiences of gender incongruence necessitates professionals provide a range of treatments or interventions based on the individual's needs. Counseling, gender exploration, mental health assessment and, when needed, treatment with MHPs trained in gender development may all be indicated with or without the implementation of medical-affirming care.

Statement 6.12.b

The experience of gender diversity/incongruence is marked and sustained over time.

Identity exploration and consolidation are experienced by many adolescents (Klimstra et al., 2010; Topolewska-Siedzik & Cieciuch, 2018). Identity exploration during adolescence may include a process of self-discovery around gender and gender identity (Steensma, Kreukels et al., 2013). Little is known about how processes that underlie consolidation of gender identity during adolescence (e.g., the process of commitment to specific identities) may impact a young person's experience(s) or needs over time.

Therefore, the level of reversibility of a gender-affirming medical intervention should be considered along with the sustained duration of a young person's experience of gender incongruence when initiating treatment. Given potential shifts in gender-related experiences and needs during adolescence, it is important to establish the young person has experienced several years of persistent gender diversity/incongruence prior to initiating less reversible treatments such as gender-affirming hormones or surgeries. Puberty suppression treatment, which provides more time for younger adolescents to engage their decision-making capacities, also raises important considerations (see Statement 6.12f and Chapter 12—Hormone Therapy) suggesting the importance of a sustained experience of gender incongruence/diversity prior to initiation. However, in this age group of younger adolescents, several years is not always practical nor necessary given the premise of the treatment as a means to buy time while avoiding distress from irreversible pubertal changes. For youth who have experienced a shorter duration of gender incongruence, social transition-related and/or other medical supports (e.g., menstrual suppression/androgen blocking) may also provide some relief as well as furnishing additional information to the clinical team regarding a young person's broad gender care needs (see Statements 6.4, 6.6, and 6.7).

Establishing evidence of persistent gender diversity/incongruence typically requires careful assessment with the young person over time (see Statement 6.3). Whenever possible and when appropriate, the assessment and discernment process should also include the parent(s)/caregiver(s) (see Statement 6.11). Evidence demonstrating gender diversity/incongruence sustained over time can be provided via history obtained directly from the adolescent and parents/caregivers when this information is not documented in the medical records.

The research literature on continuity versus discontinuity of gender-affirming medical care needs/requests is complex and somewhat difficult to interpret. A series of studies conducted over the last several decades, including some with methodological challenges (as noted by Temple Newhook et al., 2018; Winters et al., 2018) suggest the experience of gender incongruence is not consistent for all children as they progress into adolescence. For example, a subset of youth who experienced gender incongruence or who socially transitioned prior to puberty over time can show a reduction in or even full discontinuation of gender incongruence (de Vries et al., 2010; Olson et al., 2022; Ristori & Steensma, 2016; Singh et al., 2021; Wagner et al., 2021). However, there has been less research focused on rates of continuity and discontinuity of gender incongruence and gender-related needs in pubertal and adolescent populations. The data available regarding broad unselected gender-referred pubertal/adolescent cohorts (from the Amsterdam transgender clinic) suggest that, following extended assessments over time, a subset of adolescents with gender incongruence presenting for gender care elect not to pursue gender-affirming medical care

(Arnoldussen et al., 2019; de Vries, Steensma et al., 2011). Importantly, findings from studies of gender incongruent pubertal/adolescent cohorts, in which participants who have undergone comprehensive gender evaluation over time, have shown persistent gender incongruence and gender-related need and have received referrals for medical gender care, suggest low levels of regret regarding gender-related medical care decisions (de Vries et al., 2014; Wiepjes et al., 2018). Critically, these findings of low regret can only currently be applied to youth who have demonstrated sustained gender incongruence and gender-related needs over time as established through a comprehensive and iterative assessment (see Statement 6.3).

Statement 6.12.c

The adolescent demonstrates the emotional and cognitive maturity required to provide informed consent/assent for the treatment.

The process of informed consent includes communication between a patient and their provider regarding the patient's understanding of a potential intervention as well as, ultimately, the patient's decision whether to receive the intervention. In most settings, for minors, the legal guardian is integral to the informed consent process: if a treatment is to be given, the legal guardian (often the parent[s]/caregiver[s]) provides the informed consent to do so. In most settings, assent is a somewhat parallel process in which the minor and the provider communicate about the intervention and the provider assesses the level of understanding and intention.

A necessary step in the informed consent/assent process for considering gender-affirming medical care is a careful discussion with qualified HCPs trained to assess the emotional and cognitive maturity of adolescents. The reversible and irreversible effects of the treatment, as well as fertility preservation options (when applicable), and all potential risks and benefits of the intervention are important components of the discussion. These discussions are required when obtaining informed consent/assent. Assessment of cognitive and emotional maturity is important because it helps the care team understand the adolescent's capacity to be informed.

The skills necessary to assent/consent to any medical intervention or treatment include the ability to 1) comprehend the nature of the treatment; 2) reason about treatment options, including the risks and benefits; 3) appreciate the nature of the decision, including the long-term consequences; and 4) communicate choice (Grootens-Wiegers et al., 2017). In the case of gender- affirming medical treatments, a young person should be well-informed about what the treatment may and may not accomplish, typical timelines for changes to appear (e.g., with gender-affirming hormones), and any implications of stopping the treatment. Gender-diverse youth should fully understand the reversible, partially reversible, and irreversible aspects of a treatment, as well as the limits of what is known about certain treatments (e.g., the impact of pubertal suppression on brain development (Chen and Loshak, 2020)). Gender-diverse youth should also understand, although many gender-diverse youth begin gender- affirming medical care and experience that care as a good fit for them long-term, there is a subset of individuals who over time discover this care is not a fit for them (Wiepjes et al., 2018). Youth should know such shifts are sometimes connected to a change in gender needs over time, and in some cases, a shift in gender identity itself. Given this information, gender diverse youth must be able to reason thoughtfully about treatment options, considering the implications of the choices at hand. Furthermore, as a foundation for providing assent, the gender-diverse young person needs to be able to communicate their choice.

The skills needed to accomplish the tasks required for assent/consent may not emerge at specific ages per se (Grootens-Wiegers et al., 2017). There may be variability in these capacities related to developmental differences and mental health presentations (Shumer & Tishelman, 2015) and dependent on the opportunities a young person has had to practice these skills (Alderson, 2007). Further, assessment of emotional and cognitive maturity must be conducted separately for each gender-related treatment decision (Vrouenraets et al., 2021).

The following questions may be useful to consider in assessing a young person's emotional and

cognitive readiness to assent or consent to a specific gender-affirming treatment:

- Can the young person think carefully into the future and consider the implications of a partially or fully irreversible intervention?
- Does the young person have sufficient self-reflective capacity to consider the possibility that gender-related needs and priorities can develop over time, and gender-related priorities at a certain point in time might change?
- Has the young person, to some extent, thought through the implications of what they might do if their priorities around gender do change in the future?
- Is the young person able to understand and manage the day-to-day short- and long-term aspects of a specific medical treatment (e.g., medication adherence, administration, and necessary medical follow-ups)?

Assessment of emotional and cognitive maturity may be accomplished over time as the care team continues to engage in conversations about the treatment options and affords the young person the opportunity to practice thinking into the future and flexibly consider options and implications. For youth with neurodevelopmental and/or some types of mental health differences, skills for future thinking, planning, big picture thinking, and self-reflection may be less-well developed (Dubbelink & Geurts, 2017). In these cases, a more careful approach to consent and assent may be required, and this may include additional time and structured opportunities for the young person to practice the skills necessary for medical decision-making (Strang, Powers et al., 2018).

For unique situations in which an adolescent minor is consenting for their own treatment without parental permission (see Statement 6.11), extra care must be taken to support the adolescent's informed decision-making. This will typically require greater levels of engagement of and collaboration between the HCPs working with the adolescent to provide the young person appropriate cognitive and emotional support to consider options, weigh benefits and potential challenges/costs, and develop a plan for any needed (and potentially ongoing) supports associated with the treatment.

Statement 6.12.d

The adolescent's mental health concerns (if any) that may interfere with diagnostic clarity, capacity to consent, and/or gender-affirming medical treatments have been addressed.

Evidence indicates TGD adolescents are at increased risk of mental health challenges, often related to family/caregiver rejection, non-affirming community environments, and neurodiversity-related factors (e.g., de Vries et al., 2016; Pariseau et al., 2019; Ryan et al., 2010; Weinhardt et al., 2017). A young person's mental health challenges may impact their conceptualization of their gender development history and gender identity-related needs, the adolescent's capacity to consent, and the ability of the young person to engage in or receive medical treatment. Additionally, like cisgender youth, TGD youth may experience mental health concerns irrespective of the presence of gender dysphoria or gender incongruence. In particular, depression and self-harm may be of specific concern; many studies reveal depression scores and emotional and behavioral problems comparable to those reported in populations referred to mental health clinics (Leibowitz & de Vries, 2016). Higher rates of suicidal ideation, suicide attempts, and self-harm have also been reported (de Graaf et al., 2020). In addition, eating disorders occur more frequently than expected in non-referred populations (Khatchadourian et al., 2013; Ristori et al., 2019; Spack et al., 2012). Importantly, TGD adolescents show high rates of autism spectrum disorder/characteristics (Øien et al., 2018; van der Miesen et al., 2016; see also Statement 6.1d). Other neurodevelopmental presentations and/or mental health challenges may also be present, (e.g., ADHD, intellectual disability, and psychotic disorders (de Vries, Doreleijers et al., 2011; Meijer et al., 2018; Parkes & Hall, 2006).

Of note, many transgender adolescents are well-functioning and experience few if any mental health concerns. For example, socially transitioned pubertal adolescents who receive medical

gender- affirming treatment at specialized gender clinics may experience mental health outcomes equivalent to those of their cisgender peers (e.g., de Vries et al., 2014; van der Miesen et al., 2020). A provider's key task is to assess the direction of the relationships that exist between any mental health challenges and the young person's self-understanding of gender care needs and then prioritize accordingly.

Mental health difficulties may challenge the assessment and treatment of gender-related needs of TGD adolescents in various ways:

1. First, when a TGD adolescent is experiencing acute suicidality, self-harm, eating disorders, or other mental health crises that threaten physical health, safety must be prioritized. According to the local context and existing guidelines, appropriate care should seek to mitigate the threat or crisis so there is sufficient time and stabilization for thoughtful gender-related assessment and decision-making. For example, an actively suicidal adolescent may not be emotionally able to make an informed decision regarding gender-affirming medical/surgical treatment. If indicated, safety-related interventions should not preclude starting gender-affirming care.
2. Second, mental health can also complicate the assessment of gender development and gender identity-related needs. For example, it is critical to differentiate gender incongruence from specific mental health presentations, such as obsessions and compulsions, special interests in autism, rigid thinking, broader identity problems, parent/child interaction difficulties, severe developmental anxieties (e.g., fear of growing up and pubertal changes unrelated to gender identity), trauma, or psychotic thoughts. Mental health challenges that interfere with the clarity of identity development and gender-related decision-making should be prioritized and addressed.
3. Third, decision-making regarding gender-affirming medical treatments that have life-long consequences requires thoughtful, future-oriented thinking by the adolescent, with support from the parents/caregivers, as indicated (see Statement 6.11). To be able to make such an informed decision, an adolescent should be able to understand the issues, express a choice, appreciate and give careful thought regarding the wish for medical-affirming treatment (see Statement 6.12c). Neurodevelopmental differences, such as autistic features or autism spectrum disorder (see Statement 6.1d, e.g., communication differences; a preference for concrete or rigid thinking; differences in self-awareness, future thinking and planning), may challenge the assessment and decision-making process; neurodivergent youth may require extra support, structure, psychoeducation, and time built into the assessment process (Strang, Powers et al., 2018). Other mental health presentations that involve reduced communication and self-advocacy, difficulty engaging in assessment, memory and concentration difficulties, hopelessness, and difficulty engaging in future-oriented thinking may complicate assessment and decision-making. In such cases, extended time is often necessary before any decisions regarding medical-affirming treatment can be made.
4. Finally, while addressing mental health concerns is important during the course of medical treatment, it does not mean all mental health challenges can or should be resolved completely. However, it is important any mental health concerns are addressed sufficiently so that gender -affirming medical treatment can be provided optimally (e.g., medication adherence, attending follow-up medical appointments, and self-care, particularly during a postoperative course).

Statement 6.12.e

The adolescent has been informed of the reproductive effects, including the potential loss of fertility, and available options to preserve fertility, and these have been discussed in the context of the adolescent's stage of pubertal development.

For guidelines regarding the clinical approach, the scientific background, and the rationale, see Chapter 12—Hormone Therapy and Chapter 16—Reproductive Health.

Statement 6.12.f

The adolescent has reached Tanner stage 2 of puberty for pubertal suppression to be initiated.

The onset of puberty is a pivotal point for many gender diverse youth. For some, it creates an intensification of their gender incongruence, and for others, pubertal onset may lead to gender fluidity (e.g., a transition from binary to nonbinary gender identity) or even attenuation of a previously affirmed gender identity (Drummond et al., 2008; Steensma et al., 2011, Steensma, Kreukels et al., 2013; Wallien & Cohen-Kettenis, 2008). The use of puberty-blocking medications, such as GnRH analogues, is not recommended until children have achieved a minimum of Tanner stage 2 of puberty because the experience of physical puberty may be critical for further gender identity development for some TGD adolescents (Steensma et al., 2011). Therefore, puberty blockers should not be implemented in prepubertal gender diverse youth (Waal & Cohen-Kettenis, 2006). For some youth, GnRH agonists may be appropriate in late stages or in the post-pubertal period (e.g., Tanner stage 4 or 5), and this should be highly individualized. See Chapter 12—Hormone Therapy for a more comprehensive review of the use of GnRH agonists.

Variations in the timing of pubertal onset is due to multiple factors (e.g., sex assigned at birth, genetics, nutrition, etc.). Tanner staging refers to five stages of pubertal development ranging from prepubertal (Tanner stage 1) to post-pubertal, and adult sexual maturity (Tanner stage 5) (Marshall & Tanner, 1969, 1970). For assigned females at birth, pubertal onset (e.g., gonadarche) is defined by the occurrence of breast budding (Tanner stage 2), and for birth-assigned males, the achievement of a testicular volume of greater than or equal to 4 mL (Roberts & Kaiser, 2020). An experienced medical provider should be relied on to differentiate the onset of puberty from physical changes such as pubic hair and apocrine body odor due to sex steroids produced by the adrenal gland (e.g., adrenarche) as adrenarche does not warrant the use of puberty-blocking medications (Roberts & Kaiser, 2020). Educating parents and families about the difference between adrenarche and gonadarche helps families understand the timing during which shared decision-making about gender-affirming medical therapies should be undertaken with their multidisciplinary team.

The importance of addressing other risks and benefits of pubertal suppression, both hypothetical and actual, cannot be overstated. Evidence supports the existence of surgical implications for transgender girls who proceed with pubertal suppression (van de Grift et al., 2020). Longitudinal data exists to demonstrate improvement in romantic and sexual satisfaction for adolescents receiving puberty suppression, hormone treatment and surgery (Bungener et al., 2020). A study on surgical outcomes of laparoscopic intestinal vaginoplasty (performed because of limited genital tissue after the use of puberty blockers) in transgender women revealed that the majority experienced orgasm after surgery (84%), although a specific correlation between sexual pleasure outcomes and the timing of pubertal suppression initiation was not discussed in the study (Bouman, van der Sluis et al., 2016), nor does the study apply to those who would prefer a different surgical procedure. This underscores the importance of engaging in discussions with families about the future unknowns related to surgical and sexual health outcomes.

Statement 6.12.g

The adolescent had 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.

GAHT leads to anatomical, physiological, and psychological changes. The onset of the anatomic effects (e.g., clitoral growth, breast growth, vaginal mucosal atrophy) may begin early after the initiation of therapy, and the peak effect is expected at 1–2 years (T'Sjoen et al., 2019). To

ensure sufficient time for psychological adaptations to the physical change during an important developmental time for the adolescent, 12 months of hormone treatment is suggested. Depending upon the surgical result required, a period of hormone treatment may need to be longer (e.g., sufficient clitoral virilization prior to metoidioplasty/phalloplasty, breast growth and skin expansion prior to breast augmentation, softening of skin and changes in facial fat distribution prior to facial GAS) (de Blok et al., 2021).

For individuals who are not taking hormones prior to surgical interventions, it is important surgeons review the impact of hormone therapy on the proposed surgery. In addition, for individuals undergoing gonadectomy who are not taking hormones, a plan for hormone replacement can be developed with their prescribing professional prior to surgery.

Consideration of ages for gender-affirming medical and surgical treatment for adolescents

Age has a strong, albeit imperfect, correlation with cognitive and psychosocial development and may be a useful objective marker for determining the potential timing of interventions (Ferguson et al., 2021). Higher (i.e., more advanced) ages may be required for treatments with greater irreversibility, complexity, or both. This approach allows for continued cognitive/emotional maturation that may be required for the adolescent to fully consider and consent to increasingly complex treatments (see Statement 6.12c).

A growing body of evidence indicates providing gender-affirming treatment for gender diverse youth who meet criteria leads to positive outcomes (Achille et al., 2020; de Vries et al., 2014; Kuper et al., 2020). There is, however, limited data on the optimal timing of gender-affirming interventions as well as the long-term physical, psychological, and neurodevelopmental outcomes in youth (Chen et al., 2020; Chew et al., 2018; Olson-Kennedy et al., 2016). Currently, the only existing longitudinal studies evaluating gender diverse youth and adult outcomes are based on a specific model (i.e., the Dutch approach) that involved a comprehensive initial assessment with follow-up. In this approach, pubertal suppression was considered at age 12, GAHT at age 16, and surgical interventions after age 18 with exceptions in some cases. It is not clear if deviations from this approach would lead to the same or different outcomes. Longitudinal studies are currently underway to better define outcomes as well as the safety and efficacy of gender-affirming treatments in youth (Olson-Kennedy, Garofalo et al., 2019; Olson-Kennedy, Rosenthal et al., 2019). While the long-term effects of gender-affirming treatments initiated in adolescence are not fully known, the potential negative health consequences of delaying treatment should also be considered (de Vries et al., 2021). As the evidence base regarding outcomes of gender-affirming interventions in youth continues to grow, recommendations on the timing and readiness for these interventions may be updated.

Previous guidelines regarding gender-affirming treatment of adolescents recommended partially reversible GAHT could be initiated at approximately 16 years of age (Coleman et al., 2012; Hembree et al., 2009). More recent guidelines suggest there may be compelling reasons to initiate GAHT prior to the age of 16, although there are limited studies on youth who have initiated hormones prior to 14 years of age (Hembree et al., 2017). A compelling reason for earlier initiation of GAHT, for example, might be to avoid prolonged pubertal suppression, given potential bone health concerns and the psychosocial implications of delaying puberty as described in more detail in Chapter 12—Hormone Therapy (Klink, Caris et al., 2015; Schagen et al., 2020; Vlot et al., 2017; Zhu & Chan, 2017). Puberty is a time of significant brain and cognitive development. The potential neurodevelopmental impact of extended pubertal suppression in gender diverse youth has been specifically identified as an area in need of continued study (Chen et al., 2020). While GnRH analogs have been shown to be safe when used for the treatment of precocious puberty, there are concerns delaying exposure to sex hormones (endogenous or exogenous) at a time of peak bone mineralization may lead to decreased bone mineral density. The potential decrease in bone mineral density as well as the clinical significance of any decrease requires continued study (Klink, Caris et al., 2015; Lee, Finlayson et al.,

2020; Schagen et al., 2020). The potential negative psychosocial implications of not initiating puberty with peers may place additional stress on gender diverse youth, although this has not been explicitly studied. When considering the timing of initiation of gender-affirming hormones, providers should compare the potential physical and psychological benefits and risks of starting treatment with the potential risks and benefits of delaying treatment. This process can also help identify compelling factors that may warrant an individualized approach.

Studies carried out with trans masculine youth have demonstrated chest dysphoria is associated with higher rates of anxiety, depression, and distress and can lead to functional limitations, such as avoiding exercising or bathing (Mehringer et al., 2021; Olson-Kennedy, Warus et al., 2018; Sood et al., 2021). Testosterone unfortunately does little to alleviate this distress, although chest masculinization is an option for some individuals to address this distress long-term. Studies with youth who sought chest masculinization surgery to alleviate chest dysphoria demonstrated good surgical outcomes, satisfaction with results, and minimal regret during the study monitoring period (Marinkovic & Newfield, 2017; Olson-Kennedy, Warus et al., 2018). Chest masculinization surgery can be considered in minors when clinically and developmentally appropriate as determined by a multidisciplinary team experienced in adolescent and gender development (see relevant statements in this chapter). The duration or current use of testosterone therapy should not preclude surgery if otherwise indicated. The needs of some TGD youth may be met by chest masculinization surgery alone. Breast augmentation may be needed by trans feminine youth, although there is less data about this procedure in youth, possibly due to fewer individuals requesting this procedure (Boskey et al., 2019; James, 2016). GAHT, specifically estrogen, can help with development of breast tissue, and it is recommended youth have a minimum of 12 months of hormone therapy, or longer as is surgically indicated, prior to breast augmentation unless hormone therapy is not clinically indicated or is medically contraindicated.

Data are limited on the optimal timing for initiating other gender-affirming surgical treatments in adolescents. This is partly due to the limited access to these treatments, which varies in different geographical locations (Mahfouda et al., 2019). Data indicate rates of gender-affirming surgeries have increased since 2000, and there has been an increase in the number of TGD youth seeking vaginoplasty (Mahfouda et al., 2019; Milrod & Karasic, 2017). A 2017 study of 20 WPATH-affiliated surgeons in the US reported slightly more than half had performed vaginoplasty in minors (Milrod & Karasic, 2017). Limited data are available on the outcomes for youth undergoing vaginoplasty. Small studies have reported improved psychosocial functioning and decreased gender dysphoria in adolescents who have undergone vaginoplasty (Becker et al., 2018; Cohen-Kettenis & van Goozen, 1997; Smith et al.,2001). While the sample sizes are small, these studies suggest there may be a benefit for some adolescents to having these procedures performed before the age of 18. Factors that may support pursuing these procedures for youth under 18 years of age include the increased availability of support from family members, greater ease of managing postoperative care prior to transitioning to tasks of early adulthood (e.g., entering university or the workforce), and safety concerns in public spaces (i.e., to reduce transphobic violence) (Boskey et al., 2018; Boskey et al., 2019; Mahfouda et al., 2019). Given the complexity and irreversibility of these procedures, an assessment of the adolescent's ability to adhere to postsurgical care recommendations and to comprehend the long-term impacts of these procedures on reproductive and sexual function is crucial (Boskey et al., 2019). Given the complexity of phalloplasty, and current high rates of complications in comparison to other gender-affirming surgical treatments, it is not recommended this surgery be considered in youth under 18 at this time (see Chapter 13—Surgery and Postoperative Care).

Additional key factors that should be taken into consideration when discussing the timing of interventions with youth and families are addressed in detail in statements 6.12a-f. For a summary of the criteria/recommendations for medically necessary gender-affirming medical treatment in adolescents, see Appendix D.

a regression of one Tanner stage. Thus, if there is only Tanner stage 2 breast development, it typically fully regresses to the prepubertal Tanner stage 1; the same is typically true with Tanner stage 2 testes (often not even discernable to the patient and is not associated with development of secondary sex characteristics).

Given GnRHas work through GnRH receptor desensitization, if there's no uptick in endogenous GnRH stimulation of the pituitary (the first biochemical sign of puberty), there's no need for GnRH receptor desensitization. In addition, because of the wide variability in the timing of the start of puberty (as noted above), it is hard to justify using a GnRHa that might have some unknown risk if there's no physiological benefit before pubertal onset. Using a GnRHa with a child at Tanner stage 1 would only be indicated in cases of constitutional delay in growth and puberty, likely alongside the start of GAHT.

However, the use of a GnRHa could be considered in a child who, due to a constitutional delay in growth and puberty, starts GAHT while still in Tanner Stage 1. Initiating GAHT may activate the hypothalamic-pituitary gonadal axis in the beginning but may also mask the effects on the body of this activation. To avoid body changes with the potential to exacerbate an individual's gender incongruence, the GnRHa can be started as an adjunctive therapy to the GAHT shortly after the initiation of the GAHT to provide for pubertal development of the identified phenotype.

In addition, the suppression of the development of secondary sex characteristics is most effective when sex hormonal treatment is initiated in early to mid-puberty when compared with the initiation of sex hormonal treatment after puberty is completed (Bangalore-Krisha et al., 2019). Correspondingly, for adolescents who have already completed endogenous puberty and are considering starting GAHT, GnRHas can be used to inhibit physical functions, such as menses or erections, and can serve as a bridge until the adolescent, guardian(s) (if the adolescent is not able to consent independently), and treatment team reach a decision (Bangalore-Krishna et al., 2019; Rosenthal, 2021).

The onset of puberty occurs through reactivation of the hypothalamic-pituitary-gonadal axis. Clinical assessment of the stages of puberty is based on physical features that reflect that reactivation. In individuals with functioning ovaries, Tanner stage 2 is characterized by the budding of the mammary gland. The development of the mammary gland occurs from exposure to estrogen produced by the ovaries. In individuals with functioning testes, Tanner stage 2 is characterized by an increase in testicular volume (typically greater than 4 ml). The growth of the testes is mediated through the gonadotropins luteinizing hormone (LH) and follicle stimulating hormone (FSH). In the later stages, the testes produce enough testosterone to induce masculinization of the body.

Statement 12.2

We recommend health care professionals use GnRH agonists to suppress endogenous sex hormones in eligible* transgender and gender diverse people for whom puberty blocking is indicated. For supporting text, see Statement 12.4.

Statement 12.3

We suggest health care professionals prescribe progestins (oral or injectable depot) for pubertal suspension in eligible* transgender and gender diverse youth when GnRH agonists are not available or are cost prohibitive. For supporting text, see Statement 12.4.

Statement 12.4.

We suggest health care professionals prescribe GnRH agonists to suppress sex steroids without concomitant sex steroid hormone replacement in eligible transgender and gender diverse adolescents seeking such intervention who are well into or have completed pubertal development (past Tanner stage 3) but are unsure about or do not wish to begin sex steroid hormone therapy.

GnRHas reduce gonadotrophin and sex steroid concentrations in TGD adolescents and thus halt the further development of secondary sex characteristics (Schagen et al., 2016). Their use is generally safe with the development of hypertension being the only short-term adverse event reported in the literature (Delemarre-van de Waal & Cohen-Kettenis, 2006; Klink, Bokenkamp et al., 2015). GnRHas prevent the pituitary gland from

secreting LH and FSH (Gava et al., 2020). When the gonadotropins decrease, the gonad is no longer stimulated to produce sex hormones (estrogens or androgens), and the sex hormone levels in the blood decrease to prepubertal levels. GnRHa treatment leads to partial regression of the initial stages of the already developed secondary sex characteristics (Bangalore et al., 2019). TGD adolescents with functioning ovaries will experience diminished growth of breast tissue, and if treatment is started at Tanner stage 2, the breast tissue may disappear completely (Shumer et al., 2016). Menarche can be prevented or discontinued following the administration of GnRHas in adolescents with a uterus. In TGD adolescents with functioning testes, testicular volume will regress to a lower volume.

When GnRHa treatment is started in adolescents at the later phases of pubertal development, some physical changes of pubertal development, such as late-stage breast development in TGD adolescents with functioning ovaries and a lower voice and growth of facial hair in TGD adolescents with functioning testes, will not regress completely, although any further progression will be stopped (Delemarre-van de Waal & Cohen-Kettenis, 2006). GnRHas have been used since 1981 for the treatment of central precocious puberty (Comite et al., 1981; Laron et al., 1981), and their benefits are well established (please also see the statements in Chapter 6—Adolescents). The use of GnRHas in individuals with central precocious puberty is regarded as both safe and effective, with no known long-term adverse effects (Carel et al., 2009). However, the use of GnRHas in TGD adolescents is considered off-label because they were not initially developed for this purpose. Nonetheless, data from adolescents prescribed GnRHas in a similar dose and fashion demonstrate effectiveness in delaying the onset of puberty although the long-term effects on bone mass have not been well established (Klink, Caris et al., 2015). Although long-term data are more limited in TGD adolescents than in adolescents with precocious puberty, data collection specifically in this population are ongoing (Klaver et al., 2020; Lee, Finlayson et al., 2020; Millington et al., 2020; Olson-Kennedy, Garofalo et al., 2019).

We recognize even though GnRHas are a medically necessary treatment, they may not be available for eligible adolescents because it is not covered by health insurance plans in some countries or may be cost-prohibitive. Therefore, other approaches should be considered in these cases, such as oral or injectable progestin formulations. In addition, for adolescents older than 14 years, there are currently no data to inform HCPs whether GnRHas can be administered as monotherapy (and for what duration) without posing a significant risk to skeletal health. This is because the skeleton will not have any exposure to adequate levels of sex steroid hormones (Rosenthal, 2021).

A prolonged hypogonadal state in adolescence, whether due to medical conditions such as hypergonadotropic hypogonadism, iatrogenic causes such as GnRHa monotherapy or physiological conditions such as conditional delay of growth and development, is often associated with an increased risk of poor bone health later in life (Bertelloni et al., 1998; Finkelstein et al., 1996). However, bone mass accrual is a multifactorial process that involves a complex interplay between endocrine, genetic, and lifestyle factors (Anai et al., 2001). When deciding on the duration of GnRHa monotherapy, all contributing factors should be considered, including factors such as pretreatment bone mass, bone age, and pubertal stage from an endocrine perspective and height gain, as well as psychosocial factors such as mental maturity and developmental stage relative to one's adolescent cohort and the adolescent's individual treatment goals (Rosenthal, 2021). For these reasons, a multidisciplinary team and an ongoing clinical relationship with the adolescent and the family should be maintained when initiating GnRHa treatment (see Statements 6.8, 6.9, and 6.12 in Chapter 6—Adolescents). The clinical course of the treatment, e.g., the development of bone mass during GnRHa treatment and the adolescent's response to treatment, can help to determine the length of GnRHa monotherapy.

Statement 12.5

We recommend health care professionals prescribe sex hormone treatment regimens as part of gender-affirming treatment in eligible*

transgender and gender diverse adolescents who are at least Tanner stage 2, with parental/guardian involvement unless their involvement is determined to be harmful or unnecessary to the adolescent. For supporting text, see Statement 12.6.

Statement 12.6

We recommend health care professionals measure hormone levels during gender-affirming treatment to ensure endogenous sex steroids are lowered and administered sex steroids are maintained at a level appropriate for the treatment goals of transgender and gender diverse people according to the Tanner stage.

Sex steroid hormone therapy generally comprises two treatment regimens, depending on the timing of the GnRHa treatment. When GnRHa treatment is started in the early stages of endogenous pubertal development, puberty corresponding with gender identity or embodiment goals is induced with doses of sex steroid hormones similar to those used in peripubertal hypogonadal adolescents. In this context, adult doses of sex steroid hormones are typically reached over approximately a 2-year period (Chantrapanichkul et al., 2021). When GnRHa treatment is started in late- or postpubertal transgender adolescents, sex steroid hormones can be given at a higher starting dose and increased more rapidly until a maintenance dose is achieved, resembling treatment protocols used in transgender adults (Hembree et al., 2017). An additional advantage of GnRHa treatment is sex steroid hormones do not have to be administered in supraphysiological doses, which would otherwise be needed to suppress endogenous sex steroid production (Safer & Tangpricha, 2019). For TGD individuals with functioning testes, GnRHa treatment (or another testosterone-blocking medication) should be continued until such time as the TGD adolescent/young adult ultimately undergoes gonadectomy, if this surgical procedure is pursued as a medically necessary part of their gender-affirming care. Once adult levels of testosterone are reached in TGD individuals with functioning ovaries who have been initially suppressed with GnRHa's, testosterone alone at physiological doses is typically sufficient to lower ovarian estrogen secretion, and GnRHas can be discontinued as discussed below (Hembree et al., 2017). For TGD adolescents with functioning ovaries who are new to care, GAHT can be accomplished with physiological doses of testosterone alone without the need for concomitant GnRHa administration (Hembree et al., 2017).

Gender-affirming sex steroid hormone therapy induces the development of secondary sex characteristics of the gender identity. Also, the rate of bone mineralization, which decreases during treatment with GnRHa's, rapidly recovers (Klink, Caris et al., 2015). During GnRHa treatment in early-pubertal TGD adolescents, the bone epiphyseal plates are still unfused (Kvist et al., 2020; Schagen et al., 2020). Following the initiation of sex steroid hormone treatment, a growth spurt can occur, and bone maturation continues (Vlot et al., 2017). In postpubertal TGD adolescents, sex steroid hormone treatment will not affect height since the epiphyseal plates have fused, and bone maturation is complete (Vlot et al., 2017).

In TGD adolescents with functioning testes, the use of 17-ß-estradiol for pubertal induction is preferred over that of synthetic estrogens, such as the more thrombogenic ethinyl estradiol (see Appendix D (Asscheman et al., 2015). It is still necessary to either continue GnRHa's to suppress endogenous testosterone production or transition to another medication that suppresses endogenous testosterone production (Rosenthal et al., 2016). Breast development and a female-typical fat distribution are among a number of physical changes that occur in response to estrogen treatment. See Appendix C—Table 1.

For TGD adolescents seeking masculinizing treatment, androgens are available as injectable preparations, transdermal formulations, and subcutaneous pellets. For pubertal induction, the use of testosterone-ester injection is generally recommended by most experts initially because of cost, availability, and experience (Shumer et al., 2016). It is advised to continue GnRHas at least until a maintenance level of testosterone is reached. In response to androgen treatment, virilization of the body occurs, including a lowering of the voice, more muscular development particularly in the upper body, growth of facial and body hair, and clitoral enlargement (Rosenthal et al., 2016). See Appendix C—Table 1.

Ex. 29

Published in final edited form as:
Int J Transgend. 2015 ; 16(2): 97–102. doi:10.1080/15532739.2015.1075929.

The Role of Assent in the Treatment of Transgender Adolescents

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Keywords

transgender; adolescent; assent; consent; developmental delay; autism

Introduction

There is evolving evidence that individuals with certain forms of developmental disabilities may have higher prevalence of gender noncomformity than individuals without developmental disabilities (Bedard, Zhang, & Zucker, 2010; de Vries, Noens, Cohen-Kettenis, van Berckelaer-Onnes, & Doreleijers, 2010; Gallucci, Hackerman, & Schmidt, 2005; Landén & Rasmussen, 1997; Robinow, 2009; Strang et al., 2014). Gender Dysphoria (GD) is a diagnosis formalized by the Diagnostic and Statistical Manual of Mental Health Disorders, 5th edition, used to describe incongruence between the gender assigned at birth and the experienced or desired gender. GD is only diagnosed when this incongruence is accompanied by clinically significant distress or impairment in social, school, or other important areas of functioning (American Psychiatric Association, 2013). Because adolescence is a period marked by robust cognitive, social, and emotional changes, many in the field recommend that those with suspected gender dysphoria and/or gender incongruence have a careful evaluation prior to consideration of a medical intervention (e.g., Tishelman, Kaufman, Edwards-Leeper, Mandel, Shumer & Spack). The Endocrine Society and the World Professional Association of Transgender Health (WPATH) recommend treatment with medications which suppress puberty, and also with cross-sex hormones, in carefully assessed adolescents presenting in gender clinics as transgender (Coleman et al., 2012; Hembree et al., 2009).

In this paper we illustrate some of the general complexities that can occur in this field through the use of a case composite report, based on our clinical experience at a gender clinic associated with a large pediatric hospital in the United States. We describe an adolescent with co-occurring gender dysphoria and developmental challenges, and then discuss issues of patient assent and prescribing medical therapy in this patient population.

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Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

Conflict of Interest: The authors have no conflicts of interest to disclose.

Shumer 29
EXHIBIT NO.
FOR IDENTIFICATION
DATE: 4-2-24
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Case Composite Report

Psychological Evaluation

The patient's and family's initial on-site interaction with our clinic consisted of a comprehensive psychological evaluation. The goals of the evaluation, conducted by a licensed clinical psychologist, are to independently evaluate the child's gender status and identity, understand the child and family's needs, and provide information relevant to the possible initiation of medical treatment. Within this context, the evaluation provides information regarding a youth's mental health status, developmental concerns, and family and social support (see Tishelman et al, in press, for more detail). The evaluation consisted of a clinical interview with the patient and father, along with standardized measures addressing behavioral issues, anxiety, depression, and an autism and ADHD screening. These included the Child Behavior Checklist and Youth Self Report (Achenback & Rescorla, 2001), the Children's Depression Inventory 2 (Kovacs, 1992), and the Piers-Harris Children's Self-Concept Scale (Piers & Herzberg, 2002)). In addition, a number of measures were used to assess gender identity, including the Utrecht Gender Dysphoria Scale (Cohen-Kettenis & VanGoozen, 1997) and the Recalled Childhood Gender Identity/Gender Role Questionnaire (Zucker et al., 2006); relevant documents were reviewed (e.g., prior neuropsychological assessment data), and collateral informants were contacted with prior family authorization (e.g., psychotherapist; school counselor).

Referral Information

John was a 14 year-old natal male of African descent when he was referred to our clinic for a psychological evaluation, to assist in determining whether medical intervention would be beneficial. He was referred to as John, and with male pronouns, at the time of referral and had not transitioned to living as a female. John and his family expressed interest in pursuing puberty-blocking medication. His father, John's primary caretaker, stated at the outset of the evaluation that John wanted to be a girl.

Background Information

John was adopted from foster care when he was two-years old. Little is known of his early years, and he was placed into foster care after being found abandoned at a fast food restaurant at 18 months of age. His current family consisted of another, older adopted male, and his father. His adoptive mother was deceased.

According to his father, John's development was delayed, with his receptive and expressive language posing particular challenges. By the time he presented in our clinic he had been tested multiple times throughout his life. The most recent neuropsychological evaluation, conducted about 1 year prior to the evaluation, noted that his nonverbal skills were in the low average range, but that he has significant cognitive challenges related to verbal processing, expression and comprehension. Other important areas of concern for John included severe behavioral dysregulation, with a history of tantrums at school and at home, and verbal aggression. He was in a regular 8th grade classroom, at school, with a 1:1 aide at his side throughout the day, and received a range of other academic services tailored to his needs. John's father reported that he was always "different" with regard to gender. He stated

that as a toddler and preschooler he liked to play with dolls and with girls, was always disinterested in sports and other activities stereotypically often associated with boys, and very early on insisted on wearing female underwear. At approximately age 12, John started to experiment with wearing make-up. His father reported that he was very accepting, noting that they had a number of close friends and relatives who were "gay."

Given John's disruptive behavior at school, and his atypical presentation, John was often ostracized and bullied by boys at school. This had been a chronic problem, although his father had strongly advocated on his behalf. John did have some female friends at school and a couple of male and female youth in his neighborhood who were accepting of him. At about the age of 11, John started saying that he did not like boys, and did not want to be a boy. According to his father, starting at the age of 12, John started saying that he was a girl and not a real boy. His father took him to a psychotherapist with experience working with gender variant youth, where John and his family were in therapy for several months prior to the coming to our clinic. When contacted, John's therapist, Dr. Smith, stated that John's father was devoted to John, and wanted to act on his behalf, whatever that path might be. Dr. Smith also stated that he felt that John believed he was a girl, but that he was not sure that John had a grasp of what that entailed in a deeper sense.

John presented as happy to be at the evaluation. It was notably difficult for him to participate in the evaluation, however. He was observed not to comprehend some basic words, such as "sad' and "angry," and was unaware of typical terms for many body parts. He had a propensity to answer yes-no questions, even if he did not actually comprehend what was being asked. He often asked if his father could answer in his stead and stated that he was bored. Nevertheless, based on the confluence of information obtained, he appeared to meet DSM-5 criteria for gender dysphoria (American Psychiatric Association, 2013). In our clinic's multidisciplinary conference, we discussed whether the patient would be eligible to receive hormonal suppression as outline by The Endocrine Society's clinical practice guidelines (Hembree et al., 2009) and the World Professional Association for Transgender Health (WPATH) standards of care for treatment of transgender adolescents (Coleman et al., 2012). According to The Endocrine Society guidelines, patients are eligible for pubertal suppression only if they meet several readiness criteria. For example, patients must meet criteria for gender dysphoria, be at least Tanner stage 2, and have adequate psychologic and social support, all criteria met by our patient. However, they must also have "knowledge and understanding of the expected outcomes of GnRH analog treatment [the medication which blocks production of pubertal hormones], cross-sex hormone treatment, and sex reassignment surgery, as well as the medical and social risks and benefits of sex reassignment (Hembree et al., 2009). During the initial psychological assessment the patient had not demonstrated this level of understanding.

Similarly, the WPATH Standards of Care suggests that the adolescent give informed consent, in addition to consent of the parents, as a minimum criterion prior to receiving puberty suppressing medication (Coleman et al., 2012). The American Academy of Pediatrics (AAP) Committee on Bioethics recognizes that children and adolescents are not capable of providing fully informed consent, but that decision-making involving older children and

adolescents "should include, to the greatest extent feasible, the assent of the patient". The AAP describes assent as including the following:

1. Helping the patient achieve a developmentally appropriate awareness of the nature of his or her condition.
2. Telling the patient what he or she can expect with tests and treatment(s).
3. Making a clinical assessment of the patient's understanding of the situation and the factors influencing how he or she is responding (including whether there is inappropriate pressure to accept testing or therapy) (AAP, 1995).

Cameron & Murphy (2006) evaluate the process of obtaining consent in a research study with participants at four levels of comprehension ability. In their discussion, they present a number of implications of their work, and suggest that the consent process may be more time consuming, that it may need to be individualized, and that adapted procedures may be warranted. Others also explore such questions (e.g., Lewis & Porter, 2004; Lloyd, 2012), suggesting that in many cases great care must be taken, and approaches may need to be adapted to ensure no undue coercion. In addition, literature discussing pediatric assent for research emphasizes that ability to understand all nuances of the research is not required for assent (Roth-Cline & Nelson, 2013). Creative methods of informing children about risks and benefits, such as with pictures, may improve understanding and aid in obtaining assent (Adcock, Hogan, Elci, & Mills, 2012).

The clinical team turned to our hospital's Ethics Committee for further guidance. After careful consideration of the issues, the Committee and the clinical team developed an individualized strategy for understanding the patient's comprehension of the proposed intervention, and for obtaining assent, involving developmentally appropriate verbal and visual approaches. In this case, the endocrinologist created drawings demonstrating anatomy and typical male and female pubertal changes and referred to these drawings when guiding the patient through the risks and benefits of pubertal suppression. The patient was able to convey comprehension through spontaneous generation of questions indicative of his concerns ("The [GnRH analog] medication will stop my mustache from getting bigger?" and "The medication won't make me develop breasts yet?". He used verbal and nonverbal communication (pointing to the visual depictions) to express a desire to avoid further progression of male puberty, and desire to eventually progress through a female puberty. The patient was prescribed GnRH agonist therapy to suppress puberty; the potential use of cross-sex hormones will be discussed in future visits, and a careful assent procedure will need to be developed in the event that cross-sex hormones are considered. Such an assent procedure would need to include understanding of the irreversible changes resulting in estrogen therapy and implications regarding impaired fertility. In the interim, John was encouraged to further explore his gender preferences, with the flexibility of a time frame that relieved the burden of immediate decisions, through the use of puberty suppressors.

Discussion

Cases similar to the one described may become more common as providers continue to adopt The Endocrine Society's and WPATH's guidelines for treatment of transgender

adolescents. While our patient was not diagnosed with autism, there is evolving evidence that patients presenting to gender clinics have higher than expected rates of autism and autism spectrum disorder. In a study from the Netherlands the prevalence of autism spectrum disorder in children and adolescents presenting for evaluation of gender dysphoria was 7.8%, much higher than the prevalence in the Dutch pediatric population (de Vries et al., 2010). Another study from a pediatric neuropsychology program in the US demonstrated greater prevalence of gender variance in patients with autism spectrum disorder and attention deficit hyperactivity disorder than in non-referred controls (Strang et al., 2014). A small descriptive study of adults with developmental disabilities found 4 of 32 participants to have gender dysphoria (Bedard et al., 2010).

There may be clinical situations where patients with carefully diagnosed gender dysphoria, who otherwise meet eligibility and readiness criteria, are not able to provide meaningful consent due to cognitive or verbal disability. In other medical conditions, such as cancer or diabetes, medical interventions would never be withheld from these patients provided parents or guardians are available to make proxy medical decisions. This comparison requires acknowledgement that treatment of gender dysphoria with pubertal suppression and cross sex hormones continues to remain controversial, is the subject of continued research, and requires careful individualized assessment, whereas the decision to treat of cancer or diabetes with medical interventions is typically not controversial. However, as clinicians continue to prescribe hormonal interventions for gender dysphoria, they must also be prepared to prescribe these interventions in situations where patients are not able to demonstrate clear "knowledge and understanding" of the interventions. Nevertheless, the psychological evaluation would need to be carefully constructed to provide a thorough comprehension of the client's gender issues, to the extent possible.

One of the complications of working with individuals with developmental differences is that they may have a harder time understanding the spectrum of gender and sexuality options. In particular, some individuals with non-conforming gender presentations may simply be atypical males or females, and others may not fit precisely into a binary model of gender. We are hopeful that John, as well as others in similar circumstances, will use the period of time afforded by puberty-blockers, to explore their own identities in a way that will be authentic and comfortable for them.

A fresh look at the issue of consent and assent, as relevant to the care of transgender adolescents is recommended. For instance, the AAP Committee of Bioethics on notes that pediatricians "should not necessarily treat children as rational, autonomous decision makers." They should, instead, "give serious consideration to each patient's developing capacities for participating in decision-making, including rationality and autonomy". In addition to specifying the essential elements of assent, as noted above, they clarify some of the problems with relying solely on parental or guardian judgment or "proxy consent", including that the medical provider has the legal and ethical duty to render competent care based on a youth's need. This obligation can transcend and exist separately from a guardian's wishes and opinions (AAP, 1995). It is therefore imperative, especially in issues involving fundamental aspects of identity, to represent the adolescent's voice and will to the extent possible. The committee also notes that as children develop, they should be given increased

responsibility for personal health care, and be involved in an interactive process with parents and providers (AAP, 1995). We believe that this standard applies to children with developmental differences as well, as highlighted by our case composite, utilizing a flexible model based on the unique conglomeration of factors associated with every adolescent and family.

Thus, we suggest providers assess for developmental differences prior to initiation of pubertal suppression or cross sex hormones. Explanation of medical treatment options, risks and benefits of treatment, and the assent or consent process should be individualized whenever feasible for each patient based on their level of understanding, and a comprehension of their abilities. Youth who are eager for treatment should not have it withheld based on developmental differences, unless it is not possible to make a determination of treatment needs. Any other approach would present significant risk of discriminating against gender dysphoric adolescents with developmental disabilities, and potentially lead to emotional harm to youth who are already vulnerable.

Acknowledgments

Funding Sources: Dr. Shumer is supported by NIH grant 1T32HD075727-01

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Ex. 30

Journal of the Endocrine Society, 2021, Vol. 5, No. 4, 1–16
doi:10.1210/jendso/bvab011
Meta-Analysis

Meta-Analysis

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

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

Received: 5 October 2020; Editorial Decision: 25 January 2021; First Published Online: 2 February 2021; Corrected and Typeset: 19 February 2021.

Abstract

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

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

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EXHIBIT NO. 30
FOR IDENTIFICATION
DATE: 5/2/24
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ISSN 2472-1972

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

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

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

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

Search Strategy and Selection Criteria

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

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

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

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

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

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

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

Results

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

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

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

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

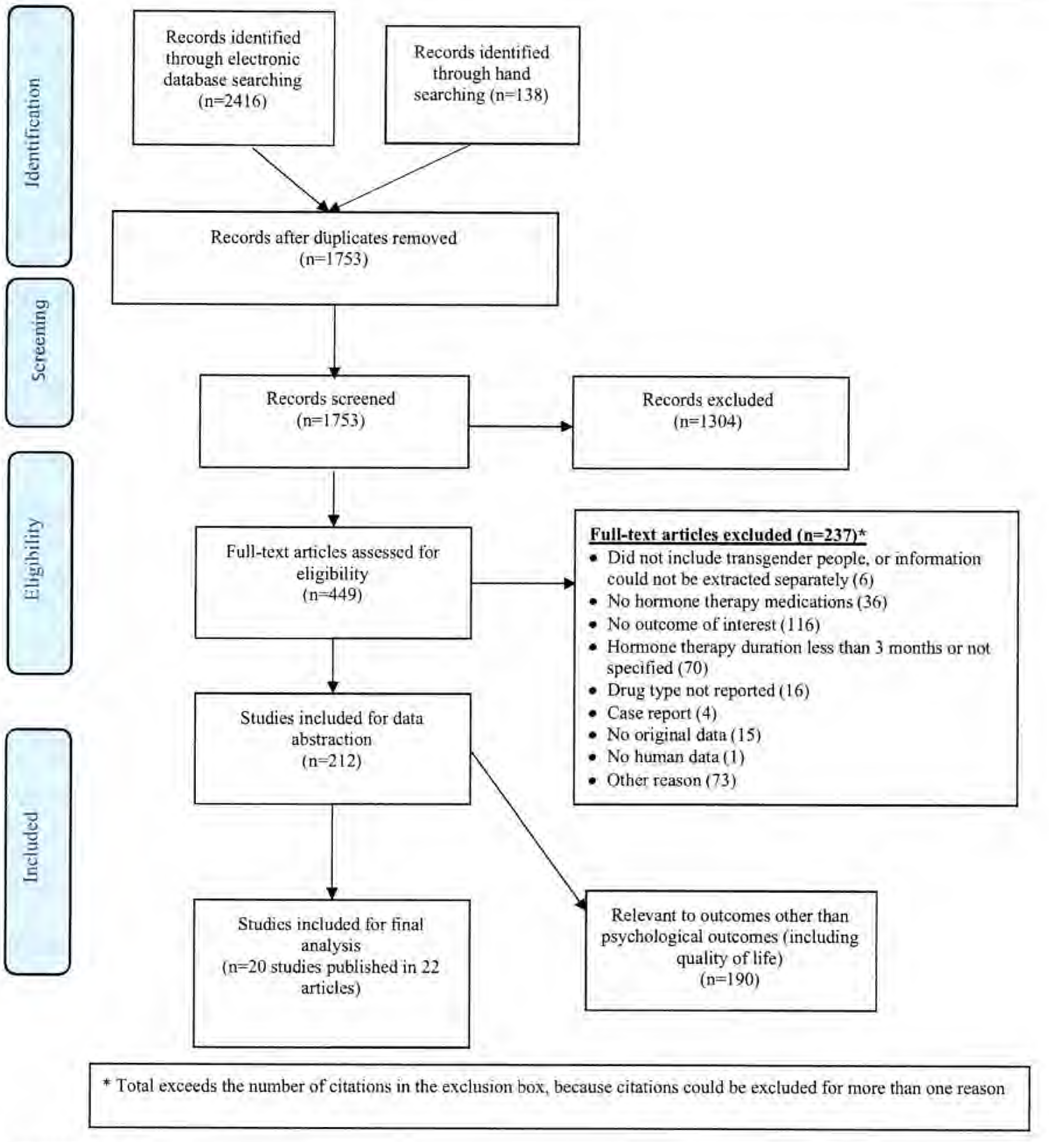

Figure 1. PRISMA flow diagram.

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

Quality of Life

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

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

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

Table 1. Continued

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

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

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

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

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

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

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

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

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

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

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

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

[d]No standard deviations reported

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

Depression

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

Anxiety

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

Death by Suicide

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

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

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

Table 3. Continued

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

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

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

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

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

[d]No standard deviations reported

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

Acknowledgments

Financial Support: This review was partly funded by the World Professional Association for Transgender Health.

Author Contributions: R.S. developed and implemented the search strategy with input from K.B., L.W., and K.R. K.B., L.W., R.S., V.D., K.M., and K.R. screened and assessed studies, extracted data, and graded strength of evidence. K.B. wrote the report, which was reviewed by all co-authors.

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Disclosure Summary: This review was partially funded by the World Professional Association for Transgender Health (WPATH). The authors of this manuscript are responsible for its content. Statements in the manuscript do not necessarily reflect the official views of or imply endorsement by WPATH.

Data Availability: Some or all data generated or analyzed during this study are included in this published article or in the data repository listed in the References.

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The NEW ENGLAND JOURNAL of MEDICINE

Ex. 31

ORIGINAL ARTICLE

Psychosocial Functioning in Transgender Youth after 2 Years of Hormones

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ABSTRACT

BACKGROUND

Limited prospective outcome data exist regarding transgender and nonbinary youth receiving gender-affirming hormones (GAH; testosterone or estradiol).

METHODS

We characterized the longitudinal course of psychosocial functioning during the 2 years after GAH initiation in a prospective cohort of transgender and nonbinary youth in the United States. Participants were enrolled in a four-site prospective, observational study of physical and psychosocial outcomes. Participants completed the Transgender Congruence Scale, the Beck Depression Inventory–II, the Revised Children's Manifest Anxiety Scale (Second Edition), and the Positive Affect and Life Satisfaction measures from the NIH (National Institutes of Health) Toolbox Emotion Battery at baseline and at 6, 12, 18, and 24 months after GAH initiation. We used latent growth curve modeling to examine individual trajectories of appearance congruence, depression, anxiety, positive affect, and life satisfaction over a period of 2 years. We also examined how initial levels of and rates of change in appearance congruence correlated with those of each psychosocial outcome.

RESULTS

A total of 315 transgender and nonbinary participants 12 to 20 years of age (mean [±SD], 16±1.9) were enrolled in the study. A total of 190 participants (60.3%) were transmasculine (i.e., persons designated female at birth who identify along the masculine spectrum), 185 (58.7%) were non-Latinx or non-Latine White, and 25 (7.9%) had received previous pubertal suppression treatment. During the study period, appearance congruence, positive affect, and life satisfaction increased, and depression and anxiety symptoms decreased. Increases in appearance congruence were associated with concurrent increases in positive affect and life satisfaction and decreases in depression and anxiety symptoms. The most common adverse event was suicidal ideation (in 11 participants [3.5%]); death by suicide occurred in 2 participants.

CONCLUSIONS

In this 2-year study involving transgender and nonbinary youth, GAH improved appearance congruence and psychosocial functioning. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development.)

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N Engl J Med 2023;388:240-50.
DOI: 10.1056/NEJMoa2206297

TRANSGENDER AND NONBINARY YOUTH comprise 2 to 9% of high-school–aged persons in the United States.[1-3] Many transgender and nonbinary youth have gender dysphoria, the persistent distress arising from incongruence between gender identity and external phenotype. Increasingly, transgender and nonbinary youth receive medical care to alleviate gender dysphoria, including gonadotropin-releasing hormone (GnRH) agonists to suppress gender-incongruent puberty and gender-affirming hormones (GAH; testosterone or estradiol) to foster gender-congruent secondary sex characteristics. An important goal of such treatment is to attenuate gender dysphoria by increasing appearance congruence — that is, the degree to which youth experience alignment between their gender and their physical appearance.

The available prospective research indicates that gender-affirming medical care is associated with improvements in psychosocial functioning.[4-9] Previously published studies with modest sample sizes[5,6,9] have examined outcomes for relatively short follow-up periods (approximately 1 year on average),[5,6,9] focused exclusively on outcomes of GnRH agonists,[7,8] or examined outcomes for mixed samples of youth initiating GnRH agonists or GAH,[4,6,9] despite evidence that such cohorts have distinct psychosocial profiles.[10] Evidence has been lacking from longitudinal studies that explore potential mechanisms by which gender-affirming medical care affects gender dysphoria and subsequent well-being.

We characterized the longitudinal course of psychosocial functioning over a period of 2 years after GAH initiation in a prospective cohort of more than 300 transgender and nonbinary young people in the United States. We hypothesized that appearance congruence, positive affect, and life satisfaction would increase and that depression and anxiety symptoms would decrease. We also hypothesized that improvements would be secondary to treatment for gender dysphoria, such that increasing appearance congruence would be associated with concurrent improvements in psychosocial outcomes. We also explored the potential moderating effects of demographic and clinical characteristics, including age, designated sex at birth, racial and ethnic identity, and the initiation of GAH in early as compared with later stages of puberty.

METHODS

STUDY DESIGN AND PARTICIPANT RECRUITMENT

Participants were recruited from gender clinics at the Ann and Robert H. Lurie Children's Hospital of Chicago, UCSF Benioff Children's Hospitals, Boston Children's Hospital, and Children's Hospital Los Angeles from July 2016 through June 2019 for the Trans Youth Care–United States (TYCUS) Study,[11] a prospective, observational study evaluating the physical and psychosocial outcomes of medical treatment for gender dysphoria in two distinct cohorts of transgender and nonbinary youth — those initiating GnRH agonists and those initiating GAH as part of their clinical care. All participating clinics employ a multidisciplinary team that includes medical and mental health providers and that collaboratively determines whether gender dysphoria is present and whether gender-affirming medical care is appropriate. For minors, parental consent is required to initiate medical treatment. Publications by individual study teams provide details on site-specific approaches to care.[12-15]

Study visits occurred at baseline and at 6, 12, 18, and 24 months after treatment initiation. Details on study procedures have been published previously,[11] and the protocol is available with the full text of this article at NEJM.org. The present analyses focus on the GAH cohort; outcomes for the cohort initiating GnRH agonists are being analyzed separately, given differences in baseline functioning between the two cohorts[10] and distinct outcomes of GnRH agonists[8] as compared with GAH treatment.[4] Participants provided written informed consent or assent; parents provided permission for minors to participate. Procedures were approved by the institutional review board at each study site.

The first and second authors analyzed the data and wrote the initial draft of the manuscript. All the authors critically reviewed the manuscript. The authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol. There were no agreements regarding confidentiality of the data among the sponsor (Eunice Kennedy Shriver National Institute of Child Health and Human Development), the authors, and the participating institutions. The sponsor had no role in the design of the study; the collection, analysis, or in-

terpretation of data; the writing of the manuscipt; or the decision to submit the manuscript for publication.

MEASURES

Participants reported age, racial and ethnic identity, gender identity, and designated sex at birth (details are provided in the Supplementary Appendix, available at NEJM.org). A small subgroup had been treated with GnRH agonists in early puberty (Tanner stage 2 or 3) (20 participants) or had a relatively late age at onset of endogenous puberty, such that they began receiving GAH in Tanner stage 3 (at 13 to 15 years of age) even without previous treatment with GnRH agonists (4 participants). These 24 participants comprise a subcohort in that they did not undergo extensive gender-incongruent puberty. Participants with a history of GnRH agonist treatment that was initiated in Tanner stage 4 (5 participants) were not included in this subcohort, because their experience of substantial gender-incongruent puberty is more similar to that of youth initiating GAH in Tanner stage 4 or 5.

With respect to longitudinal outcomes, participants completed the Transgender Congruence Scale,[16] the Beck Depression Inventory–II,[17] the Revised Children's Manifest Anxiety Scale (Second Edition),[18] and the Positive Affect and Life Satisfaction measures from the NIH (National Institutes of Health) Toolbox Emotion Battery[19] at each study visit. Scoring information and sample items from each scale are provided in the Supplementary Appendix. Higher scores on these measures reflect greater appearance congruence, depression, anxiety, positive affect, and life satisfaction, respectively.

STATISTICAL ANALYSIS

Trajectories of psychosocial functioning were examined with the use of repeated-measures multivariate analysis of variance and mixed-effects models. Multivariate analysis of variance provided a preliminary omnibus test for significant within-person change over time. Owing to listwise deletion, 150 participants were excluded from the multivariate analysis of variance (the analysis involved 141 participants). Mixed-effects modeling was therefore selected owing to greater flexibility in accommodating missing data and nonnormal distributions and examining parallel processes. Specifically, we used latent growth curve modeling, which uses a structural equation modeling framework to examine changes in mean scores over time.[20] Repeated measures are treated as indicators of latent factors: an intercept factor (estimates of initial levels) and a slope factor (rate of change). Intercept and slope factors can be regressed on covariates in adjusted models to explore moderation effects. In addition, growth curves for two different outcomes can be combined to examine how intercepts and slopes of those constructs correlate with each other. Data were Winsorized at the 95th percentile to reduce the influence of outliers.

Analyses involving latent growth curve modeling proceeded in three steps. First, we modeled trajectories of appearance congruence and psychosocial outcomes (i.e., effects of time only). Second, we adjusted models to estimate the effects of covariates on baseline scores and rates of change over time. Third, because changes in appearance congruence and psychosocial outcomes occur as parallel, simultaneous processes during GAH treatment, we examined how initial levels and rates of change in appearance congruence correlated with those of each psychosocial outcome. Standardized β levels were used as indicators of effect sizes for longitudinal models using conventional ranges (small, 0.20; medium, 0.50; and large, 0.80). Our conceptual model is shown in Figure S1 in the Supplementary Appendix. All statistical analyses were conducted with the use of SPSS software, version 27, and Mplus software, version 8.8.

RESULTS

ANALYTIC SAMPLE

There were a total of 6114 observations from 315 participants, who were assessed up to five times over a period of 2 years (data were available for 81% of all possible observations). Most participants (238 [75.6%]) completed either four study visits (76 participants) or five visits (162 participants). Tables S1 and S2 show the number of completed visits by time point and data coverage for key variables. The analytic sample for longitudinal models included 291 participants with follow-up data on primary outcome variables (Fig. S2). The analytic sample did not differ substantially from the overall sample with respect to age, designated sex at birth, racial and ethnic

identity, initiation of GAH in early puberty, or baseline scores on psychosocial measures (Table S3).

SAMPLE CHARACTERISTICS

We enrolled 315 eligible participants 12 to 20 years of age (mean [±SD], 16±1.9 years) (Table 1). Most were transmasculine (i.e., persons designated female at birth who identify along the masculine spectrum; 60.3%), designated female at birth (64.8%), and non-Latinx or non-Latine White (58.7%). Transmasculine, non-Latinx or non-Latine White, and multiracial participants were overrepresented and nonbinary and Black participants were underrepresented as compared with the study sample in the Williams Institute Executive Report[21] (Table S4); however, the study sample was representative of transgender and nonbinary youth presenting to pediatric subspecialty gender programs[22] and generalizable to this population. Two participants died by suicide during the study (one after 6 months of follow-up and the other after 12 months of follow-up), and 6 participants withdrew from the study. For these eight participants, data that had been collected before death or study withdrawal were included in the analyses. Data on adverse events are provided in Table 2.

APPEARANCE CONGRUENCE AND PSYCHOSOCIAL OUTCOMES OVER TIME

Table S5 depicts mean scores for appearance congruence, depression, anxiety, positive affect, and life satisfaction at baseline and 24 months. Results for multivariate analysis of variance indicated that there were significant within-participant changes over time for all psychosocial outcomes in hypothesized directions (Wilk's lambda, 0.32; F statistic with 20 and 122 degrees of freedom; 12.86; P<0.001). Specifically, scores for appearance congruence, positive affect, and life satisfaction increased significantly, and scores for depression and anxiety decreased significantly.

Means and variances of the variables for latent growth curve modeling, with estimated baseline levels and change over time for both time-only and adjusted models, are provided in Table 3. Scores for appearance congruence increased (annual increase on a 5-point scale, 0.48 points; 95% confidence interval [CI], 0.42 to 0.54; standardized $\beta=1.47$), as did T scores for positive affect (annual increase on a 100-point scale, 0.80 points; 95% CI, 0.08 to 1.54; $\beta=0.19$) and life satisfaction (annual increase on a 100-point scale, 2.32 points; 95% CI, 1.64 to 3.00; $\beta=0.52$). We observed decreased scores for depression (annual change on a 63-point scale, −1.27 points; 95% CI, −1.98 to −0.57; standardized $\beta=-0.29$) and decreased T scores for anxiety (annual change on a 100-point scale, −1.46 points; 95% CI, −2.13 to −0.79; $\beta=-0.35$) over a period of 2 years of GAH treatment.

Unadjusted models can be interpreted on their original scale. For instance, depression scores range from 0 to 63 (ranges of severity, minimal, 0 to 13; mild, 14 to 19; moderate, 20 to 28; and severe, 29 to 63). The model had an intercept (baseline mean) of 15.46 and estimated slope (change per year) of −1.27. Thus, on average, depression started in the mild range and decreased to the subclinical level by 24 months. Table S6 shows the percentages of youth scoring in the clinical range for depression and anxiety at each time point. Of 27 participants with depression scores in the severe range at baseline, 18 (67%) reported a depression score in the minimal or moderate ranges at 24 months. Similarly, 21 of 33 participants (64%) with depression scores in the moderate range at baseline reported a depression score in the minimal or moderate ranges at 24 months (chi-square statistic with 9 degrees of freedom, 49.85; P<0.001). With respect to anxiety, 47 of 122 participants (38.5%) with baseline scores in the clinical range (T scores, >60) were in the nonclinical range at 24 months (chi-square statistic with 1 degree of freedom, 22.05; P<0.001).

ASSOCIATIONS BETWEEN APPEARANCE CONGRUENCE AND PSYCHOSOCIAL OUTCOMES

Figure 1 depicts parallel processes between appearance congruence and each psychosocial outcome as analyzed by means of latent growth curve modeling. As described above, we used linear latent growth curve modeling to estimate baseline scores (intercepts) and linear rates of change (slopes) of each outcome (see Table 3 for details of each model). In parallel-process models, we examined how the components for latent growth curve modeling for appearance congruence related to those for scores for depression (Fig. 1A) and T scores for anxiety (Fig. 1B), positive affect (Fig. 1C), and life satisfaction

Table 1. Demographic and Clinical Characteristics of the Participants.*

Characteristic	Participants (N=315)
	no. (%)
Gender identity†	
Transmasculine	190 (60.3)
Transfeminine	106 (33.7)
Nonbinary	19 (6.0)
Designated sex at birth	
Female	204 (64.8)
Male	111 (35.2)
Racial and ethnic identity	
Non-Latinx or non-Latine White	185 (58.7)
Latinx or Latine non-White	50 (15.9)
Latinx or Latine White	25 (7.9)
Black	11 (3.5)
Asian or Pacific Islander	10 (3.2)
Multiracial	32 (10.2)
Other	1 (0.3)
Unknown	1 (0.3)
Age at baseline	
12 yr	6 (1.9)
13 yr	23 (7.3)
14 yr	38 (12.1)
15 yr	67 (21.3)
16 yr	55 (17.5)
17 yr	51 (16.2)
18 yr	48 (15.2)
19 yr	15 (4.8)
20 yr	12 (3.8)
Tanner stage at GAH initiation‡	
1	2 (0.6)
2	13 (4.1)
3	9 (2.9)
4	29 (9.2)
5	262 (83.2)
Past use of GnRH agonist	
No	290 (92.1)
Yes	25 (7.9)
Tanner stage at initiation of GnRH agonist	
2	12 (3.8)
3	8 (2.5)
4	5 (1.6)
Not applicable	290 (92.1)
Initiation of GAH in early puberty subcohort§	
No	291 (92.4)
Yes	24 (7.6)

* The table does not include demographic and clinical characteristics for one participant who was accidentally enrolled and did not meet criteria for study eligibility. Percentages may not total 100 because of rounding. GAH denotes gender-affirming hormones, and GnRH gonadotropin-releasing hormone.

† Transmasculine refers to persons designated female at birth who identify along the masculine spectrum. Transfeminine refers to persons designated male at birth who identify along the feminine spectrum.

‡ Three participants began receiving GnRH agonists in either Tanner stage 2 or 3 and subsequently had pubertal regression to Tanner stage 1 or 2 by the time of GAH initiation.

§ This subcohort includes 20 participants who began receiving GnRH agonists at Tanner stage 2 or 3 and 4 participants who had not previously received GnRH agonists but had begun receiving GAH in Tanner stage 3 owing to a relatively late onset of puberty (13 to 15 years of age) and thus did not have physical changes associated with later stages of endogenous puberty. This subcohort does not include 5 participants with a history of initiation of GnRH agonists in Tanner stage 4 and who thus did undergo substantial gender-incongruent puberty.

(Fig. 1D). Higher appearance congruence at baseline was associated with lower baseline scores for depression ($r=-0.60$) and T scores for anxiety ($r=-0.40$), and increases in appearance congruence were associated with decreases in scores for depression ($r=-0.68$) and T scores for anxiety ($r=-0.52$) over time. In addition, higher appearance congruence at baseline was associated with higher baseline T scores for positive affect ($r=0.46$) and life satisfaction ($r=0.72$), and increases in appearance congruence were associated with increases in T scores for positive affect ($r=0.74$) and life satisfaction ($r=0.84$) over time.

MODERATING EFFECTS OF DEMOGRAPHIC AND CLINICAL COVARIATES

Table 3 shows the effects of covariates on scores for appearance congruence and depression and T scores for anxiety, positive affect, and life satisfaction. Age was not associated with any outcomes at baseline or over time.

Designated Sex at Birth

Depression and anxiety scores decreased among youth designated female at birth but not among those designated male at birth. Similarly, T scores for life satisfaction increased among youth designated female at birth but not among those designated male at birth (Fig. S3). Designated sex at birth was not associated with any other outcomes at baseline or over time.

Table 2. Adverse Events.

Event	No. of Events in Sample
Any event	15
Death by suicide	2
Suicidal ideation reported during study visit	11
Severe anxiety triggered by study visit	2

Effects of Racial and Ethnic Identity

At baseline, youth of color had higher scores for appearance congruence, lower scores for depression, and higher scores for positive affect than non-Latinx or non-Latine White youth. With respect to change over time, non-Latinx or non-Latine White youth had greater decreases in depression scores than youth of color (Fig. S4). Racial and ethnic identity were not associated with any other outcomes at baseline or over time.

Initiation of GAH in Early Puberty

Youth who had initiated GAH in early puberty had higher scores for appearance congruence, positive affect, and life satisfaction at baseline and lower scores for depression and anxiety at baseline than those who had initiated GAH in later puberty. Tables S7, S8, and S9 provide more information regarding differences between youth initiating GAH in early puberty and those initiating GAH in late puberty. With respect to change over time, youth initiating GAH in later puberty had greater improvements in appearance congruence than those initiating GAH in early puberty (Fig. 2).

DISCUSSION

Understanding the effect of GAH on the psychosocial outcomes of transgender and nonbinary youth would appear crucial, given the documented mental health disparities observed in this population,[10,15,23,24] particularly in the context of increasing politicization of gender-affirming medical care.[25] In our U.S.-based cohort of transgender and nonbinary youth treated with GAH, we found decreases in depression and anxiety symptoms and increases in positive affect and life satisfaction as assessed through validated instruments. Our findings are consistent with those of other longitudinal studies involving transgender and nonbinary youth receiving GAH, which showed reductions in depression[6,9] and anxiety[6] and increases in overall well-being[5] with small-to-moderate effects over a follow-up period of up to 1 year. We replicated these findings in a larger sample of racially and ethnically diverse transgender and nonbinary youth recruited from four geographically distinct regions in the United States and found sustained improvements over a period of 2 years.

Increasing appearance congruence is a primary goal of GAH, and we observed appearance congruence improve over 2 years of treatment. This was a moderate effect, and the strongest effect observed across our outcomes, consistent with the effect seen in research involving other samples, which has noted large effects of GAH on body image and small-to-moderate effects on mental health.[6] Appearance congruence was also associated with each psychosocial outcome assessed at baseline and during the follow-up period, such that increases in appearance congruence were associated with decreases in depression and anxiety symptoms and increases in positive affect and life satisfaction. These findings suggest that appearance congruence is a candidate mechanism by which GAH influences psychosocial functioning.

The importance of appearance congruence for psychosocial well-being is further highlighted by the effect of avoiding gender-incongruent pubertal changes. Youth who had not undergone substantial gender-incongruent puberty had higher scores for appearance congruence, positive affect, and life satisfaction and lower scores for depression and anxiety at baseline than youth who had undergone substantial endogenous puberty. These observations align with other published reports that earlier access to gender-affirming medical care is associated with more positive psychosocial functioning.[10,26] Alternatively, youth who first recognize their gender incongruence in adolescence may represent a distinct subgroup of transgender and nonbinary youth who have more psychosocial complexities than youth recognizing gender incongruence in childhood.[27]

The effects of GAH on some psychosocial outcomes varied on the basis of designated sex

Table 3. Variable Estimates for Individual Latent Growth Curve Models of 2-Year Outcomes.*

Model	Appearance Congruence†	Depression‡	Anxiety§	Positive Affect¶	Life Satisfaction‖
			value (95% confidence interval)		
Unconditional model: time					
Intercept mean	2.99 (2.90 to 3.08)	15.46 (14.27 to 16.70)	59.58 (58.22 to 60.68)	42.93 (41.82 to 44.03)	40.12 (38.99 to 41.26)
Intercept variance	0.35 (0.27 to 0.50)	86.23 (68.13 to 106.85)	17.84 (11.38 to 24.54)	63.50 (46.23 to 81.79)	75.21 (59.76 to 93.98)
Slope mean	0.48 (0.42 to 0.54)	−1.27 (−1.98 to −0.57)	−1.46 (−2.13 to −0.79)	0.80 (0.08 to 1.54)	2.32 (1.64 to 3.00)
Slope variance	0.11 (0.07 to 0.15)	19.44 (12.23 to 27.14)	17.84 (11.38 to 24.54)	17.98 (9.25 to 27.57)	20.33 (14.12 to 27.70)
Conditional model					
Time					
Intercept mean	2.59 (1.91 to 3.27)	20.01 (10.79 to 29.48)	60.82 (53.56 to 67.95)	47.27 (38.93 to 55.81)	38.86 (29.90 to 47.75)
Intercept variance	0.32 (0.25 to 0.42)	80.92 (63.35 to 100.47)	114.74 (91.96 to 138.23)	56.96 (41.19 to 74.75)	71.93 (57.15 to 90.22)
Slope mean	0.51 (0.07 to 0.96)	−0.92 (−3.82 to −0.06)	−1.95 (−3.81 to −0.09)	1.79 (0.14 to 3.43)	4.54 (2.66 to 6.43)
Slope variance	0.10 (0.06 to 0.14)	18.81 (11.71 to 26.34)	18.37 (11.78 to 25.63)	17.97 (9.29 to 27.66)	19.74 (13.61 to 27.06)
Time-invariant effects on intercept					
Baseline age	0.02 (−002 to 0.06)	−0.23 (−0.08 to 0.36)	−0.20 (−0.78 to 0.38)	−0.32 (−0.84 to 0.21)	0.06 (−0.49 to 0.62)
Designated sex at birth**	−0.12 (−0.31 to 0.06)	1.74 (−0.69 to 4.09)	0.05 (−2.37 to 2.49)	−1.26 (−3.53 to 0.91)	−2.36 (−4.89 to 0.18)
Racial and ethnic identity††	0.19 (0.03 to 0.36)	−2.60 (−4.82 to −0.32)	−2.22 (−4.48 to 0.06)	2.30 (0.22 to 4.38)	1.70 (−0.58 to 3.98)
Early gender-affirming care‡‡	0.70 (0.35 to 1.04)	−5.88 (−9.67 to −1.96)	−7.41 (−11.30 to −3.52)	5.34 (1.70 to 8.98)	7.55 (2.82 to 12.28)
Time-invariant effects on slope					
Baseline age	0.00 (−0.03 to 0.03)	−0.04 (−0.18 to 0.10)	−0.02 (−0.15 to 0.12)	−0.03 (−0.15 to 0.10)	−0.09 (−0.22 to 0.05)
Designated sex at birth**	0.03 (−0.09 to 0.15)	1.91 (0.33 to 3.50)	1.56 (0.01 to 3.10)	−0.43 (−2.10 to 1.31)	−1.86 (−3.49 to −0.24)
Racial and ethnic identity††	−0.10 (−0.20 to 0.01)	1.70 (0.23 to 3.15)	0.62 (−0.77 to 1.98)	−1.42 (−2.98 to 0.13)	−1.08 (−2.52 to 0.36)
Early gender-affirming care‡‡	−0.42 (−0.66 to −0.19)	−0.73 (−3.41 to 1.93)	0.04 (−2.53 to 2.59)	−0.78 (−3.56 to 2.06)	−1.08 (−4.01 to 1.86)

* Shown are unstandardized variable estimates with 95% confidence intervals. Slope means indicate change over time, and slope variances indicate heterogeneity within the sample.
† Scores on the Appearance Congruence subscale of the Transgender Congruence Scale range from 1 to 5, with higher scores indicating greater appearance congruence.
‡ Scores on the Beck Depression Inventory–II range from 0 to 63, with scores of 20 to 28 indicating moderate depression and scores of 29 to 63 indicating severe depression.
§ T scores on the Revised Children's Manifest Anxiety Scale (Second Edition) have a mean of 50 and a standard deviation of 10, with scores of 60 or more indicating clinical levels of anxiety.
¶ T scores for the Positive Affect measure from the NIH (National Institutes of Health) Toolbox Emotion Battery have a mean of 50 and a standard deviation of 10, with higher scores indicating greater positive affect.
‖ T scores for the Life Satisfaction measure from the NIH Toolbox Emotion Battery have a mean of 50 and a standard deviation of 10, with higher scores indicating greater life satisfaction.
** Coding for designated sex at birth was as follows: 0=assigned female at birth (reference) and 1=assigned male at birth.
†† Coding for racial and ethnic identity was as follows: 0=non-Latinx or non-Latine White (reference) and 1=other racial and ethnic identities.
‡‡ Coding for early gender-affirming care was as follows: 0=initiated GAH in later puberty (Tanner stage 4 or 5) (reference) and 1=initiated GAH in early puberty (Tanner stage 2 or 3).

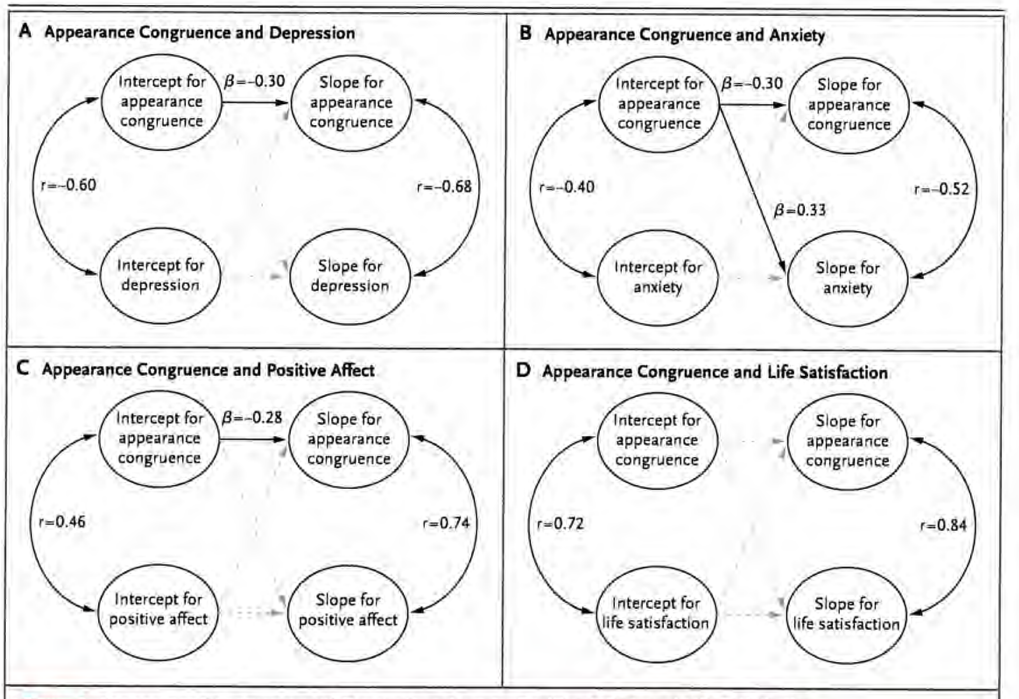

Figure 1. Appearance Congruence and Depression, Anxiety, Positive Affect, and Life Satisfaction.

Parallel-process latent growth curve models are depicted. A linear latent growth curve model was fitted for each outcome, with model-based estimates of baseline scores (intercept) and rates of linear change over time (slope). Parallel-process models can provide tests of how aspects of trajectories relate to each other. Each panel provides estimates for correlations between baseline scores of appearance congruence and each outcome (intercept correlations, arcs displayed on the left side of each panel), correlations between rate of change of appearance congruence and rate of change of each outcome (slope correlations, arcs displayed on the right side of each panel), and effects of baseline scores on slopes (straight lines in the middle of each panel). Solid black lines and arcs indicate significant effects (confidence intervals for variable estimates do not contain 0); nonsignificant effects are shown with dashed gray lines. All models were controlled for age, designated sex at birth, racial and ethnic identity, and early gender-affirming care (not shown for ease of interpretation).

at birth. Depression and anxiety symptoms decreased significantly, and life satisfaction increased significantly, among youth designated female at birth but not among those designated male at birth. Given that some key estrogen-mediated phenotypic changes can take between 2 and 5 years to reach their maximum effect (e.g., breast growth),[28] we speculate that a longer follow-up period may be necessary to see an effect on depression, anxiety, and life satisfaction. Furthermore, changes that are associated with an endogenous testosterone-mediated puberty (e.g., deeper voice) may be more pronounced and observable than those associated with an endogenous estrogen-mediated puberty. Thus, we hypothesize that observed differences in depression, anxiety, and life satisfaction among youth designated female at birth as compared with those designated male at birth may be related to differential experiences of gender minority stress, which could arise from differences in societal acceptance of transfeminine (i.e., persons designated male at birth who identity along the feminine spectrum) as compared with transmasculine persons. Indeed, gender minority stress is consistently associated with more negative mental health outcomes,[29] and research suggests that transfeminine youth may experience more minority stress than transmasculine youth.[30]

Our study has certain limitations. Because participants were recruited from four urban pediatric gender centers, the findings may not be generalizable to youth without access to comprehensive interdisciplinary services or to transgen-

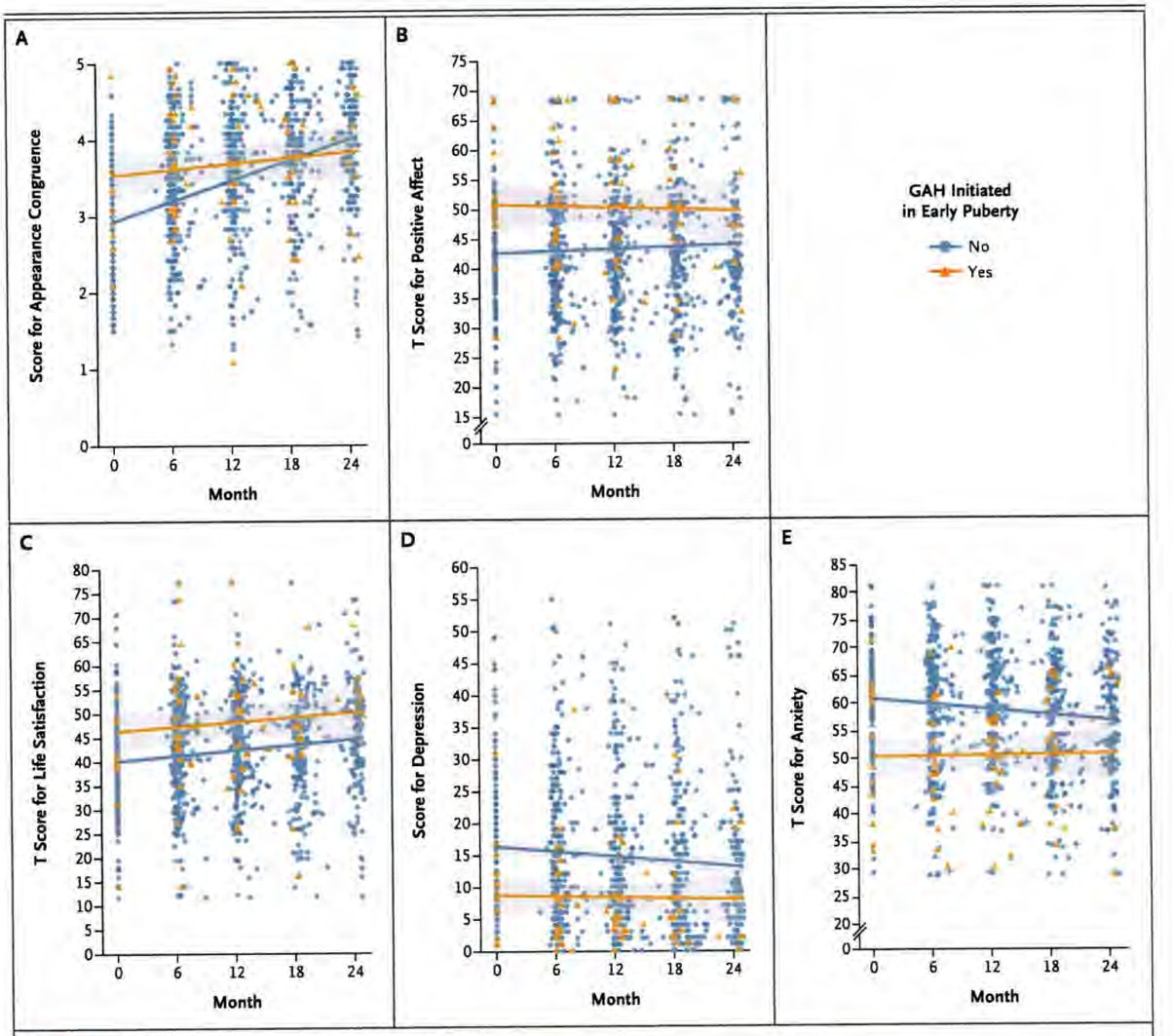

Figure 2. Psychosocial Outcomes during 2 Years of GAH.

Shown are changes in participant-reported measures over a period of 2 years of treatment with gender-affirming hormones (GAH). Scores on the Appearance Congruence subscale of the Transgender Congruence Scale (Panel A) range from 1 to 5, with higher scores indicating greater appearance congruence. T scores for the Positive Affect measure from the NIH (National Institutes of Health) Toolbox Emotion Battery (Panel B) range from 0 to 100, with higher scores indicating greater positive affect. T scores for the Life Satisfaction measure from the NIH Toolbox Emotion Battery (Panel C) range from 0 to 100, with higher scores indicating greater life satisfaction. Scores on the Beck Depression Inventory–II (Panel D) range from 0 to 63, with higher scores indicating greater depression. T scores on the Revised Children's Manifest Anxiety Scale (Second Edition) (Panel D), range from 0 to 100, with higher scores indicating greater anxiety. Individual scores are depicted with orange triangles for youth initiating GAH in early puberty ("Yes") and with blue circles for youth who did not initiate GAH in early puberty ("No"). Lines indicate mean scores for each group, with gray shaded bands for 95% confidence intervals.

der and nonbinary youth who are self-medicating with GAH. In addition, despite improvement across psychosocial outcomes on average, there was substantial variability around the mean trajectory of change. Some participants continued to report high levels of depression and anxiety and low positive affect and life satisfaction, despite the use of GAH. We plan to examine other factors that are known to contribute to psychosocial functioning among transgender and non-

binary youth and may not be affected by GAH, such as parental support,[31,32] in this cohort. Finally, our study lacked a comparison group, which limits our ability to establish causality. However, the large effects in parallel-process models examining associations between improvements in appearance congruence and improvements in psychosocial outcomes provide support for the concept that GAH may affect psychosocial outcomes through increasing gender congruence.

Despite these limitations, our findings showed improvements in psychosocial functioning across 2 years of GAH treatment, which supports the use of GAH as effective treatment for transgender and nonbinary youth. We are now following this cohort to see whether gains in functioning are sustained over a longer follow-up period, and — given substantial variability in outcomes even after controlling for a number of factors — we hope to discover additional predictors of change to identify youth for whom GAH alone is not adequate to address mental health challenges. We intend to initiate further work with this cohort to focus on understanding reasons for discontinuing GAH among the small subgroup of youth who stopped medical treatment. Overall, our results provide evidence that GAH improved appearance congruence and psychosocial functioning in transgender and nonbinary youth.

Supported by a grant (R01 HD082554) from the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the participants, their families, their referring clinicians, and the many research staff for their contributions in conducting this study, and Norman Spack, one of the original principal investigators, for his contributions to the study.

APPENDIX

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Ex. 32

the choice of aspirin or heparin for venous thromboembolism prophylaxis among patients with operatively treated extremity fractures (or any pelvic or acetabular fracture), this is by far the largest trial to date and provides compelling evidence that a readily available, inexpensive drug, taken orally, is a viable alternative to an injectable pharmacologic prophylaxis.

Are there any caveats to this message? The trial shows several secondary outcomes that support the main conclusion of the trial, including a similar risk of pulmonary embolism in the two groups and, in terms of safety outcomes, no evidence of a difference in the incidence of bleeding events, which occurred in 13.72% of patients in the aspirin group and 14.27% in the low-molecular-weight–heparin group. However, in keeping with previous trials, the authors noted that deep-vein thrombosis was more frequent in patients who had received aspirin than in those who had received heparin (2.51% vs. 1.71%), although the absolute difference was small (0.80 percentage points). Although deep-vein thrombosis is clearly not as serious as a fatal pulmonary embolism, it is not an inconsequential problem. Post-thrombotic syndrome affects some people who have had a deep-vein thrombosis of the leg, and this condition can cause chronic pain and swelling.[9]

The findings in this trial clearly indicate that guidelines for the prevention of hospital-acquired venous thromboembolism will need to be rewritten to include the option of aspirin in patients with traumatic injuries. More work is needed to determine whether aspirin should also be considered for venous thromboembolism prophylaxis after other types of surgeries and for nonsurgical patients who have risk factors for venous thromboembolism.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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DOI: 10.1056/NEJMe2214045

Growing Evidence and Remaining Questions in Adolescent Transgender Care

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This week in the *Journal*, a much-awaited primary report from Chen et al.[1] on 2 years of gender-affirming hormones (GAH) in transgender adolescents appears. The approach to adolescent transgender care with early treatment with puberty blockers, and GAH in youth from 16 years of age, originated in the Netherlands ("the Dutch model") and became the dominant medical care model for transgender adolescents.[2] Especially over the past decade, marked increases in referrals but limited evidence as to long-term outcomes have led to controversies and debate regarding this approach. Indeed, some European countries are adapting their guidelines and re-

stricting access to care for transgender youth, and some states in the United States have introduced laws to ban such care.[3] Therefore, rigorous longitudinal outcome studies that provide evidence about whether this approach is effective and safe are needed.

The results of the current study — involving a large, multisite sample of 315 participants — provide such evidence. During 24 months of GAH treatment, participant-reported appearance congruence (alignment between gender identity and physical appearance), positive affect, and life satisfaction increased and depression and anxiety decreased. In addition, initial levels and rates of change in appearance congruence correlated with the psychosocial outcomes. These results corroborate the positive effects in several earlier studies of smaller samples of adolescents and add to the evidence base that GAH can have a positive effect on mental health.[4]

Yet the study leaves some concerns unanswered. Although overall psychological functioning in the study participants improved, there was substantial variation among participants; a considerable number still had depression, anxiety, or both at 24 months, and two died by suicide. The correlation between appearance congruence and various psychological-outcome variables suggests an important mediating role of GAH and consequent bodily changes. However, other possible determinants of outcomes were not reported, particularly the extent of mental health care provided throughout GAH treatment. To date, international guidelines for transgender adolescent care recommend a psychosocial assessment and involvement of mental health professionals in a multidisciplinary care model.[5] Whether participating centers in the current study followed that approach is unfortunately unclear. Future studies that compare outcomes with different care models are needed, preferably using similar measures.

In addition, some are concerned that young persons may not be capable of making decisions regarding medical treatments that have irreversible effects that they might regret later in life. In the 2-year study by Chen et al., 9 of 314 adolescents (2.9%) stopped GAH, but it is unclear whether they detransitioned or regretted their treatment or whether they stopped because they were satisfied with treatment-related changes. Despite concerns about detransitioning, few studies have provided data on the incidence of detransitioning, and available results are inconsistent. Although one U.S. study showed that 74% of adolescents who started GAH treatment were still receiving it 4 years later, 98% of 720 Dutch adolescents who began such therapy were receiving it after a median of 2.7 years (range, 0.0 to 20.0).[6,7] Similar studies in other centers, regions, and countries are necessary to learn whether the incidence of detransitioning differs between settings and what factors are associated with these differences. It will be especially important to evaluate outcomes in adolescents starting GAH before 16 years of age, the age limit in the initial Dutch protocol.[2]

Furthermore, although Chen et al. investigated relevant psychological and gender outcome measures (e.g., depression, appearance congruence, and life satisfaction), additional factors such as autism spectrum disorder and the quality of peer relations and family support are also of interest. Social support has been hypothesized as explaining why Dutch transgender adolescents have better psychological function than those in other countries.[8] Understanding additional factors that influence outcomes should help to determine which components of care and support other than GAH might improve the lives of transgender adolescents.

Finally, benefits of early medical intervention, including puberty suppression, need to be weighed against possible adverse effects — for example, with regard to bone and brain development and fertility. At present, studies involving young adults from the Dutch adolescent transgender cohort show that accrual of bone mineral decelerates during puberty suppression but increases during GAH treatment and also that adolescents' educational achievements are as expected given their pretreatment status, which is reassuring.[9,10] However, those results from a single Dutch center should be replicated and validated in other contexts, as in a sample followed in the current study.

Despite uncertainties that call for further study, current information shows that mental health improves with GAH, whereas withholding treatment may lead to increased gender dysphoria and adversely affect psychological functioning. The study by Chen et al. adds to the

evidence of the effectiveness of the current care model that includes hormonal treatment for transgender adolescents.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

From the Departments of Child and Adolescent Psychiatry (A.L.C.V.) and Pediatrics (S.E.H.), Center of Expertise on Gender Dysphoria, Amsterdam University Medical Centers, Location Vrije Universiteit, Amsterdam.

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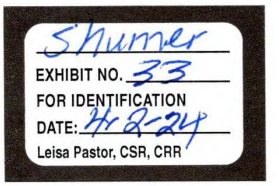
DOI: 10.1056/NEJMe2216191

Ex. 33

Protocol

Protocol for: Chen D, Berona J, Chan Y-M, et al. Psychosocial functioning in transgender youth after 2 years of hormones. N Engl J Med 2023;388:240-50. DOI: 10.1056/NEJMoa2206297

This trial protocol has been provided by the authors to give readers additional information about the work.



This supplement contains the following items:

1. Original protocol, including statistical analysis plan
2. Final protocol, including statistical analysis plan
3. Summary of IRB amendments

The Impact of Early Medical Treatment in Transgender Youth

(Trans Youth Care)

Version 1.0

April 18, 2016

Sponsored by:
The Eunice Kennedy Shriver
National Institute of Child Health and Human Development (NICHD)

TABLE OF CONTENTS

- The participant is lost to follow-up;
- The participant experiences an untoward event that warrants discontinuation form the study;
- The participant develops a health problem and needs treatment that would affect the results of this study;
- The study is cancelled by *The Eunice Kennedy Shriver* NICHD;
- The study is cancelled for other administrative reasons; and
- Death of the participant.

If a youth participant in the Blocker Cohort is prematurely discontinued from participating in the study, the parent, legal guardian, caretaker participant will also be prematurely discontinued from the study.

Complete the Off Study Form when the decision is made to permanently discontinue the participant from the study and no further data collection will occur. Data through the time that the participant is taken off study will still be used for study purposes.

9.0 MONITORING UNTOWARD EVENTS

Site staff must first follow their own IRB's procedure for reporting and managing untoward events. Project staff will record any untoward event experienced by the participant. Reporting is required for occurrences including social harms, psychological distress and serious life threatening events such as suicide attempts. These may be immediately apparent to the study staff, such as the participant's emotional upset requiring referral for counseling; or they may be delayed and reported later to study staff, such as physical harm to an individual for having participated in the study. Study staff will notify CHLA of these untoward events as soon as possible, but no later than 48 hours after awareness of the event. In addition, study staff will complete the Untoward Event Form and enter it into the study database within three working days after awareness of the event. Study staff will be briefed during the training on the scope of possible untoward events and instructed to report them.

10.0 STATISTICAL/ANALYTIC CONSIDERATIONS

10.1 Introduction

This is a longitudinal observational multi-site study to study the impact of medical treatments for gender dysphoria in youth who are initiating puberty suppression *or* pursuing a phenotypic gender change with cross sex hormones. Participants will be studied prospectively over a 24-month period.

10.1.1 Population for Analysis

Gender dysphoric youth ages 8 through 20, seeking care at one of the participating sites,
All participants with available endpoint data will be included in the analysis.

10.1.2 Study Hypotheses

Effects of Hormonal Interventions on Mental Health and Psychological Well-Being:

- Hypothesis 1a: Patients treated with GnRH agonists will exhibit decreased symptoms of gender dysphoria, depression, anxiety, trauma symptoms, self-injury, and suicidality and increased body esteem and quality of life over time
- Hypothesis 2a: Patients treated with cross-sex hormones will exhibit decreased symptoms of anxiety and depression, gender dysphoria, self-injury, trauma symptoms, and suicidality and increase body esteem and quality of life over time

Safety of Hormonal Interventions:

- Hypothesis 1b: GnRH agonists are tolerable and safe for transgender youth in Tanner stage 2 or 3 of sexual development, i.e., lipids, glucose, liver enzymes, electrolytes, and HgbA1c will not increase above clinically safe ranges

- Hypothesis 2b: Cross-sex hormones are tolerable and safe to use with transgender youth initiating phenotypic transition, i.e., will not increase lipids, glucose, liver enzymes, electrolytes, hemoglobin A1c and hemoglobin above clinically safe ranges

Bone Density in Blocker Cohort:

- Hypothesis 1c: Raw bone density scores will remain stable for youth receiving GnRH agonists; however, age-matched z-scores may decrease

10.1.3 Exploratory Aim

Risk Behavior in Cross Sex Hormone Youth:

- Based on evidence of high rates of substance use and HIV infection in some transgender adolescents, we will measure substance use and sexual risk behaviors over time

10.2 Study Endpoints

The primary study endpoint for each participant will be reached at the end of the observational period – two years after the initiation of treatment. However, it is the intention of the PIs to extend this study at a future time point. At that time, IRB approval of the extension will be obtained.

10.3 Sample Size and Power Analysis

10.3.1 Blocker Cohort – Power Analysis

Unique to the blocker cohort is the need to assess the effect of GnRH agonists on bone health (Hypothesis 1c). Although we hypothesize that there is no net change in raw bone density over time (precluding power analysis), it is important to assess nontrivial lags in development compared to age-matched peers. Using G*Power version 3.1.3 to conduct an a priori power analysis in a repeated measures MANOVA framework with effect size f=.20 (a moderate effect size equivalent to Cohen's d=.40), alpha=.05, adequate statistical power=.80, and 4 measurement time points, a sample of 73 participants would be sufficient to detect significant decrease in age-matched z-scores over time. Thus, we will recruit a sample of 80 evaluable participants, across all study sites, in the blocker cohort, which will yield comparable power to detect moderate changes in mental health outcomes over time (Hypothesis 1a) and good (.89) power to detect significant differences in metabolic and physiologic lab values of one-third of a standard deviation from clinical cutoffs (Hypothesis 1b).

10.3.2 Cross Sex Hormone Cohort – Power Analysis

In the absence of available longitudinal metabolic and physiological data, the study is powered to assess changes in mental health and psychological well-being (Hypothesis 2a) based on evidence from our preliminary data. Using G*Power version 3.1.3 and conducting an a priori power analysis in a repeated measures MANOVA framework with effect size f=.11 (a small effect size equivalent to Cohen's d=.22), alpha=.05, adequate statistical power=.80, and 4 measurement time points, with a small natural correlation among repeated measures of r=.15, a total sample of 196 participants is needed for adequate power to detect multivariate significance. This sample will generate adequate (.80) power to detect effects as small as d=.17, or less than a fifth of a standard deviation from clinical cutoffs, in the safety analyses of Hypothesis 2b. Therefore, we will recruit a total sample of 200 evaluable participants, across all study sites, in the cross sex hormone cohort to ensure adequate statistical power to test the two hypotheses of Aim 2 and to conduct the exploratory analysis.

10.4 Randomization Procedure

This is an observational study and participants will not be randomly assigned to treatment.

10.5 Statistical Analysis

10.5.1 Primary Objective: *Effects of Hormonal Interventions on Mental Health and Psychological Well-Being:*

Hypotheses under the primary objective will be tested in each cohort, respectively, using repeated measures multivariate analysis of variance (MANOVA) to assess the trajectories of continuous mental health outcomes and psychological well-being over time within each cohort. The MANOVA approach will preserve statistical power to detect significant effects among this set of related continuous outcomes without the inflated Type I error rates associated with a series of individual ANOVA or regression analyses. The MANOVA analyses will investigate the changes over time in gender dysphoria, depression, anxiety, trauma symptoms, self-injury, suicidality, body esteem, and quality of life. The model will incorporate time (i.e., measurement time point: baseline, 6-month, 12-month, 18-month or 24-month survey) as a within-participants factor. Asserted gender, age, ethnicity, and other socio-demographic variables may additionally be entered as possible covariates (i.e., ANCOVA) to improve statistical power to detect significant time effects. However, we do not propose any a priori hypotheses about demographic effects on these outcomes, and any demographic variables that do not contribute significantly to the model will be removed from the analysis in order to preserve power and increase model parsimony.

In keeping with conventional practice, analysis will first proceed with a review of Box's test for the equality of covariance matrices. Violations of this assumption would require the use of Pillai's trace, as opposed to Wilks' Lambda, to determine multivariate statistical significance. If, as hypothesized, the within-participants time variable demonstrates significant multivariate effects, the follow-up univariate results will be inspected as appropriate. The assumption of sphericity via Mauchly's test will be checked for each measured outcome; if sphericity is violated, the Huyhn-Feldt correction for degrees of freedom will be applied to that outcome. Finally, for outcomes showing significant time effects, linear and quadratic contrasts will be checked for significance and marginal means will be computed and plotted to create a visual display of significant trajectories. An a priori p-value of 0.05 will be applied as the criterion for statistical significance in all analyses.

10.5.2 Secondary Objectives

Safety of Hormonal Interventions:

Unlike the mental health and psychological well-being measures, the question of interest for these metabolic and physiological parameters is not whether they show significant fluctuation over time (which may or may not be meaningful), but rather whether development after initiation of hormonal interventions pushes any physiological indicator above the clinically safe range for that indicator, i.e., above predetermined safety cutoff values based on previous literature and clinical guidelines. Safety will be assessed cross-sectionally with one-sided one-sample t-tests comparing cohort mean scores to the cutoff value. We hypothesize that the cohort means will be significantly lower than the cutoff score. We will use the Benjamini-Hochberg procedure to account for inflated family-wise alpha due to multiple comparisons at each time point.

Additionally, ranges of raw scores from all patient labs will be computed at each time point as part of the preliminary data cleaning and descriptive analysis phase. This will provide an immediate assessment whether the indicator value for any individual patient has crossed the safety threshold for that indicator as data are collected at each time point. In the event any patient experiences an individual increase in laboratory values above the threshold, medication adjustments will be made to protect the well-being of the patient according to the discretion of the medical provider at the site where they are receiving care regardless of the whole-cohort significance test results for that time point.

Bone Density in Blocker Cohort:

We will use repeated measures ANOVA to estimate trajectories of raw and age-matched bone density scores over time in blocker cohort youth. As before, asserted gender and socio-demographic variables may be entered as possible covariates, linear and quadratic contrasts will be assessed, and marginal means will be computed and plotted to create a visual display of trajectories for both outcomes. We hypothesize that for raw scores, the linear term will not differ significantly from zero, indicating net stability in bone density over time. However, for age-matched z-scores, the linear term may be negative as gender non-conforming youth receiving GnRH agonists fail to add bone density at a rate comparable to their age-matched peers.

10.5.3 Exploratory Objective: *Risk Behavior in Youth Initiating Cross Sex Hormones*

We will conduct an exploratory assessment of sexual risk and substance use behavior in the cross sex hormone cohort, using repeated measures MANOVA to model trajectories of these risk outcomes over time. As before, asserted gender and socio-demographic variables may be entered as possible covariates. Given that sexual risk and substance use behaviors increase during adolescence in normative samples, we do not specify a priori hypotheses regarding the impact of hormone treatment on these risk outcomes in our transgender population. However, linear and quadratic contrasts will be assessed. Significant positive terms (indicating increased risk over time) would be indicative of a typical adolescent risk trajectory, whereas significant negative terms (indicating decreasing engagement in risky behaviors) or non-significant time effects (suggesting no net change in risk) would instead support a "treatment-as-prevention" explanation. Again, Box's test will be reviewed for equality of covariance matrices and multivariate test statistic determined accordingly, and sphericity will be assessed via Mauchly's test with the Huyhn-Feldt correction applied as needed.

10.5.4 Additional Analytic Considerations: Site Clustering Effects

Although the observational study will take place at four sites nationwide, we do not anticipate substantial site effects. To verify this, a group identifier for each participant is included in the merged analytic dataset, and the intra-class correlation (ICC) for each outcome will be calculated prior to conducting multivariate analyses. If, as anticipated, no significant variance is carried at the group level, we will reduce the model to a traditional one-level model. If significant group-level variance does emerge, dummy codes to control site-specific variance will be used to enhance statistical power.

10.6 Missing Data

CHLA will conduct missing data analyses in order to differentiate between data that are missing at random (MAR) and data that are missing related to gender or aspects of the treatment plan (e.g., hormone dosing). If missing data can be regarded as MAR, multiple imputations may be used. If the MAR assumption is not plausible, sensitivity analyses will be conducted to evaluate the impact of MAR violations on analyses by specifying models for non-ignorable missing data mechanisms.

11.0 HUMAN SUBJECTS

This study is being conducted in compliance with the protocol, International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and 45 Code of Federal Regulations (CFR) §46.

11.1 Participants' Confidentiality

No personal identifying information (e.g., names) of the participants will appear in any computer files associated with this research project in any location. Participants will be assigned a unique identification number code. A key file that matches the ID number to the participant and organization will be maintained in a secure data repository within the project offices at each of the four sites. Data will be kept strictly confidential, except as required by law, and stored on a secure network, with password protection

such that only authorized users will have access to the file server. All computers will be located in locked facilities, and consent forms will be filed and stored separate from the raw data in a secured location under double-lock when not in use and with restricted access during work hours and/or when unattended. Any temporary data files kept on removable storage devices, as well as printouts derived from data analysis, will be stored in a locked compartment when not in use.

11.2 Certificate of Confidentiality

To further protect the privacy of the study participants, a Certificate of Confidentiality will be obtained from the U.S. Department of Health and Human Services (DHHS). With this Certificate in place, the researchers at the study sites cannot be forced to turn over identifying information about a study participant in any Federal, State, or local criminal, administrative, legislative, or other proceedings. This Certificate does not prevent a study participant from volunteering to turn over their research information nor does it prevent researchers from providing research-related information to others when requested by the study participant, or when required by law such as in cases of suspected or actual harm to or by the study participant.

11.3 Risks and Benefits

11.3.1 Risks

The Principal Investigators have determined that this study does not involve greater than minimal risk (45 CFR §46.404 and 21 CFR §50.51). Participation in this study poses no more harms or discomforts to participants than they may experience in normal daily life or during routine psychological examinations or tests.

Due to the personal nature of the information being collected in this study, there is some risk of emotional discomfort or distress. Participants will be informed that they are free to decline to answer any questions. Furthermore, participants will be informed that at any point they may stop if they do not wish to continue the questionnaire/interview. In the event of discomfort or upset, there are counselors at study sites with whom participants can talk and who can provide ongoing support as needed. Every effort will be made to keep the participant's participation in the study and personal information private and confidential, but absolute confidentiality cannot be guaranteed.

As this is an observational study, there are no alternative treatments or procedures.

11.3.2 Benefits

There may be no direct benefit to the participants for their participation in this study, but information learned from this study may benefit other youth, now or in the future. This research provides the opportunity to obtain a better understanding of transgender youth, improve their care, and share information on a local and national level about how to provide care and hormone therapy for gender dysphoric children and adolescents. The information that is learned from this project will support innovative approaches to identifying, understanding, and providing optimal care for multi-ethnic transgender youth.

11.4 Institutional Review Board Review and Informed Consent

The Institutional Review Boards requires that all research participants review and sign an informed consent/permission/assent form. The informed consent/permission/assent form covers information about the overall purpose of the study, what the study entails, potential risks, potential benefits to participating individuals and society, the confidentiality of data, and contact information for the Principal Investigator and the IRB. Once informed consent/permission/assent has been obtained, the research staff will have the form reviewed by a fellow research team member, who will confirm that it is fully completed before it is filed in a secure location under double-lock when not in use and with restricted access during work hours and/or when unattended.

For participants aged 7 to 13 years old, the participant will sign an age-appropriate assent form, and the parent/legal guardian will sign a consent/permission/assent form. For participants aged 14 to 17 years old, the participant and the parent/legal guardian will sign a consent/permission/assent form. For participants aged 18 years or older, the participant will sign a consent/permission/assent form.

11.5 Requirement for Consenting Participants Enrolled as Minors Who Reach Age of Majority While on Study

Pursuant to guidance requested from OHRP, when a minor participant is enrolled with parental permission into the study, and the study will extend beyond the participant's age of legal majority, research staff must establish a mechanism to track the participant to obtain a legally effective consent when the participant reaches majority to remain on study.

11.6 Prisoner Participation

The Principal Investigators and NICHD have concluded that this protocol does not meet Federal requirements governing prisoner participation in human participant research and should not be considered by local IRBs for the recruitment of prisoners. Participants may not engage in study activities if they become incarcerated or are placed in detention. In addition, research staff will not collect study-related data during the time that the participant is incarcerated or placed in detention.

11.7 45 CFR Parts 160 and 164 Standards for Privacy of Individually Identifiable Health Information ("Privacy Rule" Pursuant to the Health Insurance Portability and Accountability Act - HIPAA)

Each site is responsible for adherence to their individual institution's HIPAA policies and procedures.

11.8 Study Discontinuation

This study may be discontinued at any time by *The Eunice Kennedy Shriver* NICHD.

12.0 PUBLICATION OF RESEARCH FINDINGS

Data will be made available to other NIH investigators under the data-sharing agreement with NICHD after a reasonable time period that includes enough opportunity to prepare and have submitted for publication four manuscripts presenting the basic outcomes of the project. Beginning in Year 3, peer-reviewed publications will be developed pertaining to cross-sectional hypotheses and research questions found in primary and secondary objectives, though the bulk of publications are longitudinal in nature and will be developed in Year 5. Dissemination of findings to State and County officials, policy makers, and organizations will begin in Year 3, when preliminary data become available.

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APPENDIX I: SCHEDULE OF EVALUATIONS

	Pre-screening Worksheet [1]	Participant Consent/ Assent [2]	Locator Form [3]	Eligibility Confirmation [4]	ACASI & Debriefing [5]	DISC/ CBCL/ YSR [6]	Chart Abstraction
Pre-Screening	X						
Baseline	X	X	X	X	X	X	X[7]
6 Months			X		X[8]	X	X[9]
12 Months			X		X[8]	X	X[9]
18 Months			X		X[8]	X	X[9]
24 Months			X		X[8]	X	X[9]
Premature Discontinuation			X		X	X	X[9]

1 Pre-Screening Worksheet must be completed by an IRB-approved medical provider.

2 Participant consent/assent must be obtained within 30 days prior to enrollment (baseline ACASI). Consent/assent must be reaffirmed prior to enrollment if > 30 days has elapsed.

3 The Locator Form data should be confirmed to be correct at every visit.

4 If eligibility is confirmed prior to the baseline visit date, eligibility must be reconfirmed at the baseline visit before administering the ACASI.

5 Participation in the Baseline ACASI = Enrollment. Ideally, the ACASI should be completed in a single day. If extenuating circumstances prevent completion in a single day, the subject may return within the next 7 days to retake it from the beginning again. If retaken, the subject's first ACASI will be deleted.

6 The DISC and CBCL or YSR may be completed either on the same day as the ACASI or in a separate visit within 2 weeks after the ACASI. Blocker Child participants do not complete.

7 The Baseline Chart Abstraction is for data from the most recent previous medical visit and labs.

8 For the Blocker Cohort, the timeline for the follow-up ACASIs is based on the date of the insertion of the GnRH agonist. For the Cross-Sex Hormone Cohort, the timeline for the follow-up ACASI is based on the date of the Baseline ACASI.

9 The follow-up Chart Abstractions should collect data from the previous the visit through the date of the ACASI.

APPENDIX II: MEASURES

Blocker Cohort – Youth Survey Measures	
ACASI Measures: Time of Completion	Baseline, 6-month, 12-month, 18-month, & 24-month follow-up periods
Construct	**Measure**
Weight Bearing Exercise	Physical Activity Questionnaire
Demographics	Demographic questions for Blocker Cohort Youth
Gender Dysphoria	Utrecht Gender Dysphoria Scale (UGDS)
Depression	BDI-Y
Anxiety	Revised Children's Manifest Anxiety Scale: Second Edition (RCMAS-2 – What I Think and Feel)
Quality of Life	Pediatric Quality of Life Inventory – Child Report (PedsQL–CH)
Suicidality	Suicidal Ideation Scale
Body Esteem	Body Esteem Scale
Body Image	Body Image Scale
Social Relationships	Emotional Support / Friendship / Loneliness / Perceived Hostility / Perceived Rejection – NIH Toolbox
Self-Efficacy	Self-Efficacy (CAT 8-12 / CAT 13-17)– NIH Toolbox
Perceived Parent Support	Parental Support Scale – Youth Version
Resiliency	Connor-Davidson Resilience Scale
Self-Perception	Harter's Self-Perception Profiles for Adolescents & Children

Blocker Cohort – Parent Survey Measures	
ACASI Measures: Time of Completion	Baseline, 6-month, 12-month, 18-month, & 24-month follow-up periods
Construct	**Measure**
Demographics	Demographic questions for Blocker Cohort Parents
Service Utilization	Service Utilization Questions
Socio-Economic Status	Socioeconomic Status Questions (for Adults)
Religiosity & Spirituality	Modified Duke University Religion Index (DUREL)
Calcium Intake	Daily Calcium Intake Form
Gender Identity	Parent Report Gender Identity Questionnaire (GIQC)
Social Transitioning	Social Transitioning Scale
Gender Dysphoria	DSM 5 – Chicago adapted
Quality of Life	Pediatric Quality of Life Inventory - Parent Report (PedsQL – PC)
Suicide attempts	Suicidality Questions
Parent distress/stress	Parenting Stress Index
Social Relationships	Empathic Behaviors / Peer Rejection / Positive Peer Interactions / Social Withdrawal (Parent Report) – NIH Toolbox
Negative Affect	Anger / Fear / Sadness (Parent Report) – NIH Toolbox
Psychological well-being	General Life Satisfaction / Positive Affect (Parent Report)– NIH Toolbox
Self-Efficacy	Self-Efficacy (Parent Report) – NIH Toolbox
Perceived Parent Support	Parental Support Scale – Parent Version
Autism	Autism-Spectrum Quotient (AQ-10) – Child
Additional Assessments: Time of Completion	Baseline, 12-month, & 24-month follow-up periods
Construct	**Measure**
Depression/Externalization	Child Behavior Checklist (CBCL)
DSM diagnoses	Parent Report Diagnostic Interview Schedule for Children (C-DISC IV)

Cross Sex Hormone Cohort Survey Measures	
ACASI Measures: Time of Completion	Baseline, 6-month, 12-month, 18-month, & 24-month follow-up periods
Construct	**Measure**
Demographics	Demographic questions for Cross Sex Hormone Cohort
Religiosity & Spirituality	Modified Duke University Religion Index (DUREL)
Socio-Economic Status	Socioeconomic Status Questions (for Adolescents & Young Adults)
Gender Identity	Transgender Congruence Scale
Gender Dysphoria	Utrecht Gender Dysphoria Scale (UGDS)
	Gender Identity/Gender Dysphoria Questionnaire Adolescents & Adults
	DSM 5 – Chicago adapted
Service Utilization	Dr. Olson's Service Utilization Questions
Depression	BDI-II
Anxiety	Revised Children's Manifest Anxiety Scale: Second Edition (RCMAS-2 – What I Think and Feel)
Quality of Life	Health-Related Quality of Life Scale (modified HIV QOL)
Suicidality	Suicidal Ideation Scale
Body Esteem	Body Esteem Scale
Body Image	Body Image Scale
Social Relationships	Emotional Support / Friendship / Loneliness / Perceived Hostility / Perceived Rejection – NIH Toolbox
Negative Affect	Anger / Fear / Sadness – NIH Toolbox
Psychological well-being	General Life Satisfaction / Positive Affect – NIH Toolbox
Self-Efficacy	Self-Efficacy (CAT 13-17)– NIH Toolbox
Perceived Parent Support	Parent Support Scale – Youth Version
Resiliency	Gender Minority Stress and Resilience Scale
	Connor-Davidson Resilience Scale
Sexual Behavior	Sexual Risk Behavior Questions
STI history	STI Questions
Alcohol/Drug Use	Youth Informant DISC (DISC-Y)
	Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)
Autism	Autism-Spectrum Quotient (AQ-10) – Adult

Additional Assessments: Time of Completion	**Baseline, 12-month, & 24-month follow-up periods**
Construct	**Measure**
Internalizing/Externalizing	Youth Self-Report (YSR)
DSM diagnoses	Youth Informant Diagnostic Interview Schedule for Children (DISC-Y)

Ex. 34

PLOS ONE

RESEARCH ARTICLE

Access to gender-affirming hormones during adolescence and mental health outcomes among transgender adults

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OPEN ACCESS

Citation: Turban JL, King D, Kobe J, Reisner SL, Keuroghlian AS (2022) Access to gender-affirming hormones during adolescence and mental health outcomes among transgender adults. PLoS ONE 17(1): e0261039. https://doi.org/10.1371/journal.pone.0261039

Editor: Asa E. Radix, Callen-Lorde Community Health Center, UNITED STATES

Received: August 20, 2021

Accepted: November 16, 2021

Published: January 12, 2022

Data Availability Statement: Data for this study were obtained via data sharing agreement from The National Center for Transgender Equality. Data requests may be submitted to them online via https://www.ustranssurvey.org/data-requests-general.

Funding: JLT received a pilot research award for general psychiatry residents from The American Academy of Child & Adolescent Psychiatry, supported by Industry Sponsors (Arbor and Pfizer), an award from the National Institute of

Abstract

Objective

To examine associations between recalled access to gender-affirming hormones (GAH) during adolescence and mental health outcomes among transgender adults in the U.S.

Methods

We conducted a secondary analysis of the 2015 U.S. Transgender Survey, a cross-sectional non-probability sample of 27,715 transgender adults in the U.S. Using multivariable logistic regression adjusting for potential confounders, we examined associations between access to GAH during early adolescence (age 14–15), late adolescence (age 16–17), or adulthood (age ≥18) and adult mental health outcomes, with participants who desired but never accessed GAH as the reference group.

Results

21,598 participants (77.9%) reported ever desiring GAH. Of these, 8,860 (41.0%) never accessed GAH, 119 (0.6%) accessed GAH in early adolescence, 362 (1.7%) accessed GAH in late adolescence, and 12,257 (56.8%) accessed GAH in adulthood. After adjusting for potential confounders, accessing GAH during early adolescence (aOR = 0.4, 95% CI = 0.2–0.6, p < .0001), late adolescence (aOR = 0.5, 95% CI = 0.4–0.7, p < .0001), or adulthood (aOR = 0.8, 95% CI = 0.7–0.8, p < .0001) was associated with lower odds of past-year suicidal ideation when compared to desiring but never accessing GAH. In post hoc analyses, access to GAH during adolescence (ages 14–17) was associated with lower odds of past-year suicidal ideation (aOR = 0.7, 95% CI = 0.6–0.9, p = .0007) when compared to accessing GAH during adulthood.

Mental Health (MH094612), and a fellowship from The Sorensen Foundation. ASK received a grant from Health Resources and Services Administration Bureau of Primary Health Care (U30CS22742). The sponsors of this research did not play any role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. AACAP:https://www.aacap.org/AACAP/Press/Press_Releases/2019/Jack_Turban_Receives_AACAP_Pilot_Research_Award_for_General_Psychiatry_Residents_Supported_b.aspx#:~:text=Washington%2C%20DC%2C%20September%2030%2C,2019%20Pilot%20Research%20Award%20for NIMH: nimh.nih.gov Sorensen Foundation: https://sorensenfellowship.org/ Health Resources and Services Administration Bureau of Primary Health Care: https://bphc.hrsa.gov/ The funding sources of this study played no role in study design, data collection, data analysis, or data interpretation.

Competing interests: I have read the journal's policy and the authors of this manuscript have the following competing interests: Dr. Turban reports receiving textbook royalties from Springer Nature and Dr. Keuroghlian reports receiving textbook royalties from McGraw Hill. Dr. Turban has received expert witness payments from the ACLU.

Conclusion

Access to GAH during adolescence and adulthood is associated with favorable mental health outcomes compared to desiring but not accessing GAH.

Introduction

A recent representative sample of adolescents in the United States (U.S.) found that 1.8% identified as transgender [1]. Unfortunately, these young people face a range of mental health disparities, including elevated rates of anxiety, depression, and suicide attempts [2]. Suicide attempt prevalence among transgender young adults has been estimated to be as high as 40% [3]. These disparities are generally thought to be due to two processes: gender minority stress and dysphoria related to one's body developing in ways that are incongruent with one's gender identity (i.e., a person's psychological sense of their own gender) [2].

Gender minority stress refers to the ways in which society's mistreatment of transgender people results in worse mental and physical health outcomes. This includes distal factors (gender-related discrimination, gender-related rejection, gender-related victimization, and non-affirmation of gender identity), as well as subsequent proximal factors (internalized transphobia, negative expectations, and concealment) [4]. Creating safe and affirming social environments for transgender adolescents is thus considered paramount in preventing adverse mental health outcomes [5].

In addition to creating safe and affirming environments, care for transgender people often involves the provision of gender-affirming medical interventions to alleviate the psychological distress related to one's body developing in ways that do not align with one's gender identity [6, 7]. This may include pubertal suppression for younger adolescents and gender-affirming hormones (GAH, e.g., estrogen and testosterone) from adolescence onward to induce physical changes that match the person's gender identity [6–8]. Some adolescents may undergo gender-affirming surgery to reduce psychological distress [9, 10]. Of note, past Endocrine Society guidelines recommended that GAH not be considered until an adolescent reaches age 16 [11]. More recent guidelines state that initiation of GAH can be considered as early as age 14, to allow transgender adolescents to undergo puberty at ages more comparable to their peers, and to reduce the risk of delayed bone development due to prolonged pubertal suppression [7]. In this article, we therefore consider two age groups of adolescents who initiated GAH: those who started GAH during late adolescence (i.e., between their 16^{th} and 18^{th} birthdays) and those who started GAH during early adolescence (i.e., between their 14^{th} and 16^{th} birthdays).

To date, there have been six longitudinal cohort studies examining the impact of GAH initiation during adolescence on mental health [12–17]. These studies have generally found improvement in mental health following adolescent GAH initiation, including decreases in internalizing psychopathology, improved general wellbeing, and decreased suicidality. Of note, these studies did not include a comparison group of adolescents who did not access GAH. Furthermore, these studies did not examine separately those who initiated GAH during early or late adolescence, nor did they compare initiation of GAH during adolescence with initiation of GAH during adulthood.

The impact of GAH initiated in adolescence on the mental health of transgender adults is of particular policy relevance today, as several U.S. states have introduced legislation to limit access to GAH for transgender adolescents, despite opposition from major medical organizations including The American Medical Association, The American Academy of Pediatrics,

The American Psychiatric Association, The American Academy of Child & Adolescent Psychiatry, The Endocrine Society, The Pediatric Endocrine Society, and others [18]. This is an area of active policy debate where additional quantitative data are needed to guide policy decisions. Parents of transgender youth have been particularly concerned about these restrictive legislative efforts, with a parent in one recent qualitative sudy noting, "this could mean death for my child" [19].

The current study uses the largest survey of transgender people conducted to date to examine associations between recalled access to GAH during early adolescence (ages 14–15), late adolescence (ages 16–17), or adulthood (age ≥18), and adult mental health outcomes including measures of suicidality. It is the first study of GAH initiation during adolescence that includes a comparison group of those who desired but never accessed GAH. It is also the first to compare access to GAH during adolescence with access to GAH during adulthood. Given the large sample size, we were able to adjust for a wide range of potential confounding variables known to be associated with mental health outcomes for transgender people. We hypothesized that access to GAH during both early and late adolescence would be associated with more favorable mental health outcomes reported in adulthood, when compared to desiring but never accessing GAH.

Methods

Study population

The 2015 U.S. Transgender Survey (USTS) is the largest existing dataset of transgender people to date [3]. The cross-sectional non-probability survey was conducted between August and September of 2015. Transgender adults ages 18 years or older were recruited in collaboration with over 400 community organizations and completed measures online. The final survey had 27,715 participants from all 50 U.S. states, as well as Washington D.C., Puerto Rico, and U.S. territories abroad. Because not all transgender people necessarily desire GAH, we restricted the current study to participants who reported ever desiring GAH for gender affirmation, as this is a more clinically relevant group. This was assessed by choosing "hormone therapy/HRT (an acronym for 'Hormone Replacement Therapy')" in response to the question, "Have you ever wanted any of the health care listed below for your gender identity or gender transition? (Mark all that apply)." Options included "counseling/therapy," "hormone treatment/HRT," "puberty blocking hormones (usually used by youth ages 9–16)," and "none of the above." This resulted in inclusion of 21,598 participants.

Ethical considerations

The protocol for the USTS was approved by the University of California Los Angeles Institutional Review Board. The protocol for the current study was reviewed by The Fenway Institute Institutional Review Board. All participants provided informed consent for study participation.

Age of initiation of GAH

Participants were divided into four categories. The first group, "wanted but never accessed GAH" (No GAH), reported never accessing GAH despite desiring these medications. The second group consisted of participants who reported they first accessed GAH during early adolescence, defined as the period between their 14th and 16th birthdays (GAH 14–15), which corresponds to the age group most recently added to the Endocrine Society Guidelines [7]. The third group consisted of participants who reported they first accessed GAH during late

adolescence, defined as the period between their 16th and 18th birthdays (GAH 16–17), corresponding to the narrower age group in the prior, 2009 Endocrine Society Guidelines [11]. The fourth group consisted of participants who reported they first accessed GAH after their 18th birthday (GAH $\geq$ 18).

Outcomes

Severe psychological distress in the month prior to the survey was defined as a score $\geq$ 13 on the Kessler-6 Psychological Distress Scale [20]. Binge drinking in the month prior to the survey was defined as drinking 5 or more standard alcoholic drinks on a single occasion, a threshold for use in research with transgender adults that has been discussed in prior reports [21]. Lifetime illicit drug use (excluding marijuana) was also assessed as a binary "yes" or "no" self-report outcome. Measures of suicidality were examined, including suicidal ideation during the year prior to the survey, suicidal ideation with plan during the prior year, suicide attempt during the prior year, and suicide attempt requiring hospitalization during the prior year [8]. All suicidality measures were binary outcome variables in which participants reported "yes" or "no."

Demographic and other potential confounding variables

Demographic and other potential confounding variables that are known to be associated with adverse mental health outcomes among transgender people were collected for participants and included age at time of survey completion (U.S. census categories), gender identity, sex assigned at birth, sexual orientation, race/ethnicity (U.S. census categories), level of family support for gender identity (unsupportive, neutral, supportive, or not asked because participant had not disclosed being transgender to their family) [22], relationship status, level of education, employment status, household income, having ever received pubertal suppression (e.g., treatment with gonadotropin-releasing hormone agonists) [8], having ever been exposed to gender identity conversion efforts [23], and having experienced any harassment based on gender identity in K-12 (verbal, physical, or sexual) [5].

Statistical analyses

All statistical analyses were performed with SAS 9.4. The data in the analytic sample had minimal missing data for both exposure and outcome variables. Each control variable had under 8% missing data within all comparison groups. Therefore no imputation was performed, since listwise deletion with missingness as high as 10% can be acceptable under particular assumptions of missingness [24].

Analyses were performed for the three age groups of participants who accessed GAH and participants who desired but never accessed GAH, on demographic variables listed above. Variables were analyzed with Rao-Scott χ^2 tests. Logistic regression tests were used to identify demographics and other potential confounding variables associated with each outcome.

Multivariable logistic regression was then performed, comparing mental health outcomes for participants who reported access to GAH during early adolescence, late adolescence, or adulthood with those for participants who desired but never accessed GAH. Models were fit to test associations with mental health outcomes, after adjusting for demographic and potential confounding variables that were found to be associated with each outcome. All hypothesis tests were 2-sided. The percentage decrease in adjusted odds for the outcomes was calculated from the model coefficients for each age group.

In order to account for multiple comparisons, a modified Bonferroni correction was applied for the approximately 50 comparisons performed. A significance threshold of 0.001 (.05/50) was used for our analyses.

After all aforementioned analyses were completed, we identified further analyses of interest that were not included in the original study design, and therefore not included in the Bonferroni correction. In these post hoc analyses, we compared access to GAH during adolescence (ages 14–17) to access during adulthood (ages ≥18), and access to GAH during early adolescence (ages 14–15) to access during late adolescence (ages 16–17).

Results

Demographic differences & potential confounding variables

In total, 21,598 participants (77.9%) reported ever desiring GAH. Of these, 8,860 (41.0%) never accessed GAH, 119 (0.6%) reported access to GAH in early adolescence, 362 (1.7%) reported access to GAH in late adolescence, and 12,257 (56.8%) reported access to GAH in adulthood. Significant differences were found based on age at time of study participation, gender identity, sex assigned at birth, sexual orientation, race/ethnicity, family support of gender identity, relationship status, level of education, employment status, household income, having ever received pubertal suppression, having ever been exposed to gender identity conversion efforts, and having experienced verbal, physical, or sexual harassment based on gender identity in K-12 (Table 1).

GAH during early adolescence

The median age of participants who reported accessing GAH during early adolescence was 21.0 (IQR 18.0–35.0). After adjusting for demographic and potential confounding variables, recalled access to GAH during early adolescence was associated with lower odds of past-month severe psychological distress (aOR = 0.3, 95% CI = 0.2–0.4, $p < .0001$) and past-year suicidal ideation (aOR = 0.4, 95% CI = 0.2–0.6, $p < .001$) when compared to desiring GAH but never accessed them. For participants who recalled GAH access in early adolescence, these results represent a 222% decrease in adjusted odds for past-month severe psychological distress and a 135% decrease for past-year suicidal ideation. We detected no difference for other mental health variables measured (Table 2).

GAH during late adolescence

The median age of participants who reported accessing GAH during late adolescence was 19.0 (IQR 18.0–22.0). After adjusting for demographic and potential confounding variables, recalled access to GAH during late adolescence was associated with lower odds of past-month severe psychological distress (aOR = 0.3, 95% CI = 0.3–0.4, $p < .0001$) and past-year suicidal ideation (aOR = 0.5, 95% CI = 0.4–0.7, $p < .0001$) when compared to desiring GAH but never accessing them. These results represent a 153% decrease in the adjusted odds for past-month severe psychological distress and a 62% decrease for past-year suicide ideation. We detected no difference for other mental health variables measured (Table 2).

GAH during adulthood

The median age of participants who reported accessing GAH during adulthood was 31.0 (IQR 25.0–45.0). After adjusting for demographic and potential confounding variables, participants who recalled access to GAH during adulthood had lower odds of past-month severe psychological distress (aOR = 0.6, 95% CI = 0.5–0.6, $p < .0001$) and past-year suicidal ideation

Table 1. Sample demographics.

Total N = 21,598		No GAH	GAH 14–15	GAH 16–17	GAH ≥ 18	
		n = 8860	n = 119	n = 362	n = 12257	
		n (%)	n (%)	n (%)	n (%)	p
Age (Census)						<0.001
	18–24	5315 (60.0)	75 (63.03)	297 (82.04)	2856 (23.30)	
	25–44	2653 (29.9)	23 (19.33)	54 (14.92)	6285 (51.28)	
	45–64	753 (8.5)	19 (15.97)	11 (3.04)	2660 (21.70)	
	65+	139 (1.57)	2 (1.68)	0 (0.00)	456 (3.72)	
Gender Identity						<0.001
	Trans man / male	02620 (29.57)	00048 (40.34)	00214 (59.12)	04713 (38.45)	
	Trans woman / female	02324 (26.23)	00054 (45.38)	00109 (30.11)	06340 (51.73)	
	AFAB GQ/NB	02829 (31.93)	00013 (10.92)	00035 (9.67)	00834 (6.80)	
	AMAB GQ/NB	00766 (8.65)	00004 (3.36)	00004 (1.10)	00330 (2.69)	
	Other	00321 (3.62)	00000 (0.00)	00000 (0.00)	00040 (0.33)	
Sex Assigned at Birth						<0.001
	Female	05475 (61.79)	00061 (51.26)	00249 (68.78)	05561 (45.37)	
	Male	03385 (38.21)	00058 (48.74)	00113 (31.22)	06696 (54.63)	
Sexual Orientation						<0.001
	Asexual	01220 (13.77)	00006 (5.04)	00022 (6.08)	00771 (06.29)	
	Bisexual	01391 (15.70)	00007 (5.88)	00056 (15.47)	01900 (15.50)	
	Gay/Lesbian/Same Gender Loving	01337 (15.09)	00022 (18.49)	00064 (17.68)	02535 (20.68)	
	Heterosexual/Straight	00743 (8.39)	00031 (26.05)	00071 (19.61)	02019 (16.47)	
	Pansexual	01875 (21.16)	00021 (17.65)	00066 (18.23)	01877 (15.31)	
	Queer	01573 (17.75)	00019 (15.97)	00058 (16.02)	02525 (20.60)	
	Other	00721 (08.14)	00013 (10.92)	00025 (6.91)	00630 (5.14)	
Race / Ethnicity						<0.001
	Alaska Native/American Indian	00105 (1.19)	00002 (1.68)	00003 (0.83)	00149 (1.22)	
	Asian/Native Hawaiian/Pacific Islander	00273 (3.08)	00008 (6.72)	00010 (2.76)	00292 (2.38)	
	Biracial/Multiracial	00475 (5.36)	00009 (7.56)	00027 (7.46)	00571 (4.66)	
	Black/African American	00210 (2.37)	00011 (9.24)	00016 (4.42)	00378 (3.08)	
	Latin/Hispanic	00499 (5.63)	00008 (6.72)	00025 (6.91)	00572 (4.67)	
	White/Middle Eastern/North African	07298 (82.37)	00081 (68.07)	00281 (77.62)	10295 (83.99)	
Family Support of Gender Identity						<0.001
	Not Asked (Not Out to Family as Transgender)	03067 (34.64)	00003 (2.52)	00015 (4.14)	00901 (7.36)	
	Neutral	01564 (17.66)	00012 (10.08)	00032 (8.84)	01980 (16.16)	
	Supportive	02904 (32.80)	00091 (76.47)	00291 (80.39)	07321 (59.77)	

(*Continued*)

Table 1. (Continued)

Total N = 21,598		No GAH	GAH 14–15	GAH 16–17	GAH ≥ 18	
		n = 8860	n = 119	n = 362	n = 12257	
		n (%)	n (%)	n (%)	n (%)	p
	Unsupportive	01319 (14.90)	00013 (10.92)	00024 (6.63)	02047 (16.71)	
	Missing	6 (0.07)	0 (0.00)	0 (00.00)	8 (0.08)	
Relationship Status						**<0.001**
	Partnered	04028 (46.90)	00049 (43.36)	00135 (38.03)	06257 (52.99)	
	Unpartnered	04560 (53.10)	00064 (56.64)	00220 (61.97)	05551 (47.01)	
	Other	272 (3.07)	6 (5.04)	7 (1.93)	449 (3.66)	
Education						**<0.001**
	Bachelor's degree or higher	02219 (25.05)	00023 (19.33)	00048 (13.26)	05911 (48.23)	
	Some college (no degree)/Associate's	04555 (51.41)	00061 (51.26)	00171 (47.24)	05199 (42.42)	
	High school grad (including GED)	01617 (18.25)	00023 (19.33)	00099 (27.35)	00975 (7.95)	
	Less than high school	00469 (5.29)	00012 (10.08)	00044 (12.15)	00172 (1.40)	
Employment Status						**<0.001**
	Employed	05213 (59.10)	00060 (50.85)	00189 (52.50)	08788 (72.01)	
	Out of the labor force	02038 (23.10)	00039 (33.05)	00108 (30.00)	02283 (18.71)	
	Unemployed	01570 (17.80)	00019 (16.10)	00063 (17.50)	01133 (9.28)	
	Excluded (status unclear)	4 (0.05)	0 (0)	2 (00.55)	2 (0.02)	
	Missing	35 (0.40)	1 (0.48)	0 (0)	51 (0.42)	
Household Income						**<0.001**
	$1 to $9,999	01163 (14.75)	00016 (14.81)	00041 (12.65)	01160 (10.10)	
	$10,000 to $24,999	01714 (21.73)	00013 (12.04)	00053 (16.36)	02252 (19.62)	
	$100,000 or more	01136 (14.40)	00023 (21.30)	00079 (24.38)	02064 (17.98)	
	$25,000 to $49,999	01717 (21.77)	00028 (25.93)	00059 (18.21)	02652 (23.10)	
	$50,000 to $100,000	01772 (22.47)	00024 (22.22)	00071 (21.91)	03035 (26.44)	
	No income	00385 (4.88)	00004 (3.70)	00021 (6.48)	00317 (2.76)	
	Excluded	275 (3.10)	7 (5.88)	11 (3.04)	313 (2.55)	
	Missing	698 (7.88)	4 (3.36)	27 (7.46)	464 (3.79)	
Ever Received Pubertal Suppression						**<0.001**
	Yes	00031 (0.36)	00041 (34.45)	00044 (12.15)	00221 (01.80)	
	No	08659 (99.64)	00078 (65.55)	00318 (87.85)	12036 (98.20)	
	Missing	00170 (1.92))	0 (0.00))	0 (0.00))	0 (0.00))	
Ever Experienced Gender Identity Conversion Efforts						**<0.001**

(*Continued*)

Table 1. (Continued)

Total N = 21,598		No GAH n = 8860 n (%)	GAH 14–15 n = 119 n (%)	GAH 16–17 n = 362 n (%)	GAH ≥ 18 n = 12257 n (%)	p
	Yes	00998 (11.28)	00031 (26.27)	00092 (25.48)	02208 (18.03)	
	No	07852 (88.72)	00087 (73.73)	00269 (74.52)	10037 (81.97)	
	Missing	10 (0.11)	1 (0.84)	1 (0.28)	12 (0.10)	
K-12 Harassment						**<0.001**
	Verbal, physical or sexual	2026 (22.9)	80 (67.2)	226 (62.4)	2612 (21.3)	
	None	6834 (77.1)	39 (32.8)	136 (37.6)	9645 (78.7)	

Descriptive statistics for transgender adults in the U.S. who ever desired gender-affirming hormones (GAH) for their gender identity or gender transition, comparing those who never accessed this treatment (No GAH), those who accessed GAH between their 14th and 16th birthdays (GAH 14–15), those who accessed GAH after their 16th birthday and before their 18th birthday (GAH 16–18) and those who accessed GAH after their18th birthday (GAH ≥ 18).
Abbreviations: AFAB (assigned female at birth), AMAB (assigned male at birth), GQ/NB (gender queer or non-binary).

https://doi.org/10.1371/journal.pone.0261039.t001

(aOR = 0.8, 95% CI = 0.7–0.8, p < .0001) when compared to those who desired GAH but never accessed them. Access to GAH during adulthood was associated with an 81% decrease in adjusted odds of past-month severe psychological distress and a 21% decrease in past-year suicidal ideation. Access to GAH during adulthood was also associated with greater odds of past-month binge drinking (aOR = 1.2, 95% CI = 1.1–1.3, p < .0001) and lifetime illicit drug use (aOR = 1.7, 95% CI = 1.6–1.8, p < .0001) when compared to desiring but never accessing GAH. Results indicated an adjusted odds increase of 20% for past-month binge drinking and 70% increase for lifetime illicit drug use. We detected no difference for other mental health variables measured (Table 2).

Raw frequencies of outcome variables

Raw frequencies for outcome variables are shown in Table 3.

Post hoc analyses

GAH during adolescence vs. GAH during adulthood. After adjusting for demographic and potential confounding variables, access to GAH during adolescence (ages 14–17) was associated with lower odds of past-month severe psychological distress (aOR = 0.6, 95% CI = 0.5–0.8, p < .0001), past-year suicidal ideation (aOR = 0.7, 95% CI = 0.6–0.9, p = .0007), past-month binge drinking (aOR = 0.7, 95% CI = 0.5–0.9, p = .001), and lifetime illicit drug use (aOR = 0.7, 95% CI = 0.5–0.8, p = .0003) when compared to access to GAH during adulthood. We detected no difference for other mental health variables measured (Table 4).

Access to GAH during early vs. late adolescence. After adjusting for demographic and potential confounding variables, we detected no difference in odds of any mental health variables measured when comparing access to GAH during early adolescence with access to GAH during late adolescence (Table 4).

Lifetime but no past year suicidality. Due to the cross-sectional nature of the study, it was possible that we detected an association between favorable mental health outcomes and access to GAH because people with better mental health were more likely to be able to access GAH. Given that baseline mental health status could confound associations between access to GAH and mental health outcomes, in post hoc analyses we examined two outcome measures

Table 2. Outcomes for participants who accessed gender-affirming hormones (estrogen or testosterone).

	Participants who Accessed GAH											
	N = 12,598											
	Accessed GAH at Age 14 or 15				Accessed GAH at Age 16 or 17				Accessed GAH at Age ≥ 18			
	n = 119				n = 362				n = 12257			
	OR (95% CI)	p	aOR (95% CI)	p	OR (95% CI)	p	aOR (95% CI)	p	OR (95% CI)	p	aOR (95% CI)	p
Suicidality (Past 12 months)												
Past-year suicidal ideation [a]	0.5 (0.3–0.7)	.0001	0.4 (0.2–0.6)	< **.0001**	1.0 (0.8–1.2)	.73	0.5 (0.4–0.7)	< **.0001**	0.5 (0.5–0.6)	< .0001	0.8 (0.7–0.8)	< **.0001**
Past-year suicidal ideation with plan [b]	1.3 (0.8–2.4)	.31	0.8 (0.4–1.6)	.58	1.1 (0.9–1.5)	.41	0.9 (0.7–1.2)	.49	0.8 (0.8–0.9)	< .0001	0.9 (0.8–1.0)	.09
Past-year suicide attempt [c]	1.0 (0.5–2.2)	.99	0.4 (0.2–1.1)	.08	1.4 (1.0–2.0)	.04	0.9 (0.6–1.4)	.79	0.8 (0.8–0.9)	.002	1.0 (0.9–1.1)	.89
Past-year suicide attempt requiring inpatient hospitalization [d]	--	--	--	--	2.2 (1.2–4.0)	.01	2.2 (1.2–4.2)	.01	1.4 (1.1–1.7)	.002	1.2 (0.9–1.5)	.26
Mental Health & Substance Use												
Past-month severe psychological distress (K6 ≥ 13) [c]	0.5 (0.3–0.7)	.0004	0.3 (0.2–0.4)	< **.0001**	0.6 (0.5–0.8)	< .0001	0.3 (0.3–0.4)	< **.0001**	0.4 (0.3–0.4)	< .0001	0.6 (0.5–0.6)	< **.0001**
Past-month binge drinking [e]	1.6 (1.1–2.3)	.02	1.6 (1.0–2.4)	.04	0.8 (0.6–1.1)	.17	0.9 (0.6–1.1)	.27	1.2 (1.1–1.2)	< .0001	1.2 (1.1–1.3)	< **.0001**
Lifetime illicit drug use [f]	1.8 (1.2–2.6)	.003	1.5 (1.0–2.2)	.08	1.2 (1.0–1.6)	.08	1.3 (1.0–1.6)	.07	2.1 (1.9–2.2)	< .0001	1.7 (1.6–1.8)	< **.0001**

Mental health outcomes of transgender adults who recalled access to gender-affirming hormones (GAH) during various age groups. Reference group for all analyses is participants who desired GAH but did not access them. All models adjusted for age, partnership status, employment status, K-12 harassment, and having experienced gender identity conversion efforts.

Abbreviations: OR (odds ratio), aOR (adjusted odds ratio), 95% CI (95% confidence interval).

[a] Model also adjusted for gender identity, sex assigned at birth, sexual orientation, race/ethnicity, family support of gender identity, educational attainment, and total household income.

[b] Model also adjusted for sexual orientation, race/ethnicity, educational attainment, and total household income.

[c] Model also adjusted for gender identity, sex assigned at birth, sexual orientation, race/ethnicity, family support of gender identity, educational attainment, total household income, and having received pubertal suppression.

[d] Model also adjusted for family support of gender identity. Only one participant in the GAH < 16 group endorsed a past–year suicide attempt requiring inpatient hospitalization, precluding calculation of an aOR for this outcome.

[e] Model also adjusted for gender identity, sex assigned at birth, sexual orientation, family support of gender identity, educational attainment, and total household income.

[f] Model also adjusted for gender identity, sex assigned at birth, sexual orientation, race/ethnicity, family support of gender identity, and educational attainment.

https://doi.org/10.1371/journal.pone.0261039.t002

relevant to this question of temporality: lifetime but no past-year suicidal ideation, and lifetime but no past-year suicide attempt. We found that access to GAH in adulthood was associated with greater odds of lifetime but no past-year suicidal ideation (aOR = 1.4, 95% CI = 1.3–1.5, p < .0001) when compared to desiring but not accessing GAH (Table 5). The association of access to GAH during late adolescence with lifetime but no past year suicidal ideation (aOR = 1.4, 95% CI = 1.1–1.8, p = .005) was no longer significant after Bonferroni correction, though some have noted that Bonferroni adjustment may be overly conservative, suggesting that this finding may be considered significant [25].

Discussion

In this large national cross-sectional non-probability study, transgender people who accessed GAH during early adolescence, late adolescence, or adulthood had better mental health

Table 3. Raw outcome frequencies of mental health outcomes.

Total N = 21,598	No GAH	GAH 14–15	GAH 16–17	GAH ≥ 18
	n = 8860	n = 119	n = 362	n = 12257
	n (%)	n (%)	n (%)	n (%)
Suicidality (Past 12 months)				
Past-year suicidal ideation	5144 (58.1)	48 (40.3)	40 (33.6)	5237 (42.7)
Past-year suicidal ideation with plan	2731 (30.8)	29 (24.3)	39 (32.8)	02537 (20.7)
Past-year suicide attempt	853 (9.6)	8 (6.7)	40 (33.6)	756 (6.2)
Past-year suicide attempt requiring inpatient hospitalization	220 (2.5)	1 (0.8)	40 (33.6)	247 (2.0)
Mental Health & Substance Use				
Past-month severe psychological distress (K6 ≥ 13)	4545 (51.3)	40 (33.6)	145 (40.1)	3419 (27.9)
Past-month binge drinking	2083 (23.5)	39 (32.8)	74 (20.4)	3214 (26.2)
Lifetime illicit drug use	1918 (21.6)	40 (33.6)	93 (25.7)	4455 (36.3)

https://doi.org/10.1371/journal.pone.0261039.t003

outcomes when compared to those who desired but were unable to access GAH. Given the substantial mental health disparities faced by transgender people, these results are of particular importance [26].

For each time period of GAH initiation examined (early adolescence, late adolescence, and adulthood), access to GAH was associated with lower odds of past-year suicidal ideation and past-month severe psychological distress. When we compared participants who accessed GAH during adolescence (ages 14–17) with those who accessed GAH during adulthood (18+),

Table 4. Outcomes for participants who accessed gender-affirming hormones (estrogen or testosterone).

	Accessed GAH at Age 14–17 (compared to GAH access at age ≥ 18) n = 481				Accessed GAH at Age 14 or 15 (compared to GAH access at age 16 or 17) n = 119			
	OR (95% CI)	p	aOR (95% CI)	p	OR (95% CI)	p	aOR (95% CI)	p
Suicidality (Past 12 months)								
Past-year suicidal ideation [a]	1.5 (1.3–1.8)	< .0001	0.7 (0.6–0.9)	**.0007**	0.5 (0.3–0.8)	.002	0.7 (0.4–1.2)	.16
Past-year suicidal ideation with plan [b]	1.4 (1.1–1.8)	.009	1.1 (0.8–1.5)	.51	1.2 (0.6–2.3)	.58	1.0 (0.5–1.9)	.88
Past-year suicide attempt [c]	1.6 (1.2–2.2)	.003	1.0 (0.7–1.4)	.82	0.7 (0.3–1.6)	.40	0.4 (0.1–1.3)	.12
Past-year suicide attempt requiring inpatient hospitalization [d]	1.3 (0.7–2.3)	.35	1.7 (0.9–3.2)	.08	0.2 (0.0–1.6)	.13	0.2 (0.0–2.1)	.19
Mental Health & Substance Use								
Past-month severe psychological distress (K6 ≥ 13) [e]	1.7 (1.4–2.0)	< .0001	0.6 (0.5–0.8)	**< .0001**	0.8 (0.5–1.2)	.26	0.7 (0.4–1.3)	.30
Past-month binge drinking [e]	0.9 (0.7–1.1)	.17	0.7 (0.5–0.9)	**.001**	1.9 (1.2–3.0)	.006	2.0 (1.2–3.5)	.01
Lifetime illicit drug use [f]	0.7 (0.5–0.8)	< .001	0.7 (0.5–0.8)	**.0003**	1.4 (0.9–2.3)	.10	1.0 (0.6–1.7)	.98

All models adjusted for age, partnership status, employment status, K-12 harassment, and having experienced gender identity conversion efforts.

Abbreviations: OR (odds ratio), aOR (adjusted odds ratio), 95% CI (95% confidence interval).

[a] Model also adjusted for gender identity, sex assigned at birth, sexual orientation, race/ethnicity, family support of gender identity, educational attainment, and total household income.

[b] Model also adjusted for sexual orientation, race/ethnicity, educational attainment, and total household income.

[c] Model also adjusted for gender identity, sex assigned at birth, sexual orientation, race/ethnicity, family support of gender identity, educational attainment, total household income, and having received pubertal suppression.

[d] Model also adjusted for family support of gender identity.

[e] Model also adjusted for gender identity, sex assigned at birth, sexual orientation, family support of gender identity, educational attainment, and total household income.

[f] Model also adjusted for gender identity, sex assigned at birth, sexual orientation, race/ethnicity, family support of gender identity, and educational attainment.

https://doi.org/10.1371/journal.pone.0261039.t004

Table 5. Lifetime but no past-year suicide ideation and attempts for participants who accessed gender-affirming hormones (estrogen or testosterone).

	Participants who Accessed GAH					
	N = 12,598					
	Accessed GAH at Age 14 or 15		Accessed GAH at Age 16 or 17		Accessed GAH at Age ≥ 18	
	n = 119		n = 362		n = 12,257	
	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p
Lifetime suicidal ideation and no past-year ideation [a]	1.3 (0.8–2.0)	.28	1.4 (1.1–1.8)	.005	1.4 (1.3–1.5)	< .0001
Lifetime suicide attempt and no past-year attempt [b]	0.8 (0.5–1.2)	.24	0.7 (0.6–1.0)	.03	1.0 (0.9–1.1)	.67

Mental health outcomes of transgender adults who recalled access to gender-affirming hormones (GAH) during various age groups. Reference group for all analyses is participants who desired GAH but did not access them. Both models adjusted for age, partnership status, employment status, K-12 harassment, and having experienced gender identity conversion efforts.

[a] Model also adjusted for gender identity, sex assigned at birth, sexual orientation, race/ethnicity, family support of gender identity, educational attainment, and total household income.

[b] Model also adjusted for gender identity, sex assigned at birth, sexual orientation, race/ethnicity, family support of gender identity, educational attainment, total household income, and having received pubertal suppression.

https://doi.org/10.1371/journal.pone.0261039.t005

participants who accessed GAH earlier had better mental health outcomes, including lower odds of past-year suicidal ideation, past-month severe psychological distress, past-month binge drinking, and lifetime illicit drug use. These results argue against waiting until adulthood to offer GAH to transgender adolescents and suggest that doing so may put patients at greater mental health risk.

The current study has a few advantages over past published studies in this area. While past studies have not included a comparison group of people who did not access GAH and were also underpowered to adjust for potential cofounders, this large sample size enabled comparison of participants who reported access to GAH to those who desired but did not access GAH, while adjusting for a wide range of potential confounding variables known to be associated with mental health outcomes for transgender people.

One unexpected finding was that participants who initiated GAH during adulthood, compared to those who desired but never accessed GAH, had greater odds of past-month binge drinking and lifetime illicit substance use. Transgender people often become more socially engaged following the increased confidence that results from gender affirmation, which may partly explain these results [27]. Given the high prevalence of substance use disorders in this population, clinicians ought to routinely screen for substance use disorders among transgender people, and researchers ought to focus on development of culturally responsive substance use disorder prevention and treatment interventions with transgender communities [27].

Notably, even participants who recalled access to GAH had high rates of past-year suicidal ideation. Though access to GAH during adolescence appears to be related to more favorable mental health outcomes, transgender people face a range of other psychosocial stressors that contribute to chronic minority stress, including but not limited to employment discrimination, lack of safe access to public facilities, and physical violence [4]. Future epidemiological and interventional research is needed to understand and address chronic minority stress among transgender people who access GAH as well as those who do not. For transgender adolescents, creating safe and affirming school environments appears to be of particular importance [28], in addition to providing gender-affirming medical care, as well as psychological, legal and surgical gender affirmation as needed [6].

This study also suggests that a large proportion of transgender people desire but never access GAH. Though prevalence in a non-probability sample should be interpreted with

caution, 41% of those who desired GAH in this study reported that they were unable to access them. Barriers to accessing prescribed GAH, in addition to leaving many without treatment, may also drive use of non-prescribed GAH, which is highly prevalent and associated with stigmatizing healthcare policies [29]. Future studies ought to examine if non-prescribed GAH use, when compared to prescribed GAH, is linked to worse mental health outcomes or adverse physical health outcomes (e.g., blood clot risk from estradiol use without standard medical monitoring).

Strengths and limitations

Strengths of this study include its large sample size and broad geographic representation within the U.S. The large sample size enabled adjustment for a wide range of potential confounding variables. Limitations include its non-probability cross-sectional design, which reduces generalizability and limits determination of causality. It is possible that people with better mental health status at baseline are more likely to be able to access GAH, thus confounding associations between GAH access and adult mental health outcomes measured: we therefore examined lifetime but no past-year suicidal ideation as an outcome, with results suggesting a lack of reverse causation due to such confounding. Nonetheless, this method is imperfect for investigating mental health changes following GAH, and future longitudinal studies are needed. Longitudinal waitlist control studies would be of particular value. Though a randomized controlled trial would help determine causality, many have noted that such a trial design is unethical in this context [2]. Age of GAH initiation reported by participants at time of data collection is vulnerable to recall bias. It is possible that participants in older age cohorts (45–65; 65+) were more vulnerable to recall bias; in our clinical experience, however, starting GAH is a major event in one's life, making it less susceptible to recall bias than more routine events [30]. It was unexpected that the median age at time of survey completion for participants who recalled accessing GAH in early adolescence was older than for those in the late adolescence group, which may be indicative of recall bias. Of note, though it is often presumed that GAH were not offered to adolescents in the U.S. until the past three decades, recent historical analyses have pointed out that adolescents have been receiving GAH as early as the 1970s [31]. The 2015 USTS sample is younger, with fewer racial minorities, fewer heterosexual participants, and higher educational attainment when compared with probability samples of TGD people in the U.S [32]. Because all participants identified as non-cisgender, those who initiated GAH and subsequently identified as cisgender would not necessarily be represented in this study; existing literature, however, suggests that this is a rare occurrence [2, 33].

Conclusion

This study found that transgender people who accessed GAH during early or late adolescence had a lower odds of past-month suicidal ideation and past-month severe psychological distress in adulthood, when compared to those who desired but did not access GAH, after adjusting for a range of potential confounding variables. The findings support updated 2017 recomendations from The Endocrine Society [7] and WPATH [6] that these medical interventions be made available for transgender adolescents. The results also provide additional evidence to suggest that legislation restricting transgender adolescents' access to gender-affirming medical care would result in adverse mental health outcomes [18].

Acknowledgments

The authors would like to thank The National Center for Transgender Equality for sharing data from the 2015 USTS.

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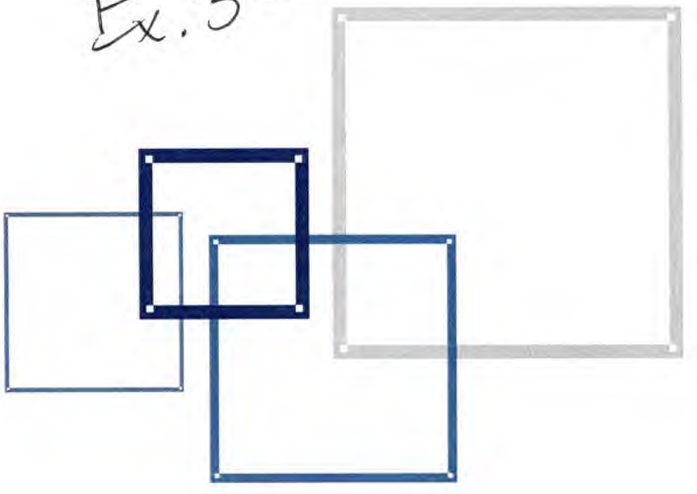
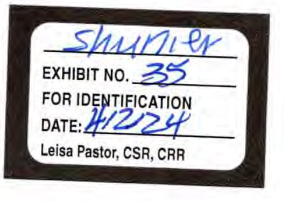
Ex. 35



THE REPORT OF THE

2015 U.S. TRANSGENDER SURVEY



National Center for TRANSGENDER EQUALITY

About the National Center for Transgender Equality

The National Center for Transgender Equality (NCTE) is the nation's leading social justice policy advocacy organization devoted to ending discrimination and violence against transgender people. NCTE was founded in 2003 by transgender activists who recognized the urgent need for policy change to advance transgender equality. NCTE now has an extensive record winning life-saving changes for transgender people. NCTE works by educating the public and by influencing local, state, and federal policymakers to change policies and laws to improve the lives of transgender people. By empowering transgender people and our allies, NCTE creates a strong and clear voice for transgender equality in our nation's capital and around the country.

RECOMMENDED CITATION

James, S. E., Herman, J. L., Rankin, S., Keisling, M., Mottet, L., & Anafi, M. (2016). *The Report of the 2015 U.S. Transgender Survey*. Washington, DC: National Center for Transgender Equality.

The Report of the
2015 U.S. Transgender Survey

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December 2016

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Acknowledgements

The report authors extend our gratitude to all the members of the transgender community who participated in the 2015 U.S. Transgender Survey and the hundreds of individuals and organizations that made this survey report possible.

The following individuals in particular are recognized for their contributions during one or more stages of the process, including survey development, implementation, distribution, data preparation and analysis, and reporting:

Osman Ahmed
M. V. Lee Badgett
Kellan Baker
Genny Beemyn
Aaron Belkin
Walter Bockting
Kyler Broadus
David Chae
Cecilia Chung
Loree Cook Daniels
Kerith Conron
Ruby Corado
Andrew Cray
Kate D'Adamo
Laura Durso
Jake Eleazer
Gary J. Gates
Jaime Grant
Emily Greytak
Ann Haas
Jack Harrison-Quintana
Mark Hatzenbuehler
Darby Hickey
Lourdes Ashley Hunter
Chai Jindasurat
JoAnne Keatley
Elliot Kennedy
Paul Lillig
Emilia Lombardi
Jenifer McGuire
Ilan Meyer
Shannon Price Minter
Aaron Morris
Asaf Orr
Dylan Orr
Sari Reisner
Gabriel Rodenborn
Shelby Rowe
Brad Sears
Jama Shelton
Jillian Shipherd
Sharon Stapel
Michael Steinberger
Catalina Velasquez
Bianca Wilson

The authors extend special gratitude to the following individuals for their contributions to the project:

Ignacio Rivera, Survey Outreach Coordinator, for leading the survey outreach efforts and building a network of individuals and organizations that led to the unprecedented levels of participation in this survey.

Andrew Flores for assistance with questionnaire development and the weighting procedures to prepare the data for analysis.

Daniel Merson for continued work in cleaning the data set, re-coding the data, and providing population numbers for comparative purposes in the final report.

Michael Rauch for programming and implementation of the complex survey.

*Appreciation is also extended to **NCTE interns, law fellows, staff, and volunteers** who assisted with the project, including outreach across the country, development of outreach materials, and translation:*

Bre Kidman
Cyres Gibson
Mati Gonzalez Gil
Romeo Jackson
Kory Masen
Imari Moon
Cullen O'Keefe
Nowmee Shehab

*A special thanks is also extended to **USTS Interns, Fellows, and Assistants** for their work at various stages of the project:*

Rodrigo Aguayo-Romero
Willem Miller
Shabab Mirza
Davida Schiffer
Jeymee Semiti
Danielle Stevens
Venus Selenite

*The authors also thank the **USTS Advisory Committee** (UAC) members, who devoted their time to the project by giving valuable recommendations around project development and community outreach:*

Danni Askini
Cherno Biko
Thomas Coughlin
Brooke Cerda Guzman
Trudie Jackson
Andrea Jenkins
Angelica Ross
Nowmee Shehab
Stephanie Skora
Brynn Tannehill

Additional acknowledgement goes to the **more than 300 transgender, LGBT, and allied organizations** that promoted and distributed the survey to its members throughout the country for completion.

The authors also acknowledge current and former NCTE staff for their work on the project, particularly:

Theo George and **Vincent Villano** for their pivotal work in survey project development and distribution through their respective roles in digital media and communication strategy.

Arli Christian, Joanna Cifredo, K'ai Smith, and **Harper Jean Tobin** for their contributions as report co-writers, including lending their subject-matter expertise and analysis to the findings included in this report.

Various individuals and firms assisted in spreading the word about the survey, both prior to and during the data collection phase, and they also assisted with survey translation, design, and reporting. Thanks goes to:

Sean Carlson
Leah Furumo
Molly Haigh
Anna Zuccaro
Design Action Collective
Dewey Square Group
ThoughtWorks
TransTech Social Enterprises
ZERN

Additionally, NCTE would like to express special appreciation to **an anonymous donor** for providing the largest share of the funds needed to conduct and report on the U.S. Transgender Survey. Other important funders were the **Arcus Foundation**, the **Gill Foundation**, the **Human Rights Campaign Foundation**, and the **David Bohnett Foundation**. NCTE is also grateful to its other funders, many of which supported this project through general operating support, including the **Ford Foundation**, the **Evelyn & Walter Haas, Jr. Fund**, and the **Tides Foundation**.

Finally, NCTE would like to give special thanks to the **National LGBTQ Task Force**, for its previous partnership in conducting the National Transgender Discrimination Survey as a joint project from 2008 to 2011, as well as for its support of NCTE's re-development of it as the U.S. Transgender Survey.

reported identifying with a range of gender identities[11] and racial and ethnic identities, including 34% who identified as people of color.[12]

In addition to providing general feedback on individual questions and the entire questionnaire, pilot study participants were asked to address specific questions as part of their evaluation, including: (1) how long it took to complete the survey, (2) what they thought about the length of the survey, (3) whether any existing questions were confusing or difficult to answer, (4) whether they found any questions offensive or thought they should be removed or fixed, (5) whether they experienced technical or computer issues while taking the survey, and (6) what they thought about the statement explaining why the term "trans" was used throughout the survey.[13] All participant feedback was compiled, discussed, and used to further develop the questionnaire, such as through the revision of language and the addition of questions to more thoroughly examine an issue.

b. Length

The final survey questionnaire contained a total of 324 possible questions in thirty-two discrete sections addressing a variety of subjects, such as experiences related to health and health care access, employment, education, housing, interactions with law enforcement, and places of public accommodation. The online survey platform allowed respondents to move seamlessly through the questionnaire and ensured they only received questions that were appropriate based on previous answers. This was accomplished using skip logic, which created unique pathways through the questionnaire, with each next step in a pathway being dependent on an individual respondent's answer choices. For example, respondents who reported that they had served in the U.S. Armed Forces, Reserves, or National Guard received a series of questions about their military service, but those who had not served did not receive those questions. Due to the customized nature of the survey, the length varied greatly between respondents, and no respondent received all possible questions. Prior to the pilot study, estimates indicated a survey-completion time of 30–45 minutes. The completion-time estimate was extended to 60 minutes based on feedback from pilot study participants, and it was consistent with many reports during the fielding period.[14]

Despite observations about survey length discussed in the NTDS,[15] evolving data needs relating to issues affecting transgender people required an in-depth treatment of multiple issue areas. This often required multiple questions to thoroughly assess an issue—including in areas where the NTDS asked only one question—and resulted in a lengthier survey. Survey instrument length was assessed throughout its development to ensure it would be manageable for as many participants as possible. Furthermore, through multiple reviews and evaluations of the survey instrument—including the pilot study—survey takers reported that the length was appropriate for a survey addressing such a wide range of issues and the need for data outweighed concerns about the overall length of the survey.

IV. Survey Distribution and Sample Limitations

The survey was produced and distributed in an online-only format after a determination that it would not be feasible to offer it in paper format due to the length and the complexity of the skip logic required to move through the questionnaire. With so many unique possibilities for a customized survey experience for each respondent, the intricate level of navigation through the survey

would have created an undue burden and confusion for many respondents. This could have led to questions being answered unnecessarily or being skipped completely, which could have increased the potential for missing data in the final dataset.[16] This made online programming the best option for ensuring that respondents received all of the questions that were appropriate based on their prior answers, decreasing the probability of missing data. However, the potential impact of internet survey bias on obtaining a diverse sample has been well documented in survey research,[17] with findings that online and paper surveys may reach transgender respondents with "vastly different health and life experiences."[18] With those considerations in mind, outreach efforts were focused on addressing potential demographic disparities in our final sample that could result from online bias and other issues relating to limited access. Although the intention was to recruit a sample that was as representative as possible of transgender people in the U.S., it is important to note that respondents in this study were not randomly sampled and the actual population characteristics of transgender people in the U.S. are not known. Therefore, it is not appropriate to generalize the findings in this study to all transgender people.

V. Outreach

The main outreach objective was to provide opportunities to access the survey for as many transgender individuals as possible in different communities across the U.S. and its territories. Additionally, outreach efforts focused on reaching people who may have had limited access to the online platform and who were at increased risk of being underrepresented in such survey research. This included, but was not limited to, people of color, seniors, people residing in rural areas, and low-income individuals. The outreach strategy was a multi-pronged approach to reach transgender people through various connections and points-of-access, including transgender- or LGBTQ-specific organizations, support groups, health centers, and online communities.

Outreach efforts began approximately six months prior to the launch of the data-collection period with a variety of tactics designed to raise awareness of the survey, inform people when it would be available, and generate opportunities for community engagement, participation, and support. A full-time Outreach Coordinator worked for a period of six months to develop and implement the outreach strategy along with a team of paid and volunteer interns and fellows.[19]

An initial phase of outreach involved developing lists of active transgender, LGBTQ, and allied organizations who served transgender people and would eventually support the survey by spreading the word through multiple communication platforms and in some cases providing direct access to the survey at their offices or facilities. Establishing this network of "supporting organizations" was an essential component of reaching a wide, diverse sample of transgender people.

Over 800 organizations were contacted by email, phone, and social media, and they were asked if they would support the survey by sharing information about it with their members and contacts. Specifically, supporting organizations were asked to share information through email blasts and social media channels, and the research team provided language and graphics for organizations to use in an effort to recruit appropriate respondents into the study. Of the organizations contacted, approximately half responded to requests for support, resulting in direct recruitment correspondence with nearly 400 organizations at regular intervals during the pre-data-collection period and while the survey was in the field.[20,21] These organizations

performed outreach that contributed to the far reach of the survey and unprecedented number of respondents.[22] The organizations were also featured on the survey website so potential respondents could determine whether organizations they knew and trusted had pledged support for the survey.

Nearly 400 organizations responded to outreach and confirmed their support for the survey. The remaining organizations did not respond directly to invitations to learn more about the survey and become supporters. Consequently, these organizations did not receive correspondence aimed at directly recruiting respondents prior to the survey launch or during the data-collection period. It is possible, however, that survey respondents were still made aware of the survey through those organizations. Since there is no information regarding whether these organizations shared information about the survey through their channels, it is difficult to assess the full scope of the outreach efforts.

a. Advisory Committee

A significant element of outreach involved convening a USTS Advisory Committee (UAC). The UAC was created to increase community engagement in the survey project and raise awareness by connecting with transgender people in communities across the country through a variety of networks. The UAC was comprised of eleven individuals with advocacy, research, and lived experience from a wide range of geographical locations.[23] Members were invited to join the committee as advisors on survey outreach to facilitate the collection of survey data that would best reflect the range of narratives and experiences of transgender people in the U.S. Each member brought unique skills and expertise to contribute to the committee's objectives. UAC members participated in five monthly calls with members of the USTS outreach team from May to September 2015. UAC monthly calls focused on providing project updates and identifying pathways by which outreach could be conducted to increase the survey's reach and promote participation from a diverse sample. Members suggested organizations, individuals, and other avenues through which to conduct outreach, shared ideas and strategies for improving outreach to specific populations of transgender people, and spread the word about the survey through their professional and personal networks.

b. Survey-Taking Events

In an effort to increase accessibility of the survey, the outreach team worked with organizations across the country to organize events or venues where people could complete the survey. *Survey-Taking Events*,[24] or "survey events," were spaces in which organizations offered resources to provide access to the survey, such as computers or other web-enabled devices. These organizations provided a location in which to take the survey at one particular time or over an extended period of time, such as during specified hours over the course of several days.[25] The events were created with the intention of providing access to individuals with limited or no computer or internet access, those who may have needed assistance when completing the survey, or those who needed a safe place to take the survey. Additionally, the population that had previously been identified as being more likely to take a paper survey than an online survey were considered,[26] and the events were developed to target those individuals.

Given the potential variety of these survey events—including the types of available resources and times at which they were conducted—guidelines were needed to maintain consistency across the events and preserve the integrity of the data-collection process. A protocol was developed outlining the rules for hosting a survey event to advise hosts on best practices for ensuring

a successful data-collection process, including guidelines to prevent the introduction of bias into survey responses. The protocols described the steps for becoming a survey-event host and tips for how to conduct outreach about the event. The protocol also specified that hosts should inform NCTE of their event prior to hosting and report on how many people attended the event and how many people completed and submitted the survey. This was helpful information for evaluating the relative success and benefits of these events. All confirmed supporting organizations were invited to become survey event hosts, and those who accepted the invitation were sent the protocol. Seventy-one (71) organizations accepted the invitation and confirmed the date(s) and time(s) of their events.[27]

Survey events were promoted on the survey website and given a specific designation on the supporting organization map (described further in the "Survey Website" section), including information about where and when people could attend. Hosts were encouraged to promote their event through multiple channels and consider outreach methods beyond online avenues, such as direct mail or flyers, to better reach transgender people with limited or no internet access. Additionally, hosts were provided with flyer templates so they could promote the events in their facilities or through communications with their members or constituents. Of the organizations who confirmed their survey events, 46 reported information about attendance at the event. The hosts reported that 341 people attended their events, including transgender and non-transgender friends, family, and volunteers. Approximately 199 respondents completed the survey at these events.[28] However, survey responses indicate that additional unreported survey events or similar gatherings may have been held where participants had an opportunity to complete the survey.[29] Event-related information submitted by organizations following the fielding period was not comprehensive enough to make a thorough determination as to whether the events had achieved their previously stated objectives.[30]

c. Incentives

As an incentive for completing the survey, participants were offered a cash-prize drawing. Incentives, such as cash prizes are widely accepted as a means by which to encourage and increase participation in survey research.[31] Studies have shown that such incentives may have a positive effect on survey response rate, which is the proportion of individuals in the population of interest that participates in the survey.[32] Research has also found that lottery-style cash drawings may be beneficial in online surveys,[33] since they offer a practical method for providing incentives in surveys with a large number of respondents by eliminating the potential high cost of both the cash incentive and prize distribution.[34]

USTS respondents were offered the opportunity to enter into a drawing for one of three cash prizes upon completion of the survey, including one $500 cash prize and two $250 cash prizes.[35] After completing and submitting their anonymous survey responses, USTS respondents were re-directed away from the survey hosting site[36] to a web page on the NCTE-hosted USTS website. In addition to being thanked for their participation on this page, respondents received a message confirming that their survey had been submitted and any further information they gave would not be connected to their survey responses. Only individuals who completed and submitted the survey were eligible for one of the cash prizes. To enter into the prize drawing, respondents were required to check a box giving their consent to be entered.[37] Respondents were also asked to provide their contact information in order to be notified if selected in the drawing. The final drawing contained 17,683 entrants. Each entrant was assigned a number, and six numbers were randomly chosen by a non-NCTE party: three

numbers for the prize winners and three for alternates if necessary. The three prize winners were contacted and awarded their prizes upon acceptance.

VI. Communications

Communications for the survey required a multifaceted approach and a coordinated effort with the outreach strategy to most effectively reach a wide range of transgender people and ensure a robust sample size. The goals of survey communications were to: (1) inform people that NCTE would be conducting a survey to further the understanding of the experiences of transgender people in the U.S initially gleaned through the NTDS, (2) communicate when the survey would be available to complete and how it could be accessed, and (3) find creative ways of reaching diverse populations of potential respondents. This involved raising awareness of the survey through several communication methods, including email, social media, and print media, as well as through additional unique campaigns. Many survey promotional materials were produced in English and Spanish to increase the accessibility of the survey.[38]

a. Survey Website

A website was created and designed specifically for the promotion and distribution of the survey.[39] This website served as a platform for providing information about the survey starting several months prior to its release in the field, such as a description of the survey, information about the team working on the survey, frequently asked questions, and sample language and graphics for individuals and organizations to use for email and social media communications, including sample Facebook and Twitter postings. The website also featured an interactive map, which included information about organizations that had pledged to support the survey. Additionally, the map distinctly indicated information about organizations that were hosting survey-taking events, including the date, time, and location of such events. The website later served as the only platform through which the survey could be accessed and provided English and Spanish links to enter the survey, since there was no direct link available to the off-site hosting platform.

b. Survey Pledge

The survey pledge campaign was developed to raise awareness about the survey and generate investment in the project. The campaign engaged potential participants and allies by inviting them to pledge to take the survey and/or spread the word about the survey. The survey pledge was a critical method of both informing people that the survey would be launching and sustaining engagement with potential respondents in the months leading up to the fielding period. Pledges received reminders about the survey launch date and availability through email communications. Beginning in January 2015, pledge palm cards were distributed at a variety of events across the country, including conferences and speaking engagements. The cards contained information about the upcoming survey and asked people to sign up to help by committing to: (1) spread the word about the survey; and/or (2) take the survey. Transgender and non-transgender individuals were asked to complete the pledge information, either through a palm card or directly online through the survey website. Individuals who completed pledge information received email communications throughout the pre-data-collection phase. Pledge information was collected continuously for several months, and by the time of the survey launch, over 14,000 people had pledged to take the survey. Additionally, more than 500 people pledged to promote the survey among their transgender friends and family.[40] The pledge proved to be

an effective method of assessing how many people had learned about the survey and were interested in completing it, where potential survey respondents were distributed geographically, and how more potential respondents could be effectively engaged.

c. Photo Booth Campaign

In January 2015, a photo booth campaign was launched as another method for engaging people and raising awareness about the survey. Individuals and groups were asked to take photos holding one of two signs with messages expressing support for the survey.[41] USTS photo booths were conducted at several conferences and events across the country. More than 300 photos were collected and shared directly through NCTE's Facebook page. Photos were also sent to most participants so they could conduct their own promotion using their photos.

d. Social Media

With the increased use of social media in the years since the previous survey (the NTDS), it was important to engage via these outlets to further the reach of the survey. Facebook and Twitter[42] became the primary social media outlets used throughout the survey project, and their use significantly amplified awareness, increasing the number of people who were exposed to the survey. A series of postings provided the ability to rapidly and succinctly communicate with individuals and groups who had an interest in contributing to the survey's success by completing the survey and spreading the word about it. Although social media reach fluctuated during the months leading up to the survey launch, over 96,000 Facebook users were estimated to have received NCTE's post announcing that the survey was live and available for completion on August 19, 2015.

e. USTS Awareness Week

Prior to launching the survey in the field, communication was maintained with thousands of individuals and organizations who fell into three categories: (1) people who had signed up to take or spread the word about the survey ("pledge list"), (2) organizations that had committed to support the survey through outreach efforts ("supporting organization list"), and (3) people who had signed up to be in communication with NCTE about the organization's work and projects ("NCTE list").

Communication with the individuals and groups on these lists through targeted messages occurred at various intervals; however, one of the most important methods for promoting the survey was through USTS Awareness Week. This campaign was designed to share a significant amount of information about the survey over a concentrated period of time in close proximity to the launch of the survey. Awareness Week occurred during the week of July 27, 2015 and highlighted different aspects of the survey focusing on a different medium each day, including social media, email, and blogs. Awareness Week was introduced to the communication lists on July 15, and recipients were invited to access and download a planning kit for the campaign, which was available on the survey website. The planning kit included language and graphics for email and social media communications. Communications were sent on each of the days devoted to social media,[43] email,[44] and blogs[45] with appeals for organizations to share the information with their membership and individuals to share the information through their personal networks. Awareness Week proved to be one of the most effective methods for increasing the number of individuals who pledged to take the survey and likely increased the number of eventual respondents.[46]

f. Additional Communications Methods

The overall approach to survey communications was diverse and captured many media forms. In addition to the previously stated campaigns and projects, communications involved working with a variety of individuals such as bloggers, artists, advocates, and others to create print blogs and videos promoting the survey. Op-eds were another medium that contributed to survey promotion, and media consultants and traditional media sources aided in expanding the survey's reach even further. Approximately 50 articles, blogs, and op-eds focused on the survey were produced and distributed by organizations, including NCTE, and individuals prior to the launch of the survey and during the data-collection period. The wide variety of approaches contributed to the number of individuals who were reached through all communications and likely impacted the final number of respondents in the sample.

VII. Language and Translation

Throughout the survey questionnaire, the use of accessible language was balanced with preserving the meaning of each question to the greatest extent possible. This was of particular importance in maintaining comparability with questions from existing surveys that allowed conclusions to be drawn about how the experiences of the USTS sample compares to the U.S. population. In order to make assessments about USTS survey respondents in relation to the U.S. population, it was important that USTS respondents had similar interpretations of questions taken from other surveys as non-transgender survey takers had to those questions in federal surveys. In many places, language was revised to use terminology that would most appropriately speak to individuals in the many communities for which the survey was intended. However, several areas required difficult choices about keeping language that may have caused discomfort for some respondents. Throughout the questionnaire, language was avoided that could be interpreted as stigmatizing or characterized as a value judgment wherever possible while maintaining objectivity in crafting sound research questions. For example, at times survey questions referred to work or activities that were "currently considered illegal." Such deliberate language was used in an attempt to separate the issue of criminalization from the activity in question while maintaining comparability with other surveys. This was a difficult balance to achieve throughout the survey. Eliminating technical language was also necessary, unless it was widely used and accepted in transgender communities, such as some medical terminology. Short descriptions or parenthetical explanations were provided whenever technical language was required for those who may not have been familiar with the language. Additionally, hyperlinked explanations of specific terms were included when those terms could be interpreted in several ways or if similar explanations were provided in the federal surveys from which the questions were taken. For example, explanations were provided for the terms "active duty" when asking about military service and "household" when asking about income.

The research team remained conscious of individual and collective identities throughout the survey instrument drafting process, and attempted to use language that acknowledged the breadth and significance of individual identities while also making the questions accessible to the widest range of transgender people possible across the U.S. and in the territories. The questionnaire was reviewed and revised for consistent readability at an eighth-grade literacy level where possible,[47] although several

terms used in the survey were at a considerably higher literacy level. This included places where language was preserved for comparability with other surveys and when language describing transgender-specific experiences or procedures was used. Additionally, community members and researchers reviewed the survey and suggested revised language throughout the development process. This collaborative process was beneficial in providing collective insight on the best language to use in each particular instance based on lived experience and research expertise. The research team acknowledges, however, a continuing need to work towards identifying suitably inclusive terminology within an evolving language and community for future iterations of the survey.

The questionnaire was translated into Spanish by a translation service, and several native-Spanish-speaking community members and NCTE staff and interns reviewed and revised the language to use terminology that was most prevalent in Spanish-speaking transgender communities in the U.S. In many instances, it was difficult to find language that accurately captured the meaning of a question or specific terms, but in each case language was selected to convey interpretations as close to the English-language question interpretations as possible.

VIII. Institutional Review

The study was vetted through an Institutional Review Board (IRB) process, which is meant to ensure confidentiality and protect the rights and welfare of individuals participating in a research study. The USTS underwent a full board review by the University of California Los Angeles (UCLA) IRB. As a requirement of approval, the questionnaire began with a study information sheet describing aspects of the study and rights of individuals as participants in the study.[48] To be included in the study, participants were required to indicate their consent at the end of the information sheet. This process established that participants were fully informed about the risks and benefits of participating in the study and that their participation was voluntary. IRB review also required the submission of all recruitment materials leading up to the launch of the survey and throughout the time the survey was in the field.[49] This required the production of a large volume of messaging for the many different types of media through which people were invited to participate in the survey in both English and Spanish. It also required anticipating how messaging might need to change while the survey was in the field and submitting this language for pre-approval for later use as needed.

IX. Survey Hosting

The survey was hosted online by Rankin & Associates Consulting, under the supervision of USTS research team member, Dr. Susan Rankin. Access to the survey was provided exclusively through the USTS website. All programming of the questionnaire and online administration of the survey was handled through Rankin & Associates Consulting, which managed the process of collecting the survey data throughout the 34-day fielding period.

The survey was anonymous, and maintaining privacy and confidentiality in the collection and maintenance of survey data was an important component of preserving participants' anonymity. Furthermore, as a condition of IRB approval, the research team was required to ensure that confidentiality protections were in place for the study and demonstrate sufficiency of data security protocols. Accordingly, data from online

participants was submitted through seven secure firewalled servers with forced 256-bit SSL (Secure Sockets Layer) security and Security-Enhanced Linux (SELinux) security extensions to encrypt and protect the survey data. Given the volume of traffic on the seven servers during the initial launch of the survey, an eighth server was added. The survey was stored in an SQL database that could only be accessed locally. The servers themselves were only accessible using encrypted SSH (Secure Shell) connections originating from the local network. The servers were also in RAID (Redundant Array of Inexpensive Disks), which is a data storage virtualization technology that combines multiple physical disk drive components into a single logical unit for the purposes of data redundancy, performance improvement, or both, to reduce the chance of any data loss due to hardware failure. The servers performed nightly security audits from data acquired via the system logs and notified the system administrators.

Despite a successful data-collection period evidenced by the large final sample size, it is important to note issues that occurred in the initial days of the survey data-collection period, given the potential impact on the data collection and the final sample. Prior to the survey launch, the online platform had been assessed and capacity was predicted for the seven dedicated servers based on reasonable estimated response rates. However, in the first days of the data-collection period, exceptionally high levels of traffic to the survey far exceeded the predicted response rates and overwhelmed the capacity of the servers, causing significant delays in accessing and completing the survey. The resulting server delays occurred within hours of the survey launch on August 19, 2015, producing unusually long page-loading times and may have served as a barrier to completing the survey.[50] The survey team notified potential respondents of the delays through email and social media communication and updated the first page of the online survey questionnaire with a note about the issues and information about the continued availability of the survey.[51] The hosting team added a server to process the high level of traffic and returned the survey to normal loading speeds within a couple days of the initial reports. Although high numbers of survey submissions were received throughout these days, it is likely that the server delays affected the completion and submission of some surveys or may have discouraged individuals from attempting to take the survey.

X. Cleaning the Data

The dataset was cleaned following collection to remove survey responses that did not belong in the final sample.[52] Data cleaning is the process of detecting and removing some survey responses (e.g., duplicate responses, incomplete responses, illogical responses) in order to improve the quality of the sample. This dataset was "cleaned" using commonly accepted procedures.[53] The first step was to remove survey responses from individuals who did not consent to take the survey and those who did not meet the eligibility criteria, such as not being at least 18 years of age and not residing in the U.S. These survey respondents had been automatically sent to a disqualification page,[54] but their responses were included in the initial dataset. Incomplete responses were then removed from the sample based on a requirement that respondents minimally complete specific questions in Section 2 of the questionnaire to be included in the final dataset.[55] Duplicate survey responses were removed next, as were those with illogical responses, such as those with contradictory responses to related questions. Missing-data analyses were then conducted to determine the percentage of missing data.[56]

The next step of the process was recoding data, including re-categorization of answer choices

in several questions for improved analysis or to match existing categories for comparison to other surveys. Answers were evaluated for those questions that allowed a write-in response when the selected option was "not listed above." In some cases, these answers were recoded into existing answer choices where appropriate, and in other cases, new answer categories were created for write-in responses that were frequently repeated. The recoding process included two coding teams. The first coding team conducted initial data recoding, and the second team reviewed the recoding and flagged areas of disagreement. A simple percent agreement score was calculated to determine inter-rater reliability.[57]

Several survey weights were developed for presentation of results in the report.[58] A race and ethnicity weight was developed based on the Census Bureau's 2014 American Community Survey (ACS).[59] Additionally, given the disproportionally large number of respondents who reported an age of 18 years old, a weight was created to balance the representation in the sample of those respondents in relation to the rest of the sample.[60] The race and ethnicity weight and the 18-year-old weight were both included in a "standard weight" applied to the dataset. All results presented in this report are weighted based on the standard weight unless otherwise noted. Additional survey weights were created for the purposes of comparability with federal government and national data sources, including weights for age and educational attainment.[61] These weights were applied in addition to the standard weight when comparing the USTS sample to the U.S. population for items that are sensitive to age and educational attainment, such as individual and household income, and are noted accordingly as the "supplemental weight."

XI. Data Analysis and Presentation of Findings

The data was first analyzed to tabulate individual responses to each of the questions in the survey. The respondents included in each tabulation differed throughout the survey due to certain questions only being asked of a particular set of respondents and/or due to some respondents choosing not to answer a question. Analyses were performed to explore how survey responses differed based on demographic characteristics—such as race, gender, and income—and non-demographic factors—such as experience with sex work, HIV status, and experiences of family support or rejection.

All findings in the report are presented as weighted percentages of the entire sample or of the subgroups being examined. For example, educational attainment is presented as a percentage of the whole sample, while much of the data related to HIV care represent percentages of those respondents who are living with HIV. In limited instances, unweighted frequencies are included where the additional information could be informative and to provide context for the weighted percentages reported.

Percentages are rounded to whole numbers, except in cases where a more exact comparison to national data sources was desired or where more precision was needed due to the reported percentages being small. When rounding to whole numbers, the following convention was generally followed: findings containing decimals of 0.50 and above were rounded up, and findings with 0.49 and below were rounded down (e.g., 1.50% was rounded to 2% and 1.49% was rounded to 1%). Additionally, a finding of 0.49% and below was generally labeled "less than 1%" or "<1%." Throughout the report, results are presented in

various figures and tables. The percentages in these figures and tables do not always add up to 100% due to respondents being able to select more than one answer to a question ("mark all that apply") or due to rounding.

Throughout the report, U.S. population findings are provided for comparison to USTS findings or to provide context for USTS findings, where available and/or applicable. Where USTS data is compared to data from existing research, the data source is specified. When providing U.S. population comparisons, the research team made efforts to limit the comparisons to adults (18 years and older) to most appropriately match the USTS sample. Whenever that was not possible, notes as to age ranges or other limitations are provided. Additionally, calculations made by the research team when necessary to present U.S. population findings are noted. Data in this report is generally presented without information regarding statistical testing.[62]

ENDNOTES | CHAPTER 2: METHODOLOGY

1 The survey included questions related to the following topics (in alphabetical order): accessing restrooms; airport security; civic participation; counseling; education; employment; faith; family and peer support; health and health insurance; HIV; housing and homelessness; identity documents; immigration; income; intimate partner violence; military service; police and incarceration; policy priorities; public accommodations; sex work; sexual assault; substance use; suicidal thoughts and behaviors; unequal treatment, harassment, and physical attack; and voting.

2 Detailed information about survey methodology is available in *Appendix C (Detailed Methodology)*.

3 www.USTransSurvey.org

4 The survey was in the field between August 19 and September 21, 2015.

5 Grant, J. M., Mottet, L. A., Tanis, J., Harrison, J., Herman, J. L., & Keisling, M. (2011). *Injustice at Every Turn: A Report of the National Transgender Discrimination Survey*. (p. 11). DC: National Center for Transgender Equality and National Gay and Lesbian Task Force.

6 Grant et al., p. 182.

7 Grant et al.

8 See Haas, A. P., Rodgers, P. L., & Herman, J. L. (2014). *Suicide Attempts Among Transgender and Gender Non-Conforming Adults*. New York, NY & Los Angeles, CA: American Foundation for Suicide Prevention & Williams Institute.

9 See e.g., The GenIUSS Group. (2014). In J. L. Herman (Ed.), *Best Practices for Asking Questions to Identify Transgender and Other Gender Minority Respondents on Population-Based Surveys* (p. vii). Los Angeles, CA: Williams Institute. ("Adolescents may have particular difficulties with complex vocabulary and sentences. Therefore, questions designed for adolescents should take extra care to use plain language and simple sentences. Terms used in measures of sex and gender should be defined since adolescents, and cisgender (non-transgender) adolescents in particular, conflate the terms sex and gender, and have varying understanding of the term *transgender*, *masculine*, and *feminine*."). Given the need to collect data about the unique experiences of transgender youth, it is important to design and conduct future studies focusing on the issue areas and needs most applicable to transgender youth.

10 Information about the source of survey questions used for comparison to the U.S. population can be found in *Appendix C (Detailed Methodology)*.

11 Forty-four (44%) of pilot participants identified as a woman or trans woman (MTF), 41% as a man or trans man (FTM), and 16% as non-binary or genderqueer.

12 These pilot participants identified as American Indian, Asian, multiracial, Black, Latino/a, and a racial/ethnic identity not listed above, in addition to 66% who identified as white.

13 The following statement was provided to explain why the word "trans" was used throughout the survey: We know that not everyone is comfortable with the word "transgender," but for this survey, we must use one word to refer to all trans and non-binary identities. Because of this we will use the word "trans" in this survey to refer to all trans and non-binary identities."

14 A notable exception to the 30–60 minute estimate for completing the survey occurred during the first days of the survey's availability, when a high volume of survey takers overwhelmed multiple servers, causing lengthy delays when completing the survey. This is discussed further in the "Survey Hosting" section.

15 Grant et al., p. 13.

16 Post-NTDS analysis of respondents who had completed that survey online or in paper format found that surveys completed online were less likely to have missing data, providing further support for the decision to only offer the survey online. See Reisner, et al. (2014). Comparing in-person and online survey respondents in the U.S. National Transgender Discrimination Survey: Implications for transgender health research. *LGBT Health, 1*(2), 98–106.

17 See Dillman, D. A., Smyth, J. D., & Christian, L. M. (2014). *Internet, Phone, Mail, and Mixed-Mode Surveys: The Tailored Design Method* (4th ed.). Hoboken, NJ: John Wiley & Sons.

18 Reisner et al., p. 98. See note 16. This analysis also found that "[a] higher proportion of in-person respondents were young, male-to-female, people of color, publicly insured, with lower incomes and lower educational attainment than online respondents (all $p<0.05$). In-person respondents also were more likely than online respondents to be current daily smokers, to endorse substance use to cope with mistreatment, and to self-report as HIV-positive (all $p<0.05$)."

19 Although outreach efforts were instrumental in obtaining the largest sample of transgender respondents ever collected, a longer outreach period may have resulted in reaching more individuals in communities that are often underrepresented in online surveys.

20 A total of 827 organizations received at least one outreach email, and organizations received additional outreach emails and/or phone calls if no response was received. Out of those organizations, 392 confirmed their support, and 435 did not respond to any communications.

21 Correspondence included almost one dozen emails with asks to spread the word about the survey and with various information about the availability of the survey.

22 The research team attempted to ascertain the level of outreach engagement of supporting organizations; however, the limited amount of information received about the outreach did not allow a calculation of a response rate. Of the 392 organizations that pledged their support, 58 (15%) reported information on their outreach activities and estimated reaching over 20,000 transgender people through their channels. In the future, researchers are encouraged to collect consistent outreach activity data from supporting organizations that will help to better assess the effectiveness of outreach and response rate estimates.

23 Information about UAC members can be found in the *Acknowledgements* section of the report.

24 These events were promoted as "Survey-Taking Events" on recruitment materials and described accordingly (see note 25). However, it is possible that the name did not appropriately capture the nature of these vastly differing events. A lack of clarity may have decreased the number of people who attempted to access the survey through organizations who offered space or computers to complete the survey online.

25 Survey-Taking Events were described as "a function in which an organization or group opens its doors and provides access to its facilities (such as community centers and office buildings) to allow trans survey participants use of its resources (including computers, tablets, and internet access) to complete the USTS. This will occur during specified periods of time or throughout the time the survey is available on a drop-in basis. For example, a community center might participate by setting aside one Saturday from 9am–6pm where some or all of its computers are available for survey takers to use, or it might host people on Monday–Friday from 5pm–9pm each evening for a week, or longer."

26 A total of 435 NTDS respondents completed the survey in paper format (7% of the sample) and were found to differ from online survey takers in sociodemographic characteristics, health outcomes, and life experiences. Reisner et al., p. 98, 103. See note 16.

27 Although only 71 organizations confirmed their events, based on information reported at various intervals throughout the data-collection period, it appeared that more organizations hosted survey events or similar gatherings to complete the survey without reporting them to the survey outreach team. Additionally, it is also possible that individuals and organizations held informal parties where groups of friends could gather to complete the survey at the same time. Data regarding this sort of activity was not collected or received.

28 This completion rate is a conservative estimate based on reports that some individuals started the survey at the event and then left to complete it on their own at a later time.

29 Four hundred and seventeen (417) respondents answered "yes" in response to the following survey question: "Are you taking this survey at a survey event or meeting, such as one hosted by an LGBTQ or Trans organization or meeting?"

30 In future iterations of the USTS and other research studies, the research team suggests a more robust approach towards organizing, conducting, and monitoring survey events to increase the reach and availability of such events in providing access to the survey. Researchers are also encouraged to conduct follow-up analyses to

determine the demographic characteristics of individuals who completed the survey at events and whether these events were successful in capturing a similar demographic to those who had completed paper surveys in the previous survey. See Reisner, et al. (discussing the demographics of online and paper respondents in the NTDS).

31 See e.g., Göritz, A. S. (2006). Incentives in web studies: Methodological issues and a review. *International Journal of Internet Science*, *1*(1), 58–70. (finding that "material incentives increase the odds of a person responding by 19% over the odds without incentives").

32 Pedersen, M. J. & Nielsen, C. V. (2016). Improving survey response rates in online panels: Effects of low-cost incentives and cost-free text appeal interventions. *Social Science Computer Review*, *34*(2), 229–243.

33 Pedersen et al., pp. 237–238.

34 Singer, E. & Ye, C. (2013). The use and effects of incentives in surveys. *The ANNALS of the American Academy of Political and Social Science*, *645*(1), 123–124.

35 Participants were informed of the cash prize incentives in several ways. The study information sheet placed at the beginning of the survey prior to obtaining each respondent's consent to enter the survey contained the following information in response to the question of whether respondents would be paid for their participation: "You will receive no payment for your participation. You will have the option to voluntarily enter a drawing to win one of three cash prizes: one prize of $500 and two prizes of $250." The frequently asked questions section of the survey website also offered the following statement: "When you complete the survey, you will have the option to enter a drawing to win one of three cash prizes: one prize of $500 and two prizes of $250. Because thousands of trans people across the country will complete the survey, we cannot offer payment to each participant." Additionally, some recruitment materials mentioned the cash-prize drawing, including email blasts.

36 The survey was hosted by Rankin & Associates Consulting. Further details are described in the "Survey Hosting" section.

37 The check box stated: "Enter me in the drawing for one of three cash prizes: one prize of $500 and two prizes of $250!"

38 Due to limited funding, it was not possible to translate all survey materials, such as email communications. Translation of all promotional materials may positively impact the response rate amongst respondents with limited English proficiency in future iterations of the study.

39 www.USTransSurvey.org

40 Final pledge numbers were 14,005 and 561 for survey takers and promoters, respectively.

41 Photo booth participants could choose from one of two signs indicating that the survey was coming in the summer of 2015 and stating the following: (1) "My Voice Counts: I'm Taking the #USTransSurvey" or (2) "Every Voice Counts: Spread the Word About the #USTransSurvey."

42 The Twitter hashtag used to promote the survey was #USTransSurvey.

43 For social media day, recipients received one of the following requests, based on whether they were organizations or individuals: (1) "Use the hashtag #USTransSurvey on social media asking your social networks to join us" or (2) "Please join Social Media day. We have sample copy and a variety of photos and graphics."

44 For email day, recipients received one of the following requests, based on whether they were organizations or individuals: (1) "Email a friend explaining why this is so important to you" or (2) "Download the sample email and send it to your membership list today."

45 For blog day, recipients were invited to share a blog written by Outreach Coordinator, Ignacio Rivera, cross post the blog on an organization's blog site, or draft a blog about the importance of the survey.

46 The number of individuals who pledged to take the survey on the pledge list increased from approximately 7,700 when the initial Awareness Week email was sent on July 15 to over 14,000 at the time the survey launched in the field. The 82% increase in the numbers of survey pledges is likely due to the increased exposure generated by Awareness Week communications.

47 The initial literacy level review and revision was conducted by a certified copy editor proficient in reading levels, and the questionnaire was determined to be at an eighth grade reading level.

48 Due to IRB requirements, the language in the study information sheet was generally at a higher literacy level than the rest of the questionnaire.

49 This included all materials aimed at "recruiting" or getting people to participate in a research study, such as website pages, flyers, emails, and social media messages.

50 The research team received reports that it took some individuals up to several hours to complete the survey on the first day, and others reported that they were not able to complete or submit their survey at all due to the technical issues.

51 The following note was added to the first page of the survey (in English and Spanish) to notify respondents of the delay: "Our servers have been overwhelmed by the number of enthusiastic participants and some are experiencing unusual delays. We apologize for the inconvenience as we work to address this issue. You can complete the survey now but may experience delays. However, the survey will be available to complete through at least September 21st. If you experience delays, we encourage you to return to this site in the coming days. If the survey is slow to respond, you can leave the page open and return later. If the survey times out, you can hit the 'back' button. However, if you close your browser, you may have to restart the survey."

52 A detailed description of the cleaning process is included in *Appendix C (Detailed Methodology)*.

53 Rahm, E. & Do, H. H. (2000). Data cleaning: Problems and current approaches. *IEEE Data Engineering Bulletin, 23*(4), 3–13.

54 Ineligible respondents were sent to one of two disqualification pages notifying them of their ineligibility and providing either an opportunity to visit the survey website for more information or giving information about their gender identity or expression and experiences related to gender identity or expression.

55 See *Appendix C (Detailed Methodology)* for more information on the Section 2 questions that were required to remain in the sample.

56 Missing-data analyses determined that there was less than 5% missing data on all but two questions. Therefore, the research team did not impute the missing data. See *Appendix C (Detailed Methodology)* for more information.

57 A modified version of an inter-rater reliability metric was used by the two teams that conducted the review. Each team included a principal researcher and an outside researcher. One researcher on each team conducted the initial coding and the other researcher reviewed the coding for approval or revisions. See *Appendix C (Detailed Methodology)* for more information.

58 "Weighting" is a common statistical technique used to adjust data with disproportionate sample sizes to be more representative of the population from which the sample was drawn. For example, the proportion of respondents aged 18–24 and 25–44 in a survey sample taken in the U.S. may differ from the proportion of those age groups in the total U.S. population. Therefore, weights are applied to survey data in order to make comparisons between the collected survey data and the total population. See *Appendix C (Detailed Methodology)* for more detailed information about weights applied to the survey data.

59 Studies using representative samples of transgender adults have found that transgender adults differ from the general population in regard to race and ethnicity, with transgender people more likely to be people of color. See e.g., Flores, A. R., Brown, T. N. T., & Herman, J. L. (2016). *Race and Ethnicity of Adults who Identify as Transgender in the United States*. Los Angeles, CA: Williams Institute; Conron, K. J., Scott, G., Stowell, G. S., & Landers, S. J. (2012). Transgender health in Massachusetts: Results from a household probability sample of adults. *American Journal of Public Health, 102*(1), 118–122. However, the USTS sample has a higher percentage of white respondents than the U.S. general population. To help correct for this sampling bias, the research team applied U.S. population weights for race and ethnicity. While this may still over-represent white respondents, this weighting procedure brings the sample closer to what is estimated to be the true population distribution for race and ethnicity for transgender people.

60 The weight for 18-year-old respondents was created with propensity scores developed using a regression discontinuity model. For more information on this process and other weighting procedures, see *Appendix C (Detailed Methodology)*.

61 The age, race, and educational attainment weights were created based on the Census Bureau's 2014 American Community Survey (ACS).

62 Due to the large sample size, bivariate statistical tests largely result in statistically significant differences among the groups being compared. Small group differences often will be found to be statistically significant, even when the differences are small and, therefore, not particularly meaningful. In writing the findings to this report, the research team considered other measures when pointing out meaningful differences among groups, such as a particular cell's contribution to an overall chi-square test statistic and effect sizes. These tests are on file with the research team. Future researchers are encouraged to use additional bivariate and multivariate modeling to provide more nuanced understanding of group differences.

Conclusion

Findings throughout the chapter indicated that respondents were impacted by substantial health-related disparities, including access to quality care and health outcomes. Respondents reported substantial barriers to receiving the care that they need, such as financial constraints, lack of health insurance or insurance that does not adequately address their health needs, and lack of access to health care providers who can administer health care respectfully and with a sufficient knowledge of transgender patients' needs. Furthermore, although some respondents were able to access health care related to gender transition, such as counseling, hormone therapy, or a variety of surgical procedures, a large number have not received such health care despite wanting to do so, often due to income and economic instability and lack of access to adequate health insurance insurance.

Results also suggest that insufficient access to quality care and coverage contributed to poor health outcomes among respondents. Respondents were substantially more likely to be living with HIV than the general population, with much higher rates among transgender women of color. Respondents were also more likely to report poor mental health outcomes, including higher rates of substance use, serious psychological distress, and suicide attempts. Findings demonstrated an association between poor health outcomes and a number of risk factors, such as economic instability, housing instability, lower educational attainment, and lack of family support.

ENDNOTES | CHAPTER 7: HEALTH

1 Bockting, W. O., Miner, M. H., Swinburne Romine, R. E., Hamilton, A., & Coleman, E. (2013). Stigma, mental health, and resilience in an online sample of the US transgender population. *American Journal of Public Health, 103(5)*, 943–951; Grant, J. M., Mottet, L. A., Tanis, J., Harrison, J., Herman, J. L., & Keisling, M. (2011). *Injustice at Every Turn: A Report of the National Transgender Discrimination Survey. (pp. 72–87).* DC: National Center for Transgender Equality & National Gay and Lesbian Task Force; Institute of Medicine. (2011). *The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding.* DC: National Academy of Sciences.

2 Kosenko, K., Rintamaki, L., Raney, S., Maness, K. (2013). Transgender patient perceptions of stigma in health care contexts. *Medical Care, 51(9)*, 819–822; Poteat, T., German, D., & Kerrigan, D. (2013). Managing uncertainty: A grounded theory of stigma in transgender health encounters. *Social Science & Medicine, 84(1)*, 22–29; Grant, et al. (2011). pp. 72–87; Lambda Legal. (2010). *When Health Care Isn't Caring: Lambda Legal's Survey of Discrimination Against LGBT People and People with HIV.* New York, NY: Lambda Legal.

3 U.S. Census Bureau. (2015). 2015 American Community Survey 1-Year Estimates. Available at: https://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=ACS_15_1YR_S2701&prodType=table.

4 U.S. Census Bureau. (2015). *2015 American Community Survey 1-Year Estimates: Private Health Insurance Coverage By Type.* Available at: https://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=ACS_15_1YR_S2703&prodType=table; U.S. Census Bureau. (2015). *2015 American Community Survey 1-Year Estimates: Public Health Insurance Coverage by Type.* Available at: https://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=ACS_15_1YR_S2704&prodType=table.

5 The estimate for the percentage of people who receive coverage through the Indian Health Service was calculated based on a 2015 statement that approximately 2.2 million American Indian and Alaska Native people were served by the Indian Health Service. https://www.ihs.gov/newsroom/factsheets/quicklook/.

6 Q. 11.9 specified that "[h]ealth insurance marketplaces are part of the new health care law, sometimes called 'Obamacare' or the 'Affordable Care Act,' where people can get insurance online, such as through healthcare.gov, over the phone, or in person."

7 "Insurer" here refers to insurers providing coverage under both private insurance plans (such as those purchased through an employer) and public plans (such as through Medicaid or Medicare).

8 The "other insurance" category includes TRICARE or other military coverage, VA, Indian Health Service, and other types of insurance not listed. See Table 7.1.

9 Respondents were asked if they had "experienced unwanted sexual contact (such as fondling, sexual assault, or rape) in a health care setting (such as a hospital, office, clinic)" in Q.12.7.

10 "People with disabilities" here refers to respondents who identified as a person with a disability in Q. 2.20.

11 Respondents on active duty in military service were asked separately about where they received transition-related health care. These results are reported in the *Military Service* chapter.

12 Although 1.5% of respondents in the sample reported having taken puberty-blocking medication, the percentage reported here reflects a reduction in the reported value based on respondents' reported ages at the time of taking this medication. While puberty-blocking medications are usually used to delay physical changes associated with puberty in youth ages 9–16 prior to beginning hormone replacement therapy, a large majority (73%) of respondents who reported having taken puberty blockers in Q.12.9 reported doing so after age 18 in Q.12.11. This indicates that the question may have been misinterpreted by some respondents who confused puberty blockers with the hormone therapy given to adults and older adolescents. Therefore, the percentage reported here (0.3% or "less than 1%") represents only the 27% of respondents who reported taking puberty-blocking medication before the age of 18.

13 "Transition-related surgery" here includes all procedures listed in Table 7.4 and 7.5, with the exception of electrolysis and non-surgical voice therapy.

14 Respondents who are "living in poverty" represent those who are living at or near the poverty line. See the *Income and Employment Status* chapter for more information about the poverty line calculation.

15 The "other insurance" category in Figure 7.11 includes TRICARE or other military coverage, VA, Indian Health Service, and other types of insurance not listed. See Table 7.1.

16 Since the available surgical procedures related to transition generally vary based on individuals' sex assigned at birth (the gender they were thought to be when they were born), respondents received different questions about surgical procedures based on their response to Q. 2.1, which asked about the sex listed on respondents' original birth certificate. Respondents who said that they had female on their original birth certificate received Q. 12.15, and respondents who said they had male on their original birth certificate received Q. 12.18. Although the vast majority of respondents received only questions about medical procedures available to them, 2.7% of respondents indicated that they were intersex, and a portion of them may not have received questions about all the surgical procedures that best fit their health care needs.

17 Respondents were asked about having "top/chest surgery reduction or reconstruction" in Q. 12.15.

18 Respondents were asked about having a "hysterectomy/'hysto' (removal of the uterus, ovaries, fallopian tubes, and/or cervix)" in Q. 12.15.

19 Respondents were asked about having a "clitoral release/ metoidioplasty/centurion procedure" in Q. 12.15. These are genital procedures that separate the clitoris from the labia.

20 Respondents were asked about having a "phalloplasty (creation of a penis)" in Q. 12.15. This is a genital procedure involving the construction of a larger phallus.

21 The U.S. Preventive Services Task Force currently recommends Pap smears every three years for adults who have a cervix and are between the ages 21 and 65. U.S. Preventive Services Task Force. (2012). *Cervical Cancer: Screening*. Available at: http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/cervical-cancer-screening.

22 Centers for Disease Prevention and Control. (2016). *2015 National Health Interview Survey: Sample Adult File*. Available at: ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Dataset_Documentation/NHIS/2015/samadult_freq.pdf

23 Respondents were asked about having a "vaginoplasty/ labiaplasty/SRS/GRS/GCS" in Q. 12.18. A vaginoplasty is a surgical creation of a vagina. A labiaplasty is a surgical modification or construction of the labia.

24 Respondents were asked about having an "orchidectomy/'orchy'/removal of the testes" in Q. 12.18.

25 Respondents were asked about having "facial feminization surgery (such as nose, brow, chin, cheek)" in Q.12.18.

26 Respondents were asked about having "breast augmentation/top surgery" in Q. 12.18. This refers to an augmentation mammoplasty, which reshapes or increases the size of the breast.

27 Respondents were asked about having a "tracheal shave (Adam's apple or thyroid cartilage reduction)" in Q. 12.18.

28 Although silicone injections are sometimes used to modify one's appearance, they are often risky and can lead to disfigurement, injury, and even death. Such injections are illegal in the United States. However, due to barriers to affordable care, some transgender people turn to silicone injections as a less expensive or more easily accessible substitute for safer treatments.

29 See e.g., Pascoe, E. A. & Richman, L. S. (2009). Perceived discrimination and health: A meta-analytic review. *Psychological Bulletin, 135*(4), 531–554.

30 See e.g., Bariola, E. Lyons, A., Leonard, W., Pitts, M., Badcock, P., Couch, M. (2015). Demographic and psychosocial factors associated with psychological distress and resilience among transgender individuals. *American Journal of Public Health, 105*(10), 2108–2116; Nuttbrock, L., Brockting, W., Rosenblum, A., Hwahng, S., Mason, M., Macri, M., & Becker, J. (2014). Gender abuse and major depression among transgender women: A prospective study of vulnerability and resilience.

American Journal of Public Health, 104(11), 2191, 2198; Bockting, W. O., Miner, M. H., Swinburne Romine, R. E., Hamilton, A., & Coleman, E. (2013). Stigma, mental health, and resilience in an online sample of the US transgender population. *American Journal of Public Health, 103*(5), 943–951; Institute of Medicine. (2011). *The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding*. DC: National Academy of Sciences.

31 The general health rating among adults in the U.S. population was calculated by the research team using data from the Behavioral Risk Factor Surveillance System (BRFSS). Centers for Disease Control and Prevention. (2015). *BRFSS Prevalence & Trends Data*. Available at: http://www.cdc.gov/brfss/brfssprevalence.

32 The Kessler Psychological Distress Scale, or K6, assesses psychological distress based on how often in the past 30 days respondents felt: so sad that nothing could cheer them up, nervous, restless or fidgety, hopeless, that everything was an effort, or worthless. See Q. 12.2. See the National Health Interview Survey for additional information about the K6 mental health screening instrument and measure of serious psychological distress in adults (available at: http://www.healthindicators.gov/Indicators/Serious-psychological-distress-adults-percent_50055/Profile).

33 The K6 scale rates how often feelings are experienced on the following scale: (0) none of the time, (1) a little of the time, (2) some of the time, (3) most of the time, and (4) all of the time. See Q. 12.2. A total score of 13 or above across all six measures indicates serious psychological distress.

34 Centers for Disease Prevention and Control. (2016). *2015 National Health Interview Survey: Sample Adult File*. Available at: ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Dataset_Documentation/NHIS/2015/samadult_freq.pdf.

35 See note 33 for an explanation of how "serious psychological distress" is calculated based on the K6 scale.

36 Center for Behavioral Health Statistics and Quality. (2016). *Results from the 2015 National Survey on Drug Use and Health: Detailed Tables*. Table 8.86B. Rockville, MD: Substance Abuse and Mental Health Services Administration. Available at: http://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2015/NSDUH-DetTabs-2015/NSDUH-DetTabs-2015.pdf.

37 Serious psychological distress is related to age and educational attainment in the U.S. general population. (see note 33; http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6340a13.htm). Those who are younger and have lower educational attainment have a higher prevalence of serious psychological distress. When the "supplemental weight" is applied to the USTS sample's prevalence of serious psychological distress to adjust the sample to reflect the age and educational attainment of the U.S. adult population, the prevalence is reduced to 30%, six times the national prevalence for U.S. adults. Based on studies using population-based samples of transgender adults, it is estimated that the transgender population is younger and has lower educational attainment than the U.S. adult population. Flores, A. R., Brown, T. N. T., & Herman, J. L. (2016). Race and Ethnicity of Adults who Identify as Transgender in the United States. Los Angeles, CA: Williams Institute; Conron, K. J., Scott, G., Stowell, G. S., & Landers, S. J. (2012). Transgender health in Massachusetts: Results from a household probability sample of adults. American Journal of Public Health, 102(1), 118–122. Therefore, the finding of 39% for prevalence of serious psychological distress is reported here using the standard weight only.

38 *Results from the 2015 National Survey on Drug Use and Health: Detailed Tables*. Table 8.86B. See note 36.

39 Results for respondents who were sexually assaulted here reflect those who reported that they had "experienced unwanted sexual contact (such as oral, genital, or anal contact or penetration, forced fondling, rape)" in the past year (see Q. 18.3).

40 Substance Abuse and Mental Health Services Administration. (2015). *Ending Conversion Therapy: Supporting and Affirming LGBTQ Youth*. Available at: http://store.samhsa.gov/shin/content//SMA15-4928/SMA15-4928.pdf.

41 Additionally, eleven percent (11%) of respondents in the sample said they were sent to a therapist, counselor, or religious advisor by immediate family members to stop them from being transgender. See the "Sent to a Professional for Being Transgender" section of the *Family Life and Faith Communities* chapter for a discussion about respondents who were sent to a professional by their family.

42 Although 0.4% of the overall sample reported that gender transition was not for them, these respondents did identify as transgender, meeting all criteria for inclusion in the survey (see Q. 1.10–1.18).

43 Haas, A. P., Rodgers, P. L., & Herman, J. L. (2014). *Suicide Attempts Among Transgender and Gender Non-Conforming Adults*. New York, NY & Los Angeles, CA; American Foundation for Suicide Prevention & Williams Institute; Moody, C. & Smith, N. G. (2013). Suicide protective factors among trans adults. *Archives of Sexual Behavior 42*(5), 739–752; Grant, J. M., Mottet, L. A., Tanis, J., Harrison, J., Herman, J. L., & Keisling, M. (2011). *Injustice at Every Turn: A Report of the National Transgender Discrimination Survey*. (p. 82). DC: National Center for Transgender Equality & National Gay and Lesbian Task Force.

44 Lipari, R., Piscopo, K., Kroutil, L. A., & Miller, G. K. (2015). *Suicidal Thoughts and Behaviors Among Adults: Results from the 2014 National Survey on Drug Use and Health*. Rockville, MD: Substance Abuse and Mental Health Services Administration.

45 Kessler, R. C., Berglund, P., Chiu, W. T., Demler, O., Heeringa, S., Hiripi, E., . . . Zheng, H. (2004). The US National Comorbidity Survey Replication (NCS-R): design and field procedures. *International Journal of Methods in Psychiatric Research, 13*(2), 69–92.

46 *Results from the 2015 National Survey on Drug Use and Health: Detailed Tables.* Table 8.70B. See note 36.

47 *Results from the 2015 National Survey on Drug Use and Health: Detailed Tables.* Table 8.69B. See note 36.

48 *Results from the 2015 National Survey on Drug Use and Health: Detailed Tables.* Table 8.70B. See note 36.

49 *Results from the 2015 National Survey on Drug Use and Health: Detailed Tables.* Table 8.70B. See note 36.

50 *Results from the 2015 National Survey on Drug Use and Health: Detailed Tables.* Table 8.70B. See note 36.

51 Whether or not a person receives medical attention following a suicide attempt is often used as a measure of the severity of the attempt. However, because many transgender people report avoiding medical professionals because of fear of mistreatment (see, for example, the previous section on "Experiences with Health Care Providers"), it may be difficult to use this measure to gauge the severity of the attempt among USTS respondents.

52 *Results from the 2015 National Survey on Drug Use and Health: Detailed Tables.* Table 8.77B. See note 36.

53 *Results from the 2015 National Survey on Drug Use and Health: Detailed Tables.* Table 8.77B. See note 36.

54 Kessler, R. C., Borges, G., & Walters, E. E. (1999). Prevalence of and risk factors for lifetime suicide attempts in the National Comorbidity Survey. *Archives of General Psychiatry, 56*(7), 617–626. See also Nock, M. K., Hwang, I., Sampson, N. A., & Kessler, R. C. (2010). Mental disorders, comorbidity and suicidal behavior: Results from the National Comorbidity Survey Replication. *Molecular Psychiatry, 15*(8), 868–876; Nock, M. K., Borges, G., Bromet, E. J., Cha, C. B., Kessler, R. C., & Lee, S. (2008). Suicide and suicidal behavior. *Epidemiologic Reviews, 30*(1), 133–154 (finding a lifetime prevalence of suicide ideation of 5.6–14.3%, a lifetime prevalence for suicide plans of 3.9%, a lifetime prevalence for suicide attempts of 1.9–8.7%).

55 Respondents who reported that they were out to all, most, or some of the immediate family they grew up with were asked to assess how supportive their family was using a five-point scale from "very supportive" to "very unsupportive". The categories were collapsed to create a new variable reflecting a supportive, neutral, or unsupportive family.

56 Results for respondents who were sexually assaulted here reflect those who reported that they had "experienced unwanted sexual contact (such as oral, genital, or anal contact or penetration, forced fondling, rape)" in their lifetime (see Q.18.1).

57 The age of the most recent suicide attempt reported here includes responses from both respondents who reported a single attempt and those who reported multiple attempts. For respondents who reported a single suicide attempt, the age of the most recent suicide attempt is also the age of their first suicide attempt as reported in the previous section.

58 See e.g., Cleveland, M. J., Feinberg, M. E., Bontempo, D. E., & Greenberg, M. T. (2008). The role of risk and protective factors in substance use across adolescence. *Journal of Adolescent Health, 43*(2), 157–164; Kilpatrick, D. G., Ruggiero, K. J., Acierno, R., Saunders, B. E., Resnick, H. S., & Best, C. L. (2003). Violence and risk of PTSD, major depression, substance abuse/dependence, and comorbidity: Results from the National Survey of Adolescents. *Journal of Consulting and Clinical Psychology, 71*(4), 692–700.

59 Center for Behavioral Health Statistics and Quality. (2015). *2015 National Survey on Drug Use and Health Questionnaire.* Available at: http://www.samhsa.gov/data/population-data-nsduh/reports?tab=39.

60 Center for Behavioral Health Statistics and Quality. (2015). *Results from the 2014 National Survey on Drug Use and Health: Detailed Tables.* Table 2.6B. Rockville, MD: Substance Abuse and Mental Health Services Administration. Available at: http://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2015/NSDUH-DetTabs-2015/NSDUH-DetTabs-2015.pdf.

61 *Results from the 2014 National Survey on Drug Use and Health: Detailed Tables.* Table 2.6B. See note 60.

62 This report follows the 2014 National Survey on Drug Use and Health (NSDUH) definition for binge drinking, which is defined as "drinking five or more drinks on the same occasion on at least 1 day in the past 30 days." As this definition differs from the 2015 NSDUH definition, general population comparisons for binge and heavy drinking in this report will be drawn from the 2014 NSDUH data. Hedden, S. L., Kennet, J., Lipari, R., Medley, G., Tice, P., Copello, E. A. P., & Kroutil, L. A. (2015). *Behavioral Health Trends in the United States: Results from the 2014 National Survey on Drug Use and Health.* Rockville, MD: Substance Abuse and Mental Health Services Administration. Available at: http://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf.

63 *Results from the 2014 National Survey on Drug Use and Health: Detailed Tables.* Table 2.46B. See note 60.

64 *Results from the 2014 National Survey on Drug Use and Health: Detailed Tables.* Table 2.46B. See note 60.

65 *Results from the 2015 National Survey on Drug Use and Health: Detailed Tables.* Table 2.28B. See note 36.

66 *Results from the 2015 National Survey on Drug Use and Health: Detailed Tables.* Table 2.16B. See note 36.

67 *Results from the 2015 National Survey on Drug Use and Health: Detailed Tables.* Table 6.7B. See note 36.

68 Respondents were instructed to include products such as "weed, joints, hashish, hash, or hash oil" when reporting on marijuana use. See Q. 15.1.

69 *Results from the 2015 National Survey on Drug Use and Health: Detailed Tables.* Table 1.35B. See note 36.

70 *Results from the 2015 National Survey on Drug Use and Health: Detailed Tables.* Table 1.35B. See note 36.

71 For the purposes of this report, "illicit drugs" include those such as cocaine, crack, heroin, LSD, methamphetamine, and inhalants, but does not include marijuana or nonmedical use of prescription drugs. See Q. 15.1. This differs from illicit drugs as reported in the NSDUH, which includes "the misuse of prescription psychotherapeutics or the use of marijuana, cocaine (including crack), heroin, hallucinogens, inhalants, or methamphetamine." *Results from the 2015 National Survey on Drug Use and Health: Detailed Tables.* Table 1.30B. See note 36. Due to the difference between the two definitions, a comparison to the U.S. general population for the overall use of illicit drugs (not including marijuana or nonmedical use of prescription drugs) is not possible.

72 *Results from the 2015 National Survey on Drug Use and Health: Detailed Tables.* Table 1.22B. See note 36.

73 *Results from the 2015 National Survey on Drug Use and Health: Detailed Tables.* Table 1.30B. See note 36.

74 Centers for Disease Control and Prevention. (2016). *HIV and Transgender Communities.* Available at: http://www.cdc.gov/hiv/pdf/policies/cdc-hiv-transgender-brief.pdf; Baral, S. D., Poteat, T., Strömdahl, S., Wirtz, A. L., Guadamuz, T. E., & Beyrer, C. (2013). Worldwide burden of HIV in transgender women: a systematic review and meta-anaylsis. *The Lancet Infectious Diseases, 13*(3), 214–222; Grant, J. M., Mottet, L. A., Tanis, J., Harrison, J., Herman, J. L., & Keisling, M. (2011). *Injustice at Every Turn: A Report of the National Transgender Discrimination Survey.* (p. 80). DC: National Center for Transgender Equality & National Gay and Lesbian Task Force; Reisner, S. L., Poteat, T., Keatley, J., Cabral, M. Mothopeng, T., Dunham, E., Holland, C. E., Max, R., Baral, S. D. (2016). Global health burden and needs of transgender populations: a review. *The Lancet Infectious Diseases, 388*(10042), 412–436.

75 Centers for Disease Control and Prevention. (2016). *HIV and Transgender Communities.* Available at: http://www.cdc.gov/hiv/pdf/policies/cdc-hiv-transgender-brief.pdf.

76 Centers for Disease Control and Prevention (2015). *National Health Interview Survey: Survey Description.* Available at: ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Dataset_Documentation/NHIS/2014/srvydesc.pdf .

77 Centers for Disease Control and Prevention (2014). *2015 Behavioral Risk Factor Surveillance System Questionnaire.* Available at: http://www.cdc.gov/brfss/questionnaires/pdf-ques/2015-brfss-questionnaire-12-29-14.pdf.

78 Centers for Disease Control and Prevention. (2015). *BRFSS Prevalence & Trends Data.* Available at: http://www.cdc.gov/brfss/brfssprevalence.

79 Centers for Disease Control and Prevention. (2016). *Behavioral Risk Factor Surveillance System: 2015 Codebook Report.* Available at: http://www.cdc.gov/brfss/annual_data/2015/pdf/codebook15_llcp.pdf.

80 Centers for Disease Prevention and Control. (2016). *2015 National Health Interview Survey: Sample Adult File.* Available at: https://www.cdc.gov/nchs/nhis/nhis_2015_data_release.htm.

81 Percentages related to HIV status are presented with one decimal place throughout the section for more accurate comparison with general population figures.

82 The rate of respondents living with HIV includes those who were HIV-positive or reactive. Among respondents who had been tested, the rate of those who tested positive for HIV was 2.6%.

83 Centers for Disease Control and Prevention. (2015). HIV Surveillance Report, 2014; vol. 26. Table 18a. Available at: http://www.cdc.gov/hiv/library/reports/surveillance/. The HIV Surveillance Report provides data for those who were living with diagnosed HIV infection in the U.S. population in 2013. The U.S. population data includes those who are 15 years of age and older and does not include rate for those who are under 18, so it was not possible to exactly match the USTS sample with the U.S. population data. However, when estimating the impact of including 15–17 year olds in the U.S. population rate of those living with HIV, research team calculations estimated a difference of approximately 0.002% in the rate, which would not impact the rate of those living with HIV in the U.S. population as reported here.

84 Ninety-seven percent (97%) of those who were tested for HIV were HIV negative.

85 AIDS.Gov. (2015). *HIV Care Continuum.* Available at: https://www.aids.gov/federal-resources/policies/care-continuum.

86 Due to a low sample size, response figures could not be reported for those who had not seen a doctor for HIV care in the past 6 months.

87 Due to a low sample size, response figures could not be reported for those who had not seen a doctor for HIV care in the past 12 months.

88 See AIDS.Gov. (2015). *Overview of HIV Treatments.* Available at: https://www.aids.gov/hiv-aids-basics/just-diagnosed-with-hiv-aids/treatment-options/overview-of-hiv-treatments.

89 Centers for Disease Control and Prevention. (2016). Behavioral and Clinical Characteristics of Persons Receiving Medical Care for HIV Infection–Medical Monitoring Project, United States, 2013 Cycle (June 2013-May 2014). HIV Surveillance Special Report 16. Available at: http://www.cdc.gov/hiv/pdf/statistics/systems/mmp/cdc-hiv-hssr-mmp-2013.pdf.

Updated December 2017

THE REPORT OF THE 2015 U.S. TRANSGENDER SURVEY

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EXHIBIT 36

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Young Adult Psychological Outcome After Puberty Suppression and Gender Reassignment

Ex. 37

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

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

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

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

abstract

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

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

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

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

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

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www.pediatrics.org/cgi/doi/10.1542/peds.2013-2958

doi:10.1542/peds.2013-2958

Accepted for publication Jul 7, 2014

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(Continued on last page)

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

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

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

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

METHODS

Participants and Procedure

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

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

TABLE 1 Age at Different Treatment Milestones and Intelligence by Gender

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

PostT, post-treatment; PreT, pre-treatment.
[a] Comparisons between those who had complete data (n = 40) and those who had missing data on the CBCL/ABCL (n = 15) reveal no significant differences between the groups in age at any point in the study or in natal sex.
[b] WISC-R, the WISC-III, or the WAIS-III at first assessment, depending on age and time.[45–47]

Measures

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

Gender Dysphoria/Body Image

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

Psychological Functioning

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

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

Objective and Subjective Well-Being (T2 Only)

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

Data Analyses

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

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

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

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

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

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

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

RESULTS

Gender Dysphoria and Body Satisfaction

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

Psychological Functioning

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

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

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

	N[a]	T0	T1	T2	T0–T2	Time	Time × Sex
					t test	Linear Effect Quadratic Effect	Linear Effect Quadratic Effect
		Mean (SD)	Mean (SD)	Mean (SD)	*P*	*P*	*P*
Global functioning (CGAS)	32	71.13 (10.46)	74.81 (9.86)	79.94 (11.56)	<.001	<.001	.89
						.61	.68
MtF	15	74.33 (7.53)	78.20 (9.56)	82.40 (8.28)	<.001		
FtM	17	67.65 (11.87)	70.65 (9.89)	76.29 (14.48)	.02		
Depression (BDI)	32	7.89 (7.52)	4.10 (6.17)	5.44 (8.40)	.21	.23	.66
						.04	.49
MtF	12	4.73 (4.20)	2.25 (3.54)	3.38 (4.40)	.12		
FtM	20	10.09 (8.34)	5.05 (7.08)	6.95 (9.83)	.32		
Anger (TPI)	32	17.55 (5.72)	17.22 (5.61)	16.01 (5.28)	.20	.15	.04
						.52	.12
MtF	12	14.17 (3.01)	14.00 (3.36)	5.58 (3.92)	.18		
FtM	20	19.55 (5.96)	19.25 (5.69)	16.56 (6.06)	.05		
Anxiety (STAI)	32	39.57 (10.53)	37.52 (9.87)	37.61 (10.39)	.45	.42	.05
						.47	.52
MtF	12	31.87 (7.42)	31.71 (8.36)	35.83 (10.22)	.14		
FtM	20	44.41 (9.06)	41.59 (9.03)	39.20 (10.53)	.12		
CBCL–ABCL							
Total *T* score	40	60.20 (12.66)	54.70 (11.58)	48.10 (9.30)	<.001	<.001	.25
% Clinical		38_x	20_y	5_y		.68	.03
MtF	15	57.40 (12.76)	49.67 (12.29)	48.13 (12.58)	.002		
FtM	25	61.88 (12.56)	57.72 (10.23)	48.08 (6.95)	<.001		
Int *T* score	40	60.83 (12.36)	54.42 (10.58)	50.45 (10.04)	<.001	<.001	.91
% Clinical		30_x	12.5_y	10_y		.42	.33
MtF	15	59.40 (10.03)	50.93 (11.15)	48.73 (12.61)	<.001		
FtM	25	61.68 (13.70)	56.52 (9.86)	51.48 (8.25)	<.001		
Ext *T* score	40	57.85 (13.73)	53.85 (12.77)	47.85 (8.59)	<.001	<.001	.19
% Clinical		40_x	25_x	2.5_y		.43	.12
MtF	15	52.53 (14.11)	47.87 (12.07)	48.33 (10.95)	.10		
FtM	25	61.04 (12.71)	57.44 (12.01)	48.76 (6.89)	<.001		
YSR-ASR							
Total *T* score	43	54.72 (12.08)	49.16 (11.16)	48.53 (9.46)	.005	.005	.28
% Clinical		30_x	14_{xy}	7_y		.07	.75
MtF	17	50.65 (12.19)	45.94 (12.24)	47.24 (12.28)	.28		
FtM	26	57.38 (11.47)	51.27 (10.08)	49.38 (7.21)	.01		
Int *T* score	43	55.47 (13.08)	48.65 (12.33)	50.07 (11.15)	.03	.03	.87
% Clinical		30_x	9.3_y	11.6_{xy}		.008	.73
MtF	17	54.00 (12.31)	47.59 (14.26)	48.12 (12.54)	.04		
FtM	26	56.42 (13.86)	49.35 (11.13)	51.35 (10.19)	.17		
Ext *T* score	43	52.77 (12.47)	49.44 (9.59)	49.44 (9.37)	.14	.14	.005
% Clinical		21_x	11.6_x	7_x		.09	.14
MtF	17	46.00 (11.58)	44.71 (9.53)	50.24 (11.18)	.17		
FtM	26	57.16 (11.14)	52.54 (8.43)	48.92 (8.18)	.006		

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

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

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

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

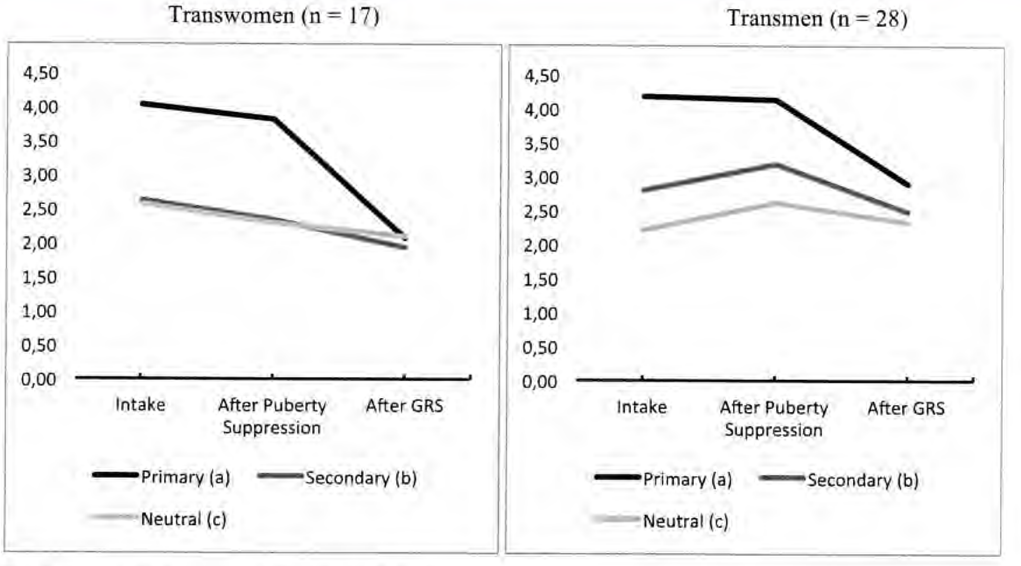
Objective Well-Being

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

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

Subjective Well-Being

None of the participants reported regret during puberty suppression, CSH



Eta Squared for Linear and Quadratic Effects

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

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

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

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

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

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

Correlations With Residual Change Scores

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

DISCUSSION

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

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

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

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

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

not (further) develop contrary to their experienced gender.

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

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

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

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

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

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

P values are in parentheses.

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

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

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

CONCLUSIONS

Results of this study provide first evidence that, after CSH and GRS, a treatment protocol including puberty suppression leads to improved psychological functioning of transgender adolescents. While enabling them to make important age-appropriate developmental transitions, it contributes to a satisfactory objective and subjective well-being in young adulthood. Clinicians should realize that it is not only early medical intervention that determines this success, but also a comprehensive multidisciplinary approach that attends to the adolescents' GD as well as their further well-being and a supportive environment.

ACKNOWLEDGMENTS

The authors thank the young adults and their parents for their repeated participation in this study over the years.

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(Continued from first page)

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by a personal grant awarded to the first author by the Netherlands Organization for Health Research and Development (ZonMw 100002028).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

Young Adult Psychological Outcome After Puberty Suppression and Gender Reassignment

Annelou L.C. de Vries, Jenifer K. McGuire, Thomas D. Steensma, Eva C.F. Wagenaar, Theo A.H. Doreleijers and Peggy T. Cohen-Kettenis

Pediatrics 2014;134;696
DOI: 10.1542/peds.2013-2958 originally published online September 8, 2014;

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American Academy of Pediatrics
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Published in final edited form as:
Nat Rev Urol. 2015 January ; 12(1): 12–13. doi:10.1038/nrurol.2014.316.

Ex 38

Paediatrics:

Transgender medicine: long-term outcomes from 'the Dutch model'

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Abstract

Medical intervention for transgender adolescents is a controversial issue but a recently published article describing long-term psychological outcomes using 'the Dutch model' of care should help to silence critics and reassure the growing number of clinicians treating this patient population.

Medical intervention for transgender adolescents has been controversial since it was first described in the Netherlands in 1998.[1] In the October 2014 edition of *Pediatrics*, De Vries and colleagues present data from 55 young transgender adults followed up from before pubertal suppression (mean age 13.6 years) to at least 1 year after gender reassignment surgery (mean age 20.7 years).[2] This eagerly anticipated report suggests that patients cared for at the Dutch clinic showed improvements in psychological functioning and resolution of gender dysphoria after gender reassignment surgery.

Prior to the medical treatment of children, all transgender persons would have to suffer through an unwanted puberty, a puberty that permanently masculinized or feminized their faces and bodies. Suicide rates remained high despite treatments in adulthood with cross-sex hormones and gender reassignment surgeries.[3] The so-called Dutch model of care was designed to treat carefully identified patients with pubertal suppression using gonadotropin-releasing hormone (GnRH) analogues at the age of 12 years, followed by the use of cross-sex hormones (oestrogen or testosterone) at age 16 years and consideration of gender reassignment surgery at age 18 years.[4] This approach aimed to eliminate the exposure to unwanted pubertal hormones, limit gender dysphoria, and improve the ability to 'pass' as the affirmed gender in adulthood. Opponents decried the protocol as radical and potentially harmful. These opponents feared that GnRH analogue therapy in 'normal' puberty could have negative impacts on cognitive development, or potentially reinforce the desire to live as the other gender, fears that have not been substantiated to date.

In the era that followed, clinics around the world formed and began incorporating this protocol into clinical care. In some countries, however, opponents resisted and provided no medical intervention to youths in early puberty Our Gender Management Services Clinic at Boston Children's Hospital, the first in the USA, began treating adolescent patients in 2007,

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Competing interests: The authors declare no competing interests.

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including several patients from countries that did not allow GnRH analogue treatments. The Endocrine Society and the World Professional Association of Transgender Health (WPATH) have formalized versions of the Dutch model into published guidelines.[5,6] Today, only 8 years after our centre opened, dozens of centres across the USA are treating patients using the Dutch model. We are motivated by the psychological improvements and physical transformations that we see in our own patients. We see depressed and anxious youths grow into happy and well-adjusted adults; however, we had been proceeding with some trepidation while we awaited long-term outcomes data.

De Vries and colleagues should be commended for their pioneering work in this controversial field. The fact that psychological functioning improved and resulted in rates of clinical problems indistinguishable from those in the general Dutch population is a triumph. The authors' ability to follow this cohort from early adolescence into young adulthood allows for a rich insight into the consequences of the treatment protocol described. This report should further promote the treatment of adolescents with pubertal suppression and cross-sex hormones as a safe and effective way to manage gender dysphoria.

It should be noted that the patients described were well supported, brought to care in early adolescence, and cared for as part of a carefully structured multidisciplinary care team in a small, supportive country. Generalizing the Dutch clinic's success to clinics in other settings might be problematic. Therefore, clinicians must take note of the positive findings from this report, and consider carefully how to best incorporate these results into their own clinical care settings.

It is also notable that the largest improvements in psychological functioning occurred following gender reassignment surgery. It is now of utmost importance to publicize the critical role of gender reassignment surgery in resolving gender dysphoria. In the USA, such surgeries are rarely covered by medical insurance and only affordable to high-income families, creating inequity of care. These types of surgery are also infrequently part of urology or plastic surgery training programmes, leading to a scarcity of surgeons competent in the procedures. The ability for transgender persons to live full and happy lives without lifelong gender dysphoria will increase as the affordability and availability of gender reassignment surgery improves.

De Vries *et al.*[2] are conscientious to note that the age criteria used for pubertal suppression (12 years) and cross-sex hormone use (16 years) are controversial. Arbitrarily halting puberty at the age of 12 years rather than at Tanner stage 2 (the beginning of puberty) might unnecessarily subject patients to dysphoric puberty simply because they are relatively precocious. Timing pubertal suppression according to the maturation of individual patients seems a more logical course. We would expect more flexible and individualized treatment protocols to become standard of care in the future.

Finally, although clinicians might be reassured by the psychological and quality of life outcomes reported, they will await the group's data outlining physical parameter outcomes. Some information on bone density outcomes has been published and seems reassuring.[4] However, the long-term safety profile of pubertal suppression, including effects on bone

density and other metabolic parameters, is of keen interest to providers caring for transgender adolescents.

We live in a time of dramatic change; LGBT (Lesbian Gay Bisexual Transsexual) rights have become the civil rights issue of our day. Transgender people, often the forgotten caboose on the LGBT train, are emerging and demanding competent and compassionate medical care. This latest report on long-term psychological functioning following pubertal suppression, treatment with cross-sex hormones, and gender reassignment surgery is a giant step forward for this important patient population.

Acknowledgments

Dr. Shumer is supported by a grant from the Eunice Kennedy Shriver National Institute of Child Health and Human Development

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Ex. 39

Challenges in Timing Puberty Suppression for Gender-Nonconforming Adolescents

Annelou L.C. de Vries, MD, PhD

Sorbara et al,[1] in their report "Mental Health and Timing of Gender-Affirming Care" in this issue of *Pediatrics*, focus on the interesting matter of age of clinical presentation for gender-affirming medical interventions and its association with mental health in transgender youth. Because experiencing puberty is often stressful for gender-nonconforming youth, puberty suppression as a reversible medical intervention was introduced in clinical care in the early 2000s by Dutch clinicians Cohen-Kettenis et al.[2] The aim of puberty suppression was to prevent the psychological suffering stemming from undesired physical changes when puberty starts and allowing the adolescent time to make plans regarding further transition or not. Following this rationale, younger age at the time of starting medical-affirming treatment (puberty suppression or hormones) would be expected to correlate with fewer psychological difficulties related to physical changes than older individuals. Sorbara et al[1] confirmed this in their study. Adolescents presenting at younger age (<15 years) reported lower rates of self-reported diagnosed depression, self-harm, suicide thoughts or attempts, and use of psychoactive medication.

One could claim from these findings that gender-affirming medical interventions including puberty suppression should be offered at an early age (age <15 in the Sorbara study). Some caution is warranted, however, as the authors acknowledge in their report. One reason is that, despite the increased availability of gender-affirming medical interventions for younger ages in recent years, there has not been a proportional decline in older presenting youth with gender incongruence (GI), which is the discrepancy between one's birth-assigned sex and experienced gender identity.[3] It is even the case that most transgender people still present as older adolescents, as in the study by Sorbara et al[1], or as adults.[4] Interestingly, this older adolescent group did not only have more mental health difficulties but also a later age of onset of GI. As seen by using medical records, the older presenting youth "simply experienced gender history events at older ages" before attending the clinic.[1]

According to the original Dutch protocol, one of the criteria to start puberty suppression was "a presence of gender dysphoria from early childhood on."[2] Prospective follow-up studies evaluating these Dutch transgender adolescents showed improved psychological functioning.[5] However, authors of case histories and a parent-report study warrant that gender identity development is diverse, and a new developmental pathway is proposed involving youth with postpuberty adolescent-onset transgender histories.[6–8] These youth did not yet participate in the early evaluation studies.[5,9] This raises the question whether the positive

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DOI: https://doi.org/10.1542/peds.2020-010611

Accepted for publication Jul 14, 2020

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The author has indicated she has no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The author has indicated she has no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/2019-3600.

To cite: de Vries ALC. Challenges in Timing Puberty Suppression for Gender-Nonconforming Adolescents. *Pediatrics*. 2020;146(4):e2020010611

outcomes of early medical interventions also apply to adolescents who more recently present in overwhelming large numbers for transgender care, including those that come at an older age, possibly without a childhood history of GI. It also asks for caution because some case histories illustrate the complexities that may be associated with later-presenting transgender adolescents and describe that some eventually detransition.[9,10]

A study at the Amsterdam transgender clinic, one of the oldest in the world, whose researchers aimed to gain insight in the possible changes of certain key characteristics of earlier compared with recent applicants, revealed no changes in intensity of gender dysphoria, psychological functioning, and age over time between 2000 and 2016.[11] The only yet-unexplained observed change was a shift in sex ratio in favor of assigned female individuals. However, researchers of this time-trend study did not focus on differences between younger and older referred youth nor on the age of onset of gender nonconformity. In future, more-detailed studies like the one by Sorbara et al[1] and the time-trend study by Arnoldussen et al,[11] researchers should investigate whether older transgender adolescents might include individuals who experience later onset of GI, possibly postpuberty, and with more mental health challenges.

So far, researchers of the limited follow-up studies after puberty suppression show that the rate of adolescents that stop the reversible blockers is low (1.4%, 1.9%, and 3.5%).[4,12,13] However, systematic studies on the rate of adolescents who discontinue their transitions after they have started affirming hormones or surgeries with lasting effects are lacking at present. Given these uncertainties, providing early medical treatment to transgender adolescents remains a challenging area to work in. Prospective longer-term follow-up studies of clinical samples like the study of Sorbara et al[1] are needed to inform clinicians so that an individualized approach can be offered that differentiates who will benefit from medical gender affirmation and for whom (additional) mental health support might be more appropriate.

ABBREVIATION

GI: gender incongruence

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Challenges in Timing Puberty Suppression for Gender-Nonconforming Adolescents

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Pediatrics 2020;146;
DOI: 10.1542/peds.2020-010611 originally published online September 21, 2020;

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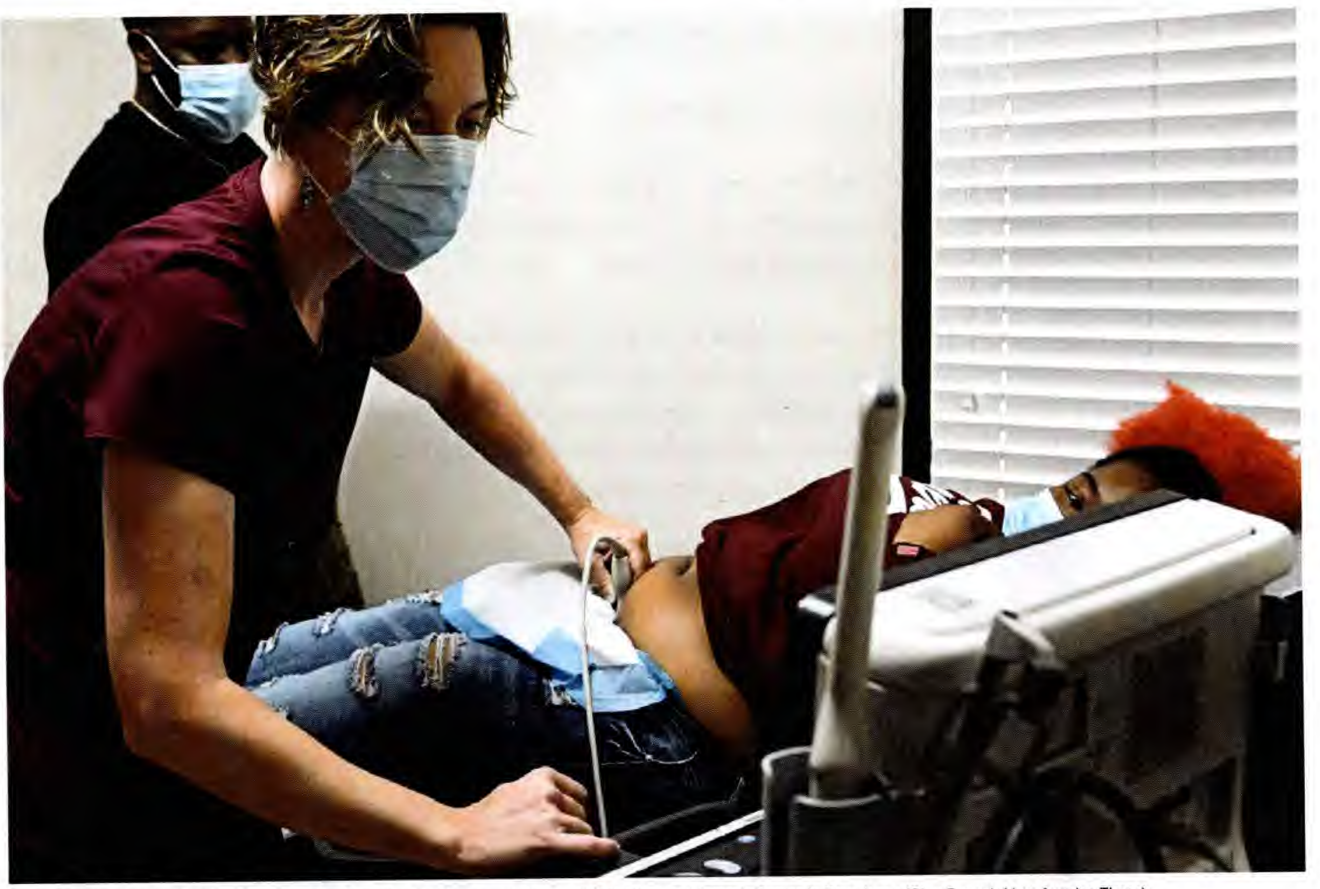
Pediatrics 2020;146;
DOI: 10.1542/peds.2020-010611 originally published online September 21, 2020;

Ex. 40

Los Angeles Times

WORLD & NATION

This abortion doctor is not ready to leave Alabama. 'You don't want me here? That's why I'm gonna stay'



Dr. Leah Torres administers an ultrasound on a woman seeking prenatal care at West Alabama Women's Center in Tuscaloosa.(Gina Ferazzi / Los Angeles Times)

BY JENNY JARVIE | NATIONAL CORRESPONDENT

APRIL 28, 2023 3 AM PT

TUSCALOOSA, Ala. — People often ask Dr. Leah Torres why she stays in Alabama.

The 43-year-old OB-GYN — who strides into her clinic most mornings wearing a clitoris pendant and T-shirts with a slogan declaring "ABORT THE PATRIARCHY" — does not consider this conservative Deep South state her home.

A few weeks after she arrived, the state Board of Medical Examiners revoked her temporary medical license to practice, accusing her of ethical violations.

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It took her seven months to get it back, a legal battle that cost her $115,360.93, according to the price tag she affixed to the framed license hanging in her office at the West Alabama Women's Center.

The center was one of the busiest abortion clinics in the state, until the Supreme Court struck down Roe vs. Wade last year. Abortion became illegal in Alabama, one of over a dozen states with full bans. Now that doctors who perform the procedure in Alabama risk up to 99 years in prison, Torres finds herself, once again, unable to offer the full spectrum of reproductive medical care she was trained for.

But Torres has no intention of backing down.

"You don't want me here? That's why I'm gonna stay," she said, sitting at a desk strewn with laboratory invoices and a tiny fetus replica handed out by antiabortion campaigners. "I'm not leaving, just out of spite!"

Torres believes her work is not done in Alabama, a state with the third-highest maternal mortality rate in the nation and the sixth-highest infant death rate. The Republican-dominated Legislature joined nine other conservative states in refusing to expand Medicaid, which would allow more than 200,000 uninsured non-elderly adults in the state to become eligible for coverage.

A 27-year-old woman holds images of her 10-week-old fetus at West Alabama Women's Center in Tuscaloosa. The clinic, which shut down briefly after Alabama banned abortion, now focuses on prenatal care, birth control, miscarriage treatment and transgender care. (Gina Ferazzi / Los Angeles Times)

After shutting down for a week in July after the U.S. Supreme Court ruling, her clinic reopened its doors as a "pay what you can" nonprofit offering low-income and uninsured women basic reproductive health services that can be hard to access in Alabama.

Torres and the clinic are offering hormone therapy for transgender people, including teenagers — wading into another culture-wars fray at a time when Alabama and other conservative states are moving to ban such treatment for minors.

"There's so much work here," Torres said. "Alabama's really dead set on compromising people's lives, especially LGBTQ+ youth, especially pregnant people. These are expendable people in the eyes of the state of Alabama."

'We have to push back'

When Tina Collins, the front office manager, picks up the phone — "West Alabama Women's Center!" — she frequently has to inform callers the clinic no longer provides abortions.

"No ma'am, we do not," she says gently in her south Georgia drawl. "They are illegal in Alabama. You can go to our website, the West Alabama's Women's Center, or you can go to the website redstateaccess.org."

In July, when the tiny brick clinic reopened with abortions no longer on its list of services, staff members were nervous. Robin Marty, the clinic's director of operations, gave everyone firm instructions not to provide callers with information on obtaining abortions out of state or by mail.

Now they've adopted a slightly bolder approach, plastering the reception window with stickers offering website links for abortion information. "Need to be unpregnant?" asks a sticker at eye level of the front desk. "RED STATE ACCESS CAN HELP."

"Safe. Private. Informed," another says. "Learn about self-managed abortion."

"We have to push back," Marty said. "If we don't test these things, then they won already ... and we're going to be trapped forever."

As abortion clinics have shuttered across Alabama, Mississippi and Louisiana, national organizations have devoted resources to setting up new centers and mobile clinics in blue states. But women who travel for abortions still need care when they come home.

Earlier this month, a 20-year-old nursing student came to the clinic with her mother for a follow-up appointment a month after driving to Georgia for a medication abortion.

A TV news report about the court battle over the abortion pill mifepristone plays in the waiting room of West Alabama Women's Center, once one of the busiest abortion clinics in Alabama. (Gina Ferazzi / Los Angeles Times)

After passing a sign that said "Still Open for Non-Abortion Services," they slipped through a glass door into an empty waiting room that used to teem with patients. On the day before Roe was overturned, 67 people came to the clinic for medication abortions. Now the clinic sees about 15 patients a week.

The medication had worked and there were no complications, but the woman's mother was indignant that politicians had forced them to take a day off work and school to make the six-hour round trip to Atlanta.

"I feel like your body is yours, not the government's," said Renetha Abernathy, a 57-year-old nurse. "We should have full healthcare right here in our own area, so we can make that choice."

WORLD & NATION

Abortion pill ruling: Texas judge revokes FDA approval, but another judge contradicts him

April 7, 2023

POLITICS

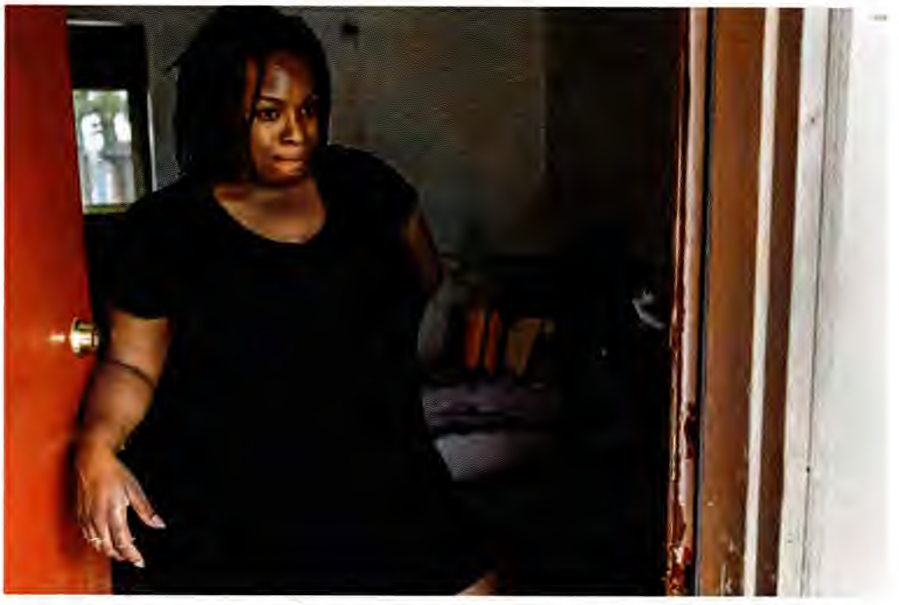
Supreme Court sides with FDA on abortion pills, blocks Texas rulings for now

April 21, 2023

Earlier that week, Torres met a pregnant patient who told her that the local OB-GYN clinic that gave her prenatal care and delivered her baby 15 months ago made her wait nearly three hours for an appointment and rebuked her when she complained.

The woman suspected — as did Torres — that the stark discrepancy in care was because she had switched from Blue Cross Blue Shield to Medicaid.

Even patients with insurance have trouble accessing care. Tyeshia Smith, 31, a mental health worker who has done sex work, came to the clinic because she wanted another child but worried about her fertility. Her menstrual cycle had become irregular in recent months, and she feared sexually transmitted diseases had taken a toll on her body.



Tyeshia Smith, 31, a mental health worker who lives with her mother in Tuscaloosa, went to the West Alabama Women's Center after having trouble getting appointments at other area facilities. (Gina Ferazzi / Los Angeles Times)

The first clinic she called couldn't see her until July. Another didn't answer, so she left a voicemail.

"Every aspect of healthcare here in Alabama to me is 20 years back," Smith, who is from Ohio, said as she waited in an exam room for a Pap smear.

Over the last year, Torres has treated women who have miscarried or learned their pregnancies are nonviable and have trouble finding care, as physicians across the state become more fearful of ending up in jail.

WORLD & NATION

The woman who brought down Roe vs. Wade wants to take abortion battle to California

June 24, 2022

In February, Alison, a 36-year-old in Montgomery who spoke on condition that her full name not be used, started bleeding about seven weeks after getting pregnant via artificial insemination. When she went to her OB-GYN for an emergency ultrasound,

she was told the pregnancy wasn't viable — there was a sac, but no fetal tissue or heartbeat. The doctor, seeming uncomfortable, told her to go home and wait for her body to pass the tissue.

Over the next few days, Alison bled and cramped so badly she could not get out of bed. Her grief and anxiety swelled as she read online about sepsis and fretted that if the sac did not pass it could harm her fertility.

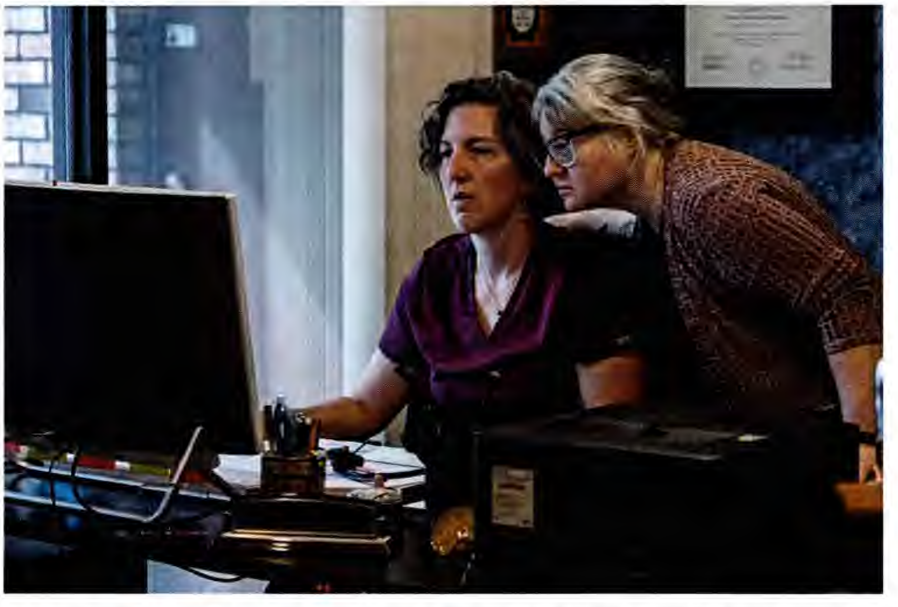
After the bleeding subsided the fifth day, she decided to drive 100 miles to Tuscaloosa to see Torres. The ultrasound showed she was out of danger. Torres spent 20 minutes reassuring her she had not done anything wrong.

"This is our body's way of preventing us from heartache," Torres told her, noting that sometimes bodies reject cells that are unhealthy. "Miscarriage is terrible; this was a blessing."

For the first time during the ordeal, Alison said, she felt seen and taken care of.

Escaping 'corporate medical hell'

The door to Torres' office is usually open, adorned with buttons that say "TRUST WOMEN" and "I'M ON YOUR SIDE" and a flag that proclaims "ROUND THESE PARTS, WE RESPECT PRONOUNS."



Dr. Leah Torres, left, consults with Robin Marty, director of operations at West Alabama Women's Center in Tuscaloosa. (Gina Ferazzi / Los Angeles Times)

As an activist who promotes herself in her Twitter bio as a "sex+, gender-affirming repro health specialist"— tagline "GTFO of my uterus" — Torres has always chafed at

the idea of the paternalistic physician.

"I am not going to be the 'Do as I say' doctor," she said before meeting a transgender patient last week for a telehealth appointment. "I want them to understand that this is a team effort and that I'm not a magic wizard with all of the answers. I am a human being too."

Thank-you notes to the staff hang on a bulletin board inside West Alabama Women's Center. (Gina Ferazzi / Los Angeles Times)

Throughout her medical career, Torres has often felt thwarted.

A Michigan native who also grew up in Florida, she studied medicine at the University of Illinois. After completing her OB-GYN and specialized family planning training in Philadelphia and Salt Lake City, she got a job in 2014 at a community clinic in northern Utah. The clinic would not let her incorporate abortion care into her general practice.

Her frustration built as she got embroiled in campaigns against Utah lawmakers' attempts to restrict abortion.

In 2018, Torres found herself at the center of an online firestorm after someone on Twitter accused her of infanticide and asked: "Do you hear their heartbeats when you lay down at night?"

Torres replied: "You know fetuses can't scream, right? I transect the cord 1st so there's really no opportunity, if they're even far enough along to have a larynx."

CALIFORNIA

Horrifying stories of women chased down by the LAPD abortion squad before Roe vs. Wade

March 31, 2023

She refers to this incident now as the "tweet that broke my entire life."

Conservative pundit Ben Shapiro shared her tweet, commenting, "This is like a James Bond villain explaining his plan to 007, but a lot less self-aware." Torres deleted the post and clarified that she meant umbilical cord, not vocal cord. But the Daily Caller and a string of right-wing outlets posted articles naming Torres. Eventually, she was asked to sign a mutual separation agreement due to the death threats being received at the clinic.

Unable to find another job in Utah, she sued the Daily Caller for defamation, reaching a settlement in which she got $40,000. After a year without work, she moved to New Mexico to work at a hospital that did not perform abortions.

She earned enough to pay off her student loans but felt disenchanted. The system, as she saw it, did not just prevent doctors from performing a necessary procedure; it encouraged them to perform unnecessary ones, such as caesarean sections. "If a vaginal delivery pays half of what a C-section is, why would you do a vaginal delivery ever?" she said.

"Pregnant women — and I'll just be cis-normative for a second — are walking dollar signs," she railed. "They're not people. They are a commodity that makes money for the hospital, for the healthcare network, for the insurance company and for the doctor."

When Marty called Torres in March 2020 to ask if she would be interested in leaving New Mexico to take on the role of medical director of an abortion clinic in a different state, Torres jumped at the offer.

"Sign me up," she said.

"Do you want to know where it is?" Marty asked.

"I don't care," Torres said. "I'm in corporate medical hell."

Alabama is not a haven for Torres. The state faces a critical shortage of OB/GYNs. In 1980, 45 of the state's 54 rural counties provided obstetric services; by 2019, the number was 16. A family of four qualifies for Medicaid benefits there only if the household income is under $450 dollars a month.

But the Tuscaloosa clinic offers Torres a place to serve the needy in a state that, as she sees it, is the "quintessential example of what corporate medicine really is."

For Torres, it is nothing short of a miracle that the clinic is still open.

Dr. Leah Torres, left, consults with Raven Williams, 17, with her boyfriend, Ethan Williams, 22, on prenatal care after confirming that she is pregnant. (Gina Ferazzi / Los Angeles Times)

Before Roe was overturned, when 95% of patients came to the clinic for abortions, the clinic brought in $200,000 a month. In the last 10 months, revenue from patients has totaled $20,000. Marty laid off five of the clinic's 11 staff members in August. But revenue has totaled $998,000, mostly through grants and fundraising, ensuring that the clinic can stay open at least through September.

A key prong of its new work is bringing in LGBTQ+ patients from across Alabama via telehealth appointments. The clinic is now offering HIV testing and medication to prevent HIV transmission.

It also provides hormone therapy to transgender patients, including minors — a move that is almost certain to bring the clinic into conflict with Alabama officials.

Transgender care, a new battleground

A year ago, Alabama became the first state to pass a law making it a felony for a doctor to prescribe or administer puberty blockers or hormone treatment to anyone younger than 19 "for the purpose of attempting to alter the appearance of or affirm the minor's perception of his or her gender or sex" — with prison sentences of up to 10 years.

But the law is partially blocked by a federal court until a September hearing. After consulting with attorneys, the Tuscaloosa clinic is, for now, quietly offering minors hormone treatment. The clinic's website states that it can "provide hormone therapy

and other care to those over the age of 19," but Torres said that a "whisper network" promoted services for minors.

Over the last year, Torres said, she has prescribed hormone treatment to about 50 transgender patients. Two were younger than 19.

"This is the healthcare people need to keep them safe," Torres said. "I will fight for that."

Across the U.S. and Europe, debate is raging among health professionals about how to treat a rising number of adolescents who identify as transgender. There are no long-term clinical studies looking at how hormone treatments may affect fertility and sexual function. Countries such as Sweden, France and the U.K. have in recent years reversed course and adopted a more cautious approach, citing potential side effects and a growing number of people who regret transitioning.

Last year, the World Professional Assn. for Transgender Health, the leading medical group for transgender care, published new standards of care for gender-diverse adolescents seeking medical treatment, recommending that healthcare professionals carry out "comprehensive biopsychosocial assessment" before providing them with puberty blockers, sex-changing hormones or mastectomies.

Torres does not believe adolescents seeking hormones require mental health evaluations.

"No, I don't need a psychologist or psychiatrist to evaluate someone who's telling me, 'This is how I felt for years,'" she said. "I know that how they felt for years is not pathological."

When meeting trans patients, Torres is upfront that she has been practicing such care for only a year.

"Full disclosure," she tells them, "this area of medicine is pretty new to me." She also points out that this is a relatively experimental area of medicine without a lot of data.

One transgender patient Torres recently started seeing through telehealth was referred to her because the teen's pediatrician and staff at a psychiatric hospital did not respect his gender identity and used his old name. The teen, who had a history of depression and anxiety, told Torres he had known he was a boy for years and wanted to take sex-changing hormones.

"There's so much work here," Dr. Leah Torres said of the women's clinic. "Alabama's really dead set on compromising people's lives, especially LGBTQ+ youth, especially pregnant people. These are expendable people in the eyes of the state of Alabama." (Gina Ferazzi / Los Angeles Times)

Torres told him straight up that she would prescribe a low dose of testosterone. She let the boy know she was glad he was seeing a therapist, even though she didn't require it. She believes trans people need to deal with the trauma of trans bigotry in Alabama, she said.

When she told him she was prescribing testosterone, his face lit up, she said. He asked her, "You mean right today?"

And that, she said, was why she did her job. The teen had tried for so long to get healthcare and been unsuccessful. She believes she is offering lifesaving care.

"I will do whatever I can within legal parameters," Torres said later. "But at the end of the day, if it's somebody's life versus a bad law, I'm choosing that person's life."

Hopefully, she said, there would never be a conflict.

MORE TO READ

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March 5, 2024

Jenny Jarvie

Jenny Jarvie is a national correspondent for the Los Angeles Times based in Atlanta.

EXHIBIT 41

Please use the following credentials to access the exhibit:

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Ex. 42

Gender Identity Disorder in Twins: A Review of the Case Report Literature

Gunter Heylens, MD,* Griet De Cuypere, MD, PhD,* Kenneth J. Zucker, PhD,† Cleo Schelfaut, MD,‡ Els Elaut, MSc,* Heidi Vanden Bossche, MSc,§ Elfride De Baere, MD, PhD,¶ and Guy T'Sjoen, MD, PhD*‡

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DOI: 10.1111/j.1743-6109.2011.02567.x

ABSTRACT

Introduction. The etiology of gender identity disorder (GID) remains largely unknown. In recent literature, increased attention has been attributed to possible biological factors in addition to psychological variables.
Aim. To review the current literature on case studies of twins concordant or discordant for GID.
Methods. A systematic, comprehensive literature review.
Results. Of 23 monozygotic female and male twins, nine (39.1%) were concordant for GID; in contrast, none of the 21 same-sex dizygotic female and male twins were concordant for GID, a statistically significant difference ($P = 0.005$). Of the seven opposite-sex twins, all were discordant for GID.
Conclusions. These findings suggest a role for genetic factors in the development of GID. **Heylens G, De Cuypere G, Zucker KJ, Schelfaut C, Elaut E, Vanden Bossche H, De Baere E, and T'Sjoen G. Gender identity disorder in twins: A review of the case report literature. J Sex Med 2012;9:751–757.**

Key Words. Twins; Gender Identity Disorder; Genetics; Biologic Factors in GID; Transsexualism

Introduction

After decades of research, the etiology of gender identity disorder (GID) remains largely unknown. Developmental psychological models have identified temperamental vulnerabilities of the GID child, particular patterns of parent–child interaction, family dynamics, and traumatic events as possible risk factors [1–3], although, in one recent study, there was a failure to identify parental problems [4].

Recent literature has focused more on genetic and other biological factors, rather than on psychological factors, when trying to explain the genesis of GID. Research on biological factors is multifaceted: from size and cell number of different sex-dimorphic brain nuclei [5–7], prenatal exposure to abnormal androgen levels [8], and to genetically based sex hormone abnormalities [9]. The research of Hare et al. [9] provided evidence that male-to-female transsexualism was associated with gene variants responsible for less androgen sensitivity. The percentage of false positives in their control group was, however, extremely high, which weakens the results.

Coolidge et al. [10] studied parents of 314 twins to estimate the prevalence of GID in children and adolescents. They found a 2.3% prevalence and 62% heritability, while 38% of the variance was explained by a nonshared environmental component. These results confirmed the earlier findings of Bailey et al. [11], who, in a retrospective design, found that childhood gender nonconformity was substantially heritable for adult twins. Knafo et al. [12] examined genetic and environmental influences on 3- and 4-year-old twins' atypical gender development based on parental ratings of 5,799 pairs. They concluded that the genetic effects were less strong than the environmental effects, with the exception of behaviorally classified masculine girls.

Focusing on familial studies, Gómez-Gil et al. [13] reported on a sample of 995 consecutive applicants for sex reassignment surgery and found 12 pairs of transsexual nontwin siblings. The study suggested that although the risk was low, siblings of persons with GID may have a higher risk of being transsexual than the general population. The risk was higher for brothers than sisters of transsexual persons.

Case studies of monozygotic (MZ) and dizygotic (DZ) twins are helpful for investigation of the influence of genetic factors in GID development vs. environmental influences. By researching the literature of twin case studies concordant or discordant for GID, we will focus our evaluation on the role of genetic factors in the development of GID.

Table 1 Female twin pairs concordant/discordant for gender identity disorder (GID)

Reference	Zygosity	Concordant/discordant for GID
Sadeghi and Fakhrai [14]	Monozygotic	Concordant
Knoblauch et al. [15]	Monozygotic	Concordant
Heylens and De Cuypere	Monozygotic	Concordant
Green and Stoller [16]	Monozygotic	Discordant
Garden and Rothery [17]	Monozygotic	Discordant
Segal [18]	Two monozygotic	Both discordant
Zucker [19]	Monozygotic	Discordant
Heylens and De Cuypere	Dizygotic	Discordant
Zucker [19]	Dizygotic	Discordant
Segal [20]	Dizygotic	Discordant
Zucker et al. [21]	Dizygotic	Discordant
Vujovic et al. [22]	Dizygotic	Discordant

Method

For the review of case studies on twins with concordant and discordant GID, we searched PubMed, Web of Knowledge/Web of Science, and Google Scholar using the following key words: transsexual, gender identity disorder, twins, genetics. For unpublished data sets, we contacted the authors directly. We also included three twin pairs who attended the Gender Clinic of Ghent University Hospital during the period 1985–2010, from a pool of about 450 attendees and an additional three twin pairs who attended the Child and Adolescent Gender Clinic of Ghent University Hospital. Concerning the case reports examined at our clinic, all twin pairs (as well as their mothers) gave their informed consent to use their data for research. A total of 25 twin pairs (all children) were also available for analysis from the Gender Identity Service at the Centre for Addiction and Mental Health in Toronto, who were evaluated between 1975 and 2011.

Results

Female Twins

Table 1 shows the data on 13 female twins. Of the eight MZ twin pairs, three (37.5%) were concordant for GID and five (62.5%) were discordant. Of the five DZ twin pairs, all were discordant for GID.

MZ Female Twins Concordant for GID

The two MZ twins concordant for GID described by Sadeghi and Fakhrai [14] and Knoblauch et al. [15], respectively, shared certain common features: they both had troublesome childhoods, a difficult relationship with their parents (particularly with the mother), cross-gender behavior since early childhood on, and a good relationship with each other. In contrast, the MZ twins evaluated at our gender clinic in Ghent mentioned no specific problems with their parents, although the communication was rather superficial and the father was often absent. Throughout childhood, the twin sisters were very close, but when growing older, their relationship deteriorated. They both suffered from gender dysphoria since a young age. Going through puberty was very problematic for both of them and they developed anorexia nervosa to put a stop to their female pubertal body development. This problem was never resolved by one of the twin sisters, and her mental state and physical health deteriorated progressively. She died in January 2010 from the consequences of her anorexia. In all three MZ female twins concordant for GID, a normal karyotype of the sex chromosomes and no hormonal abnormalities were found.

MZ Female Twins Discordant for GID

Five MZ female twins have been identified in the literature as discordant for GID [16–19]. As they share the same genetic background, we focused our attention in these case reports on the existence of different environmental factors (hormonal and/or psychological), which might give an explanation for different development concerning gender identity. In three out of the five pairs, the transsexual twin had a higher birth weight, and a higher adult height in the transsexual twin was reported in two of the three pairs. For two of the transsexual twin sisters, the menarche occurred a

year later than in the nontranssexual sisters. In all these cases, the gender behavior of the twin sisters differed from an early age on cross-gender behavior for the transsexual twin sister and very female behavior for the nontranssexual twin. Concerning the parental rearing, Segal [18] described a very different approach from the mother in one of the twin pairs toward the girl with the gender-atypical behavior. Segal considered the maternal physical abuse directed to the GID sister to be a consequence of the outspoken tomboyish behavior of the girl than as causal but acknowledged that the abuse may have reinforced the already atypical gender identification. In the other three pairs, the different parental approach regarding toy preferences and childhood activities was interpreted as the reaction of parents on the different toy preferences and childhood behavior of their children. Segal concluded that higher birth weight and later age of menarche observed in the GID twin sisters might reflect differential prenatal hormonal exposure and/or gene expression, resulting in differences in brain development and gender identity [18].

DZ Female Twins Discordant for GID

There were a total of five DZ female twins with discordant GID [19–22]. The DZ twins seen in Ghent were born by Cesarean section. Their mother and father divorced when the twins were a year old. The mother remarried when the twins were 9 years old. They connected well with their stepfather, while they had no further contact with their biological father. Although the twins are DZ, they have many phenotypic characteristics in common and were often mistaken as identical. They expressed no outspoken cross-gender behavior in childhood. They both were raised as girls and the mother did not seem to make a difference between her daughters. However, when the menarche started at age 12, one of the sisters became increasingly gender-dysphoric. The other sister had no gender-dysphoric feelings but considered herself as being attracted to females. When one declared herself as transsexual, she was referred by the general practitioner to our department. After a 9-month period of regular visits to our psychiatrist, the diagnosis of GID according to the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (Text Revision) criteria could be made and, in the absence of other comorbidity, gender reassignment was started. The other sister was the only twin sister of the case studies reported here who was homosexual, as all the other twin sisters discordant for GID were sexually attracted to males. All the girls with GID and the twins concordant for GID for whom their sexual orientation was known considered themselves as asexual or heterosexual and were sexually attracted to females.

The DZ twins discordant for GID reported on by Zucker et al. [21] were unique in that the unaffected twin had a normal XX karyotype, whereas the affected twin had an ovotesticular disorder of sex development. The karyotype revealed a 45X (13%) and 47XYY (87%) sex chromosome mosaic pattern in blood, whereas all cells (N = 25) checked in the skin fibroblast culture were 45X. The GID twin had an IQ of 113 and the co-twin an IQ of 118. Despite a comparable IQ, the GID twin was perceived by the mother as having substantially more general behavior problems than the co-twin; however, this was much less true of the father. The mother reported feeling much closer to the co-twin than to the GID twin, whereas the reverse was true for the father. Zucker et al. suggested that the prenatal hormonal predisposition for masculinized behavior in the affected twin was exacerbated by nonshared environmental influences in the rearing environment compounded by complex family dynamic factors.

Male Twins

Table 2 shows the data on 31 male twins. Of the 15 MZ twin pairs, six (40.0%) were concordant for

Table 2 Male twin pairs concordant/discordant for gender identity disorder (GID)

Reference	Zygosity	Concordant/ discordant for GID
Heylens and De Cuypere	Monozygotic	Discordant
Green and Stoller [16]	Monozygotic	Discordant
Zucker [19]	Three monozygotic	All discordant
Hyde and Kenna [23]	Monozygotic	Concordant
Tsur et al. [24]	Monozygotic	Concordant
Green [25]	Monozygotic	Concordant
Ancherson [26]	Monozygotic	Concordant
Stoller and Baker [27]	Monozygotic	Concordant
Gooren et al. [28]	Monozygotic	Concordant
Gooren et al. [28]	Monozygotic	Discordant
Stoller [29]	Monozygotic	Discordant
Hepp et al. [30]	Monozygotic	Discordant (concordant in childhood)
Segal [31]	Monozygotic	Discordant
Heylens and De Cuypere	Three dizygotic	All discordant
Zucker [19]	12 dizygotic	All discordant
Vujovic et al. [22]	Dizygotic	Discordant

GID and nine (60.0%) were discordant. Of the 16 DZ twin pairs, all were discordant for GID.

MZ Male Twins Concordant for GID

From the identical twins described by Hyde and Kenna [23], both were concordant for transsexualism but discordant for schizophrenia. The brothers did not have a good relationship and considered themselves as very different. Both were sexually attracted to men. Hyde and Kenna suggested that a more subtle relationship is possible of transsexualism occurring as a schizophrenic spectrum disorder. The twins from the case report of Tsur et al. [24] were raised in an orthodox Jewish family. They developed GID from an early age. Estrogen treatment was started from the age of 21. They were both sexually attracted to men and lived a normal life as women. Green [25] described a MZ twin pair concordant for GID. It was striking that as identical twins, they were never close to each other. Green reported that they were treated equally by their parents. One of the twin brothers had GID in early childhood; the co-twin developed transvestic fetishism and only later on GID. They both were sexually attracted to women. One of the brothers suffered from psychotic periods after starting estrogen treatment. The other MZ male twins concordant for GID, reported in the literature, are not from recent date; no further follow-up details are known [26–28].

MZ Male Twins Discordant for GID

The MZ twin pair discordant for GID described by Green and Stoller [16] were prepubertal children when assessed. One of the twin brothers presented cross-gender behavior since the age of 4. He was diagnosed with tuberculosis in that period, and the relationship with his mother became closer. The co-twin, however, had a better relationship with his father and behaved in a very male-typical manner. This family constellation continued later on with a different rearing of the two boys. In the case study of Stoller [29], a Native American twin pair of 30 years old was described, and they were the ninth and 10th child from 14. The father was an alcoholic, and the parents divorced when the children were very young. They were often left to their own fate. According to the mother, there was a difference between the two boys from an early age on. One of the twin brothers behaved as a sissy boy, preferred to play with his sisters and to dress as a girl; the co-twin liked horse riding and hunting. The twin with feminine behavior wanted to become a woman, more because he felt more comfortable in the female world than because he claimed a female identity. In the MZ twins reported by Hepp et al. [30], one felt as a girl and had cross-gender behavior as long as he could remember. He asked for gender reassignment at the age of 18. He was sexually attracted to men and considered himself as "heterosexual." At that time, he was diagnosed with anorexia nervosa. The co-twin also preferred girls' games and toys, but his gender identification was male. He considered himself as homosexual. He periodically cross-dressed after puberty. At the age of 16, his mental state deteriorated with anorexia and depression. Psychiatric in-treatment was needed. Hepp et al. hypothesized that "GID in childhood is mainly hereditary whereas the development of the later phenotype of the gender identification is determined by environmental factors and psychiatric co-morbidity." Segal [31] described a MZ twin pair, thin, with fair hair who behaved both rather feminine in childhood. They loved to mix with the female friends of their mother. Already at the age of 5, the mother wondered if her sons were not gay. Indeed, a few years later, both were sexually attracted to boys. Only one of the twins felt distressed about his gender. So one twin became gay; the co-twin became a transsexual woman attracted to men. The MZ male twin seen at the Child and Adolescent Gender Clinic in Ghent behaved very differently from early age on. One twin brother was diagnosed as GID and met all criteria for receiving puberty blockers at the age of 13. The co-twin was involved in masculine games and had male interests. There were no arguments to hypothesize that the rearing methods from the parents was differential toward the twin brothers. Their sexual orientation is not yet clear.

DZ Male Twins Discordant for GID

Of the 16 discordant DZ male twins, the Ghent clinic saw three of them (the first pair at the Adult Gender Clinic, the two other pairs at our Child and Adolescent Gender Clinic). The first twin pair, 17 years old, differed in behavior from early childhood on. The parents divorced when they were toddlers. The relationship between mother and the GID child was closer than with the co-twin. The GID adolescent was reluctant to visit his father because he did not feel at ease with him. This was not the case for his brother. The differential approach from the parents was likely elicited by the cross-gender behavior of the child. Most striking about the other two twin pairs discordant for GID, seen at our Child and

Adolescent Gender Clinic, is that they were born after in vitro fertilization.

Male and Female DZ Twins

Zucker [19] reported on seven opposite sex twin pairs. Of the probands with GID, six were male and one was female. In all cases, there was discordance for GID with the co-twin.

Statistical Analysis

If we combine the same-sex MZ and DZ twin pairs across sex, there were a total of nine (39.1%) MZ twin pairs concordant for GID and 14 (60.9%) discordant for GID; of the 21 DZ twin pairs, all were discordant for GID. The difference in concordance between the MZ and DZ twin pairs was significant, $\chi^2(1) = 8.08$, $P = 0.005$. If one adds to the DZ group the data on opposite sex twins, the difference from the MZ twin pairs was even stronger, $\chi^2(1) = 10.74$, $P = 0.001$.

The largest sample of twins (N = 25 pairs) comes from the series reported on by Zucker [19,21]. These twins were culled from a total sample of 561 children evaluated between 1976 and 2011. These twins ranged in age from 2.9–11.9 years. Quantitative measures of sex-typed behavior showed that the GID probands had significantly more cross-gender behavior than the unaffected co-twins, which meshed with the clinical diagnosis. On the Child Behavior Checklist, a parent report measure of behavior problems, the GID probands had significantly more difficulties than the unaffected co-twins. The affected twins did not differ significantly from the unaffected co-twins in birth weight.

Discussion

Based on the literature and our own unpublished twin cases seen for clinical evaluation, nine (39.1%) of the 23 MZ female and male twins were found to be concordant for GID. In contrast, none of the 21 DZ twin pairs were concordant for GID. Diamond and Hawk [32] reported fairly similar results. According to their Internet survey and the data known from the medical literature, two of 10 MZ female twins and 48% of the MZ male twin pairs were found to be concordant for GID, while none of the three DZ female twins and 14% of the DZ male twins were concordant. Unfortunately, it is not clear to what extent a largely Internet-recruited sample can be considered representative of the GID clinical population, and the degree of overlap with the literature here cited is unknown.

The higher concordance for GID in MZ than in DZ twins is consistent with a genetic influence on its genesis although shared and nonshared environmental factors cannot be ruled out. Indeed, from these case reports, very little is known about the "equal environments assumption," that is, the assumption that MZ twins are not treated more similarly than DZ twins in ways that might affect their gender identity [33]. The discordance for GID in five (62.5%) out of eight of the described MZ female twin pairs might have several explanations. For example, differential prenatal and postnatal environmental factors might both contribute to discordance between MZ twins [34]. In terms of parental rearing, mostly twins are treated equally, and parents usually make efforts to do so. However, Segal [18] described a totally different attitude from the mother toward her transsexual child in a MZ female twin pair, with expressing abusive behavior. It was thought that the mother's attitude was a consequence of the gender-atypical behavior of her daughter rather than a cause of GID in the transsexual daughter.

In addition, several epigenetic differences may underlie phenotypic discordance between the MZ twin pairs. In female MZ twins, skewed X inactivation in the affected twin might be an illustration of an epigenetic difference explaining phenotypic discordance [35]. A study by Fraga et al. [36] demonstrated that epigenetic differences increase during the lifetime of MZ twins, which may help to understand phenotypic differences. Genetic differences between concordant and discordant MZ twins are illustrated in a recent study by Bruder et al. [37], showing copy number variations (CNVs) in their genomes. These findings suggested that CNV analysis in phenotypically discordant MZ twins may provide a powerful tool for identifying disease predisposition loci.

In the studies on genetics and sexual orientation, a higher concordance for homosexuality has been found in MZ versus vs. DZ twins. Using family methodology, there is also evidence for genetic influences [38]. In the reviewed case studies of twins with GID, from those whose sexual orientation is known, all, with the exception of Green [25], were attracted to their biological sex and nearly 50% of the non-GID twins were also homosexual, reflecting a higher percentage than found in the general population [39]. In all the cases reported to be concordant for GID, there was also concordance for sexual orientation. A genome-wide scan of 146 families of male homo-

sexual persons has already been performed [40], but to date, no such studies have been performed in transsexual individuals.

This review shows also that systematically collected data on different topics such as physical development, childhood development, educational background, and sexual preference are lacking so that conclusions about the different etiological components are difficult to be drawn.

Conclusion

The etiology of GID is a complex process of biopsychosocial components with unexplained interactions. Twin literature on GID supports the contribution of genetic factors to the development of gender identity with a higher tendency in males than in females.

Since sample size is still limited and genotype studies are lacking, conclusions must be drawn with caution.

Therefore, detailed registers of GID twins, preferably on MZ twins discordant for GID and DZ twins are needed, to gain more decisive information about the influence of genetic vs. environmental factors in the development of GID.

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Conflict of Interest: None.

Statement of Authorship

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