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Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals

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ABSTRACT

Background. We prospectively studied outcomes of sex reassignment, potential differences between subgroups of transsexuals, and predictors of treatment course and outcome.

Method. Altogether 325 consecutive adolescent and adult applicants for sex reassignment participated: 222 started hormone treatment, 103 did not; 188 completed and 34 dropped out of treatment. Only data of the 162 adults were used to evaluate treatment. Results between subgroups were compared to determine post-operative differences. Adults and adolescents were included to study predictors of treatment course and outcome. Results were statistically analysed with logistic regression and multiple linear regression analyses.

Results. After treatment the group was no longer gender dysphoric. The vast majority functioned quite well psychologically, socially and sexually. Two non-homosexual male-to-female transsexuals expressed regrets. Post-operatively, female-to-male and homosexual transsexuals functioned better in many respects than male-to-female and non-homosexual transsexuals. Eligibility for treatment was largely based upon gender dysphoria, psychological stability, and physical appearance. Male-to-female transsexuals with more psychopathology and cross-gender symptoms in childhood, yet less gender dysphoria at application, were more likely to drop out prematurely. Non-homosexual applicants with much psychopathology and body dissatisfaction reported the worst post-operative outcomes.

Conclusions. The results substantiate previous conclusions that sex reassignment is effective. Still, clinicians need to be alert for non-homosexual male-to-females with unfavourable psychological functioning and physical appearance and inconsistent gender dysphoria reports, as these are risk factors for dropping out and poor post-operative results. If they are considered eligible, they may require additional therapeutic guidance during or even *after* treatment.

INTRODUCTION

The phenomenon of transsexualism refers to individuals who are born with the normal sexual characteristics of one sex, but have the irrefutable conviction of belonging to the other.

Nowadays, many professionals who specialize in the treatment of transsexuals regard the conviction of transsexuals as belonging to someone of the other sex as authentic and, consequently, their wish for a sex change to be justified. The recommended procedure of the Harry Benjamin International Gender Dysphoria Association (Meyer *et al.* 2001), an international professional organization regarding transsexualism, is to approach the referral for sex reassignment (SR) in two phases. In the first phase, a DSM-IV diagnosis (APA, 1994) is made. In addition, the eligibility of the patient to move on to the second phase, the Real-life

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Table 1. *Progression in the SR procedure and matching sample sizes used in analyses*

SR procedure	Diagnostic 1st phase[a] (Applicants)	Not referred for 2nd phase[b] (Non-starters)	Referred for, started, continued 2nd phase[b] (Starters)	Referred for, started, dropped out 2nd phase[b] (Drop-outs)	Referred for, completed SR surgery (Completers)	1–4 years after SR surgery (Follow-up)
MFs	220	74	146	29	117	94
FMs	105	29	76	5	71	64
Included	325	103	222	34	188	158

[a] In the first phase a DSM diagnosis is made and eligibility is assessed for starting hormone treatment and the Real-life Experience.
[b] In the second phase hormone treatment and the Real-life Experience is started.

Experience (RLE), is assessed. In this phase the applicant's ability to live in the desired role and its consequences, and the strength of the desire for SR are evaluated. If the social role change during the RLE, which is usually supported by hormonal therapy, results in a satisfactory outcome, the applicant will be referred for surgery (see Table 1).

Although SR is presently regarded as effective in treating transsexualism, the most extreme end of Gender Identity Disorder (GID) (Pfäfflin & Junge, 1992, 1998; Eldh *et al.* 1997; Cohen-Kettenis & Gooren, 1999; Rehman *et al.* 1999; Meyer *et al.* 2001; Smith *et al.* 2001, 2002; Day, 2002; Lawrence, 2003), prospective studies are needed to enhance knowledge about the benefits and limitations of SR. In spite of strict prior selection and counselling during treatment, an estimated 1–2% of those treated express regrets about SR (Pfäfflin, 1992; Pfäfflin & Junge, 1992, 1998; Kuiper & Cohen-Kettenis, 1998). Considering the invasive and irreversible treatment of SR, it is imperative to try and prevent post-operative regret. This requires the identification of predictors of regret or poor post-operative functioning. In some follow-up studies different factors are proposed as influencing the outcomes of SR negatively (e.g. Wålinder *et al.* 1978; Spengler, 1980; Lothstein, 1982; Lundström *et al.* 1984; Blanchard, 1985; Lindemalm *et al.* 1987; Blanchard *et al.* 1989; Ross & Need, 1989; Pfäfflin, 1992; Pfäfflin & Junge, 1992; Kuiper & Cohen-Kettenis, 1998; Landén *et al.* 1998). These factors lie in the area of psychological functioning, sexual orientation, age at assessment, onset age of gender dysphoria, family history and support, professional support during SR, and surgical outcomes. However, the quality of the few existing follow-up studies is rather poor given their mostly retrospective nature. Sound prospective studies are needed to identify predictors of post-operative functioning more consistently and reliably.

In the present large-scale prospective follow-up study, we investigated two separate though related topics: the outcomes of SR and the prediction of favourable or poor outcomes. Therefore, we first evaluated whether transsexuals actually improve in important areas after SR, and confirm some of the beneficial effects of SR previously established in the mostly retrospective follow-up studies (e.g. Mate-Kole *et al.* 1990; Day, 2002; Lawrence, 2003). Secondly, we studied differences between sexes [male-to-females (MFs) and female-to-males (FMs)] and subtypes (homosexuals and non-homosexuals) in various areas of functioning (e.g. gender dysphoria, body dissatisfaction, physical appearance, psychological functioning) after SR. To our knowledge, subtype differences have not yet been prospectively studied. These research questions were, however, only studied in *adult* transsexuals, because the adolescent results have been published previously (Smith *et al.* 2001, 2002). Post-operatively, feelings of regret, evaluation of treatment, satisfaction with surgical results, social and sexual functioning were evaluated.

The other topic concerned predictors of the course and outcomes of SR. We examined which factors clinicians based their referral on for SR. The factors were age, sex, sexual orientation, onset age of gender dysphoria, gender dysphoria in childhood and at application, social support, body dissatisfaction, physical appearance and psychological functioning. Finally, we examined which factors predicted treatment course (i.e. dropping out), post-operative functioning, and treatment satisfaction.

METHOD

Subjects

A total of 325 consecutive adolescents and adults, who applied for SR at VU University Medical Centre in Amsterdam (VUmc) or University Medical Centre Utrecht (UMCU), participated. Of these, 222 (146 MFs, 76 FMs) started hormone treatment: the 'starter' group. Twenty-nine MFs and 5 FMs stopped hormone treatment: the 'drop-out' group. The group who completed SR consisted of 188 patients (117 MFs, 71 FMs): the 'completer' group. The group who never started hormone treatment consisted of 103 patients (74 MFs, 29 FMs). Pre-test data from this 'no-starter' group varied from 89 to 103. At follow-up, some participants had moved abroad, while others were untraceable, which resulted in 158 (94 MFs, 64 FMs) participants who were interviewed. Follow-up data ranged between 136 and 158 because not all participants were willing or able to take part in both an interview and a questionnaire session (Table 1).

To examine the outcome issue we used data of 162 adults. Pre-test data were obtained from all adults (104 MFs, 58 FMs; 94 homosexuals, 68 non-homosexuals). Follow-up interview data were gathered from 126 adults (i.e. 78%; 77 MFs, 49 FMs; 71 homosexuals, 55 non-homosexuals). Questionnaire data for different measures fluctuated from 101 to 126. Since SR patients do not undergo all possible operations, data on breast augmentation were gathered from 52 MFs (21 homosexuals, 31 non-homosexuals), and on metaidoioplasty or phalloplasty from 10 FMs (4 homosexuals, 6 non-homosexuals). Scores on the Appraisal of Appearance Inventory were obtained from 57 adults.

Instruments

Biographical data

The Biographical Questionnaire for Transsexuals, a semi-structured interview, contains 211 items on variables, such as cross-gender feelings and behaviour, social and sexual contacts (Verschoor & Poortinga, 1988; Doorn *et al.* 1994). The following items were used: sex (MF or FM), onset age of cross-gender feelings, childhood GID symptoms (11 items, see below), age at application, and sexual orientation. Concerning this last item, participants who exclusively reported a homosexual preference (MFs sexually attracted to biological males; FMs to biological females) were included in the homosexual group. Participants with an asexual, heterosexual, and/or bisexual preference were included in the non-homosexual group. Age at the start of hormone therapy and surgery were obtained from medical files.

The GID in Childhood Scale was constructed from the Biographical Questionnaire for Transsexuals (Verschoor & Poortinga, 1988; Doorn *et al.* 1994) to measure the self-reported presence of GID symptoms in childhood. There are 11 items (Cronbach's $\alpha = 0{\cdot}81$) concerning the strong wish to be of the opposite sex in early childhood, cross-gender appearance of the child, cross-dressing, play and peer preference, and cross-gender behaviour. Because of differences in the numbers and types (i.e. quantitative *versus* qualitative) of response categories, answers were dichotomized, resulting in a total score ranging between 0 and 11, with the higher scores indicating more childhood GID symptoms.

The Social Support Scale. This scale has 10 items enquiring about the patient's eight closest acquaintances (Van Tilburg, 1988). Scalability coefficient H, calculated by means of a Mokken analysis (Molenaar, 1982) and calculated for all relationships together, was 0·38. Sumscores range from 0 to 160, with the higher scores indicating more support.

Gender dysphoria. This was measured with the Utrecht Gender Dysphoria Scale, containing 12 items on which the subject rated agreement on a 5-point scale. Scores range from 12 to 60. Higher scores indicate more gender dysphoria (Cohen-Kettenis & van Goozen, 1997).

Body dissatisfaction. A Body Image Scale (Lindgren & Pauly, 1975), adapted for a Dutch sample (Kuiper, 1991), was used. There are 30 items divided into three subscales: primary and secondary sex characteristics, and neutral body parts, with higher scores representing more dissatisfaction.

Physical appearance. On the Appraisal of Appearance Inventory three independent observers

(the diagnostician, a nurse, the researcher) rated the subject's appearance on 14 five-point scales of gender compatibility. The characteristics were: hair, facial hair, larynx, voice, figure, height, skin, hands/feet, muscularity, chin, nose, jaw, speech, and gestures/movement. Lower scores reflect a better appearance in matching the new gender. Intra-class correlation coefficients between observers for each of the 14 items ranged from 0·68 to 0·79.

Psychological functioning. The Dutch Short MMPI (Luteyn *et al.* 1980) contains 83 items measuring Negativism, Somatization, Shyness, Psychopathology, and Extroversion. Higher scores indicate more dysfunction on the first four scales but less on Extroversion.

The Dutch version of the Symptom Check List (Derogatis *et al.* 1973; Arrindell & Ettema, 1986) has 90 items enquiring about recent complaints. Subscales are: Agoraphobia, Anxiety, Depression, Somatization, Obsession/Compulsion, Suspicion, Hostility, and Sleeping problems. The total score for Psychoneuroticism ranges from 90 to 450. Higher scores indicate more psychological instability.

Treatment evaluation and post-treatment functioning. To evaluate post-operative functioning 13 items measured post-operative functioning and (dis)satisfaction (e.g. with questions about treatment, regret, social and sexual functioning, and social experiences) (Doorn *et al.* 1996). Patients also completed a questionnaire about the functioning of vagina/penis and breasts (augmentation or removal), and surgical satisfaction (Cohen-Kettenis & van Goozen, 1997).

Post-operative Functioning Scale. Twenty-one items (Cronbach's $\alpha = 0{\cdot}87$) measured post-operative functioning and satisfaction with SR (Doorn *et al.* 1996) and resulted in a single score with higher scores reflecting worse functioning and more dissatisfaction. (See Journal's website for Appendix with specific items.)

Procedure

The GID in Childhood Scale and the Social Support Scale were used at pre-test. Gender dysphoria, body dissatisfaction, physical appearance and psychological functioning were assessed before and after SR to measure change. The remaining instruments were administered at follow-up.

Except for the GID in Childhood Scale, the Social Support Scale, and the Post-operative Functioning Scale, all instruments were used to examine the issue of outcome. All instruments administered at pre-test were used to investigate predictors of eligibility for and drop-outs of SR. Follow-up data of the 'completer' group were used to develop the Post-operative Functioning Scale, investigating predictors of outcomes of SR.

Pre-test data were gathered during the first diagnostic procedure after the first interview. Follow-up data were gathered at least 1 year after surgery. Sessions took between 2 and 3 hours. The Ethics Committees of the UMCU and VUmc approved the study.

Statistical analyses

Changes over time in treated adults were analysed with univariate paired-sample *t* tests, applying the Bonferroni correction [dividing the number of tests (19) by 5%] and using a significance level of 0·003 for these results (Table 2). Post-operative Sex (MF *v.* FM) and Subtype (homosexual *v.* non-homosexual) differences were studied with univariate or multivariate analyses of variance [(M)ANOVAs] (Table 3). Nominal or ordinal data were analysed per item with the χ^2 test or Mann–Whitney *U* test respectively.

To identify which factors predicted eligibility for hormone treatment and premature drop-out, logistic regression analyses were performed with group membership as the criterion variable (no-starter and starter, completer and drop-out respectively). Since we had no *a priori* hypotheses about group prediction, the first (stepwise) analysis included all 17 factors: age, sex, sexual orientation, onset age of gender dysphoria, GID symptoms in childhood, gender dysphoria at assessment, social support, body dissatisfaction (3 scales), physical appearance, and psychological functioning (2 tests: 1 and 5 scales). Next, we conducted a (simultaneous) logistic regression analysis using the significant predictors. In case of unequal sample sizes cut values were reset to achieve the highest sensitivity and specificity.

Table 2. *Pre-test and post-test scores of the adult follow-up sample*

	Pre-test		Post-test		Paired	Two-tailed
	Mean	S.D.	Mean	S.D.	*t*	*p*
Gender dysphoria	54·3	7·1	14·8	3·0	49·5	<0·001
Physical appearance	44·7	9·6	33·8	10·2	10·9	<0·001
Body dissatisfaction						
Primary sex characteristics	18·1	2·7	6·6	3·2	25·5	<0·001
Secondary sex characteristics	34·8	6·9	25·2	6·8	13·7	<0·001
Neutral body characteristics	46·8	9·6	36·5	8·0	11·3	<0·001
Psychological functioning						
Negativism	22·6	7·7	17·1	7·8	6·8	<0·001
Somatization	9·1	7·6	6·6	5·3	3·1	0·003
Shyness	14·7	9·3	10·0	7·3	5·8	<0·001
Psychopathology	3·2	3·0	2·4	2·6	2·8	0·006
Extraversion	13·8	6·5	15·5	5·6	2·9	0·005
Psychoneuroticism	143·0	40·7	120·3	31·4	5·5	<0·001
Anxiety	15·2	5·3	13·0	4·5	4·0	<0·001
Agoraphobia	9·4	3·6	8·6	3·2	2·1	0·040
Depression	29·3	11·3	22·5	8·4	5·3	<0·001
Somatization	18·2	7·0	16·7	4·4	2·3	0·024
Inadequacy	15·8	5·8	13·5	4·5	4·1	<0·001
Sensitivity	28·2	9·1	24·4	6·5	4·4	<0·001
Hostility	7·8	2·4	7·4	2·1	1·5	0·147
Sleeping problems	5·4	2·9	4·6	2·2	2·3	0·024

Table 3. *Differences between the adult sexes and subtypes at follow-up*

	MFs [mean (S.D.)]	FMs [mean (S.D.)]	HOs [mean (S.D.)]	NHs [mean (S.D.)]	Sex *F*(*p*)	Subtype *F*(*p*)
Age	38·6 (12·3)	29·6 (8·3)	31·7 (10·7)	39·6 (11·7)	16·0 (<0·001)	6·4 (0·01)
Gender dysphoria	15·4 (3·1)	13·9 (2·8)			6·6 (0·01)	1·3 (0·27)
Physical appearance	38·2 (9·3)	26·0 (6·9)			28·3 (<0·001)	2·0 (0·16)
Body dissatisfaction					3·1 (0·03)	1·2 (0·33)
Primary sex characteristics	6·0 (2·2)	7·6 (4·2)			7·0 (0·01)	
Dutch Short MMPI					2·1 (0·07)	2·2 (0·06)
Somatization			5·6 (4·8)	7·9 (5·5)		4·0 (0·047)
Extraversion	13·8 (5·4)	18·0 (5·0)	17·1 (5·3)	13·6 (5·4)	9·2 (0·003)	6·9 (0·01)
Symptom Check List					2·4 (0·02)	2·6 (0·009)
Depression	24·6 (9·8)	19·7 (4·7)			6·5 (0·01)	
Somatization			15·2 (3·7)	18·2 (4·7)		11·0 (0·001)
Sleeping problems			4·3 (2·0)	5·0 (2·3)		5·2 (0·02)

MFs, male-to-female transsexuals; FMs, female-to-male transsexuals; HOs, homosexual transsexuals; HNs, non-homosexual transsexuals.

Predictors of post-operative functioning were identified with a multiple linear regression analysis with the Post-operative Functioning Scale as the dependent variable. Seven of the 17 factors were relatively independent and included as predictors in the first (stepwise) analysis: sex, sexual orientation, physical appearance, secondary sex characteristics, extroversion, psychopathology, and psychoneuroticism. Patients with missing values were deleted listwise. Significant predictors were analysed in a second (simultaneous) multiple linear regression.

RESULTS

Outcomes of the adult transsexuals

Biographical data

The mean age of the transsexuals who completed SR was 30·9 years (range 17·7–68·1 years) at application and 35·2 years (range 21·3–71·9 years) at follow-up. Cross-sex hormone treatment started at the mean age of 31·6 years (range 17·9–68·3 years). The average duration between starting hormone treatment and surgery was 20·4 months (range 12–73 months). The

average duration between surgery and follow-up was 21·3 months (range 12–47 months).

At follow-up, main effects for Sex and Subtype were found for age. FMs and homosexuals were younger than MFs and non-homosexuals respectively (Table 3).

At follow-up 5 subjects (4·9%) were students, 38 (36·9%) had jobs, 3 (1·9%) had retired, and 58 (56·3%) were unemployed. The majority ($n=59$) lived independently (56·2%), 27 subjects (25·7%) each lived together with another adult with or without children, 9 (8·6%) were living with (one of) their parents, 2 (1·9%) were head of an incomplete family, and the remaining 8 (7·6%) lived in a guest house or boarding house.

Gender dysphoria. At follow-up there was less gender dysphoria; the low post-test scores represent a virtual absence of gender dysphoria after SR (Table 2). A main effect of Sex was found with FMs feeling less gender dysphoric. No Subtype difference in post-operative gender dysphoria was found (Table 3).

Body dissatisfaction. The majority ($n=98$, 91·6%) were (very) satisfied with their overall appearance; 9 (8·4%) were neutral; no one was dissatisfied. Satisfaction with primary sex, secondary sex, and neutral characteristics had increased after SR (Table 2). A MANOVA showed that FMs were more dissatisfied with their primary sex characteristics at post-test than MFs. No Subtype differences were found (Table 3).

Physical appearance. The group scored lower on the Appraisal of Appearance Inventory at post-test (Table 2), indicating that their appearance better matched the new gender. The physical appearance of FMs was more compatible than that of the MFs, but there was no Subtype difference (Table 3).

Psychological functioning. At follow-up the group functioned psychologically better. Scores on Negativism and Shyness had improved. Scores on Somatization, Psychopathology, and Extroversion showed a tendency towards improvement ($p \leqslant 0{\cdot}006$). In general, follow-up scores indicated fewer psychological problems (Table 2). Comparing pre- and post-test group means with Dutch normative data, most scores remained within the average range at follow-up, although Extroversion scores were below average. Somatization scores were high at pre-test.

The mean Psychoneuroticism score was lower after SR [see Table 2 for lower scores on four of the eight subscales ($p<0{\cdot}001$)]. These scores can only be compared with Dutch normative data for males and females separately. Both the MF ($p=0{\cdot}001$) and FM ($p<0{\cdot}001$) group showed improvement in mean scores. The MFs went from above average at pre-test (mean = 143, S.D. = 38·0) to average at post-test (mean = 123, S.D. = 36·0); the FMs went from high (mean = 143, S.D. = 44·8) to above average at follow-up (mean = 116, S.D. = 22·8).

The Dutch Short MMPI showed a marginally significant Sex effect, with FMs being more extrovert. The Sex effect on the Symptom Check List showed MFs as being more depressed than FMs (Table 3). There was also a marginally significant Subtype effect on the Dutch Short MMPI, with homosexuals scoring more favourably on Somatization and Extroversion. The Symptom Check List showed a Subtype effect with homosexuals scoring lower on Sleeping Problems and Somatization (Table 3).

Thus, although the group as a whole functioned psychologically rather well at application, their psychological stability had improved after SR. In addition, and post-operatively, FMs and homosexuals functioned psychologically better than MFs and non-homosexuals respectively.

Treatment evaluation and post-treatment functioning. The vast majority (98·4%) expressed no regrets about SR. One non-homosexual MF had experienced such strong regrets during and after treatment that she would not elect for SR again, if given a second opportunity. In contrast, a second non-homosexual MF, who expressed some regrets, reported she would choose SR again. Five non-homosexuals (4 MFs, 1 FM) reported some regrets during treatment only, but expressed no desire or intention to resume their original gender role. No differences were found between the sexes in reported regret during ($Z=-1{\cdot}4$, $p=0{\cdot}2$) or after SR ($Z=-1{\cdot}1$, $p=0{\cdot}3$). During treatment more non-homosexuals reported feelings of regret ($Z=-3{\cdot}1$, $p=0{\cdot}002$).

Social life and social contacts. The majority ($n=90$, 89·1%) felt accepted by most people, 8 (7·9%) by some, 3 (3%) by no one. Altogether 84 individuals (83·2%) felt supported in their new gender role by (almost) everyone they knew, whereas 11 (10·9%) felt supported by some people. Despite the fact that 6 subjects (5·9%) did not feel supported, they were able to rely on some individuals during difficult times. Four subjects (3·9%) had no one to turn to when times got hard. Still, the vast majority (99, 96·1%) could rely on at least some others during difficult times. In total, 18 individuals (17·3%) sometimes felt they were being laughed at, 2 (1·9%) had experienced being ridiculed by strangers; 84 (80·8%) had never experienced any such adverse reactions. Over 98% ($n=102$) felt they were completely taken seriously by most people. Two (1·9%) only felt taken seriously by a few close friends. No one reported not being taken seriously by anyone.

MFs and FMs felt equally accepted ($Z=-0·8$, $p=0·4$). However, FMs had more support in the new gender role ($Z=-2·5$, $p=0·01$) and were more able to rely on significant others during difficult times ($Z=-2·2$, $p=0·03$). Although MFs were more often laughed at or ridiculed ($Z=-3·5$, $p<0·001$), they reported feeling taken equally seriously by (almost) all people ($Z=-1·7$, $p=0·08$). Homosexuals felt more supported ($Z=-2·0$, $p=0·04$) and taken more seriously than non-homosexuals ($Z=-2·5$, $p=0·01$).

Relationships and sexuality. The majority ($n=46$, 88·5%) of the 50 subjects who had a steady sexual partner were satisfied with their sex life, 3 (5·8%) expressed a neutral view, and 3 (5·8%) were dissatisfied. Of the 84 subjects (82·4% of the follow-up sample) who were sexually active, the majority (53, 63·1%) achieved orgasm always or regularly, 16 (19%) sometimes, and 15 (17·9%) never.

A larger percentage ($\chi^2=4·2$, $p=0·04$) reported a homosexual (94, 58·0%) than a non-homosexual orientation (68, 42·0%). Within the FMs a greater proportion ($\chi^2=5·9$, $p=0·015$) had a homosexual orientation (70·7%) than the MFs (51·0%). More of the sexually active FMs (81·6%) than of the MFs (42·1%) achieved orgasm always or regularly ($Z=-2·4$, $p=0·01$). Yet, both sexes reported equal satisfaction with their sex life ($Z=-0·6$, $p=0·5$). No Subtype differences were found.

Satisfaction with surgery. For FMs breast removal is emotionally the most important surgery. They are advised to postpone metaidoioplasty (transformation of the hypertrophic clitoris into a micropenis) or phalloplasty in view of the fact that surgical techniques are steadily improving. Eleven FMs (28·9%) were satisfied with their breast removal, 5 (13·2%) were dissatisfied due to the visibility of the scars, and 22 (57·9%) were not completely satisfied. Four FMs were satisfied with their metaidoioplasty or phalloplasty. One FM was dissatisfied because of urinary problems, while four were not completely satisfied.

For the MFs vaginoplasty is the most important surgical intervention. The majority of MFs (47, 70·1%) were satisfied; 15 (22·4%) were not completely satisfied, mostly because they considered their vagina not deep or feminine enough. Five MFs (7·5%) were dissatisfied, because they were unable to achieve sexual arousal or orgasm, or because corrective surgery was needed. The majority (34, 65·4%) were satisfied with their breast augmentation; 15 (28·8%) were not completely satisfied, and three felt uneasy about their breasts being too far apart.

Predictors of the course and outcomes of adolescent and adult transsexuals

Prediction of eligibility criteria

Eligibility for SR was largely based upon the factors gender dysphoria, psychoneuroticism, and physical appearance. For the precise weight of each predictor variable and the constant in this equation model, see Table 4. Stronger gender dysphoria (higher scores), more psychological stability (lower scores on Psychoneuroticism), and a feminine look for MFs and a masculine look for FMs (lower scores on physical appearance), increased the probability of the clinician referring the applicant to start hormone treatment. With these three predictor variables 78% of the applicants were correctly assigned to the 'no-starter' (52%) or the 'starter' (88%) group (cut value = 0·63).

Table 4. *B coefficients and constants of the factors predicting group membership*

	Starter group		Drop-out group	
Predictor variables	*B*	*p* value	*B*	*p* value
Sex			−1·82	0·006
Sexual orientation				
Onset age of gender dysphoria				
Age at application				
GID symptoms in childhood			0·18	0·026
Gender dysphoria	0·08	<0·001	−0·05	0·030
Social support				
Primary sex characteristics				
Secondary sex characteristics				
Neutral sex characteristics				
Physical appearance	−0·05	0·003		
Psychoneuroticism	−0·01	<0·001		
Negativism				
Somatization				
Shyness				
Psychopathology			0·12	0·024
Extroversion				
Constant	1·00	0·442	−0·04	0·972

Prediction of the course of treatment

The probability that a transsexual discontinued hormone treatment depended on sex, psychopathology, childhood GID symptoms, and gender dysphoria (Table 4). A negative coefficient means that a factor contributes negatively to the probability of being a drop-out. The relatively high beta value of the factor sex reflects being a FM. Thus, the combination of being a MF with more psychopathology and childhood GID symptoms, yet less gender dysphoria at assessment, increased the likelihood of premature drop-out. Together these four predictors correctly assigned 68% of the transsexuals to the 'completer' (68%) or the 'drop-out' (69%) group (cut value = 0·15).

Prediction of post-operative functioning

The level of post-operative functioning could be predicted by the patient's sexual orientation, psychological stability, and dissatisfaction with secondary sex characteristics at assessment. The beta weights (see Beta column in Table 5) show the relative importance of the variables contributing to the predictability of the quality of post-operative functioning ($R^2 = 0{\cdot}17$). As higher scores on the Post-operative Functioning Scale reflect more dysfunction and dissatisfaction, the predicted score of an applicant on this scale increased with a non-homosexual orientation, more psychopathology and dissatisfaction with secondary sex characteristics at assessment.

Table 5. *Factors predicting post-operative functioning*

Model	*B*	Beta	*p* value
Sexual orientation	−3·70	−0·24	0·002
Psychopathology	0·43	0·17	0·028
Dissatisfaction secondary sex characteristics	0·31	0·28	<0·001
Constant	16·80		<0·001

DISCUSSION

One aim of this prospective study was to investigate which areas of functioning improve as a consequence of SR. The main symptom for which the patients had requested treatment, gender dysphoria, had decreased to such a degree that it had disappeared. Satisfaction of the patients with their sex characteristics had improved to the point of content, confirming previous results (Green & Fleming, 1990; Pfäfflin & Junge, 1998), and according to observers, their appearance better matched the new gender. Psychological functioning had also improved (see Mate-Kole *et al.* 1990). Thus, it seems safe to conclude that the transsexuals had improved in important areas of functioning and that 1–4 years after surgery, SR appeared therapeutic and beneficial. Furthermore, the vast majority expressed no regrets about their SR.

Post-operative evaluation showed that the majority functioned quite well socially. A small minority, however, lacked support and acceptance, and were ridiculed. Surprisingly, 98% felt taken seriously. This somewhat rose-coloured view may be explained by the fact that the social support received and the relief about the new situation may have put adverse reactions into perspective, whereas disappointing experiences may have been played down to reduce cognitive dissonance after undergoing such invasive and irreversible interventions.

At follow-up, the majority were content with their sex life, and those who were sexually active, reported achieving orgasm. This has been reported previously (e.g. Rakic *et al.* 1996; Rehman *et al.* 1999), but in MFs the capacity

for orgasm has been reported to decrease post-surgically (Lief & Hubschman, 1993).

The findings support the conclusion that after SR most transsexuals functioned socially and sexually well. One MF expressed deep regrets. She indicated that professional guidance regarding adverse consequences (i.e. intolerance of society, family and her own children), would have made the transition more endurable. This stresses the need for good aftercare.

Comparing the sexes, the FMs showed better results, supporting the results of earlier studies (see Introduction). This might be due to their more convincing gender role behaviour and looks and their 'type' of transsexualism, implying an earlier age at application. More FMs than MFs were capable of achieving orgasm. This can be attributed to hormonal effects (van Goozen *et al.* 1995) or to the fact that most FMs lived with their enlarged clitoris. Then again, it may also portray different meanings of sexuality in males and females, since both sexes reported equal satisfaction with their sex life. Contrasting most of the more favourable FM findings are the greater reported satisfaction of the MFs with surgical results. This is understandable given that most FMs did not (yet) have a penis. For the FMs the ability to live in the new gender and sexual role clearly awaits the advancement of surgical techniques.

With respect to subtype differences, homosexuals were younger and functioned psychologically better than non-homosexuals. No differences were found in gender dysphoria, body dissatisfaction, or physical appearance. Only non-homosexuals reported some regrets *during* treatment, and two during *and* after SR, which they all related to a lack of acceptance and support from others. The better functioning of homosexuals may also be explained by their sexual orientation. Subtype differences could reflect different aetiological backgrounds. Because the onset age and age at application have been found to be earlier in homosexuals, it is likely that non-homosexuals encounter more problems in life before applying for SR. Also, post-surgically, 'homosexuals' will have opposite gender partners, thus forming heterosexual couples. This still is socially more acceptable.

The less favourable outcomes of the non-homosexuals carry significant implications for clinical practice. If considered eligible for SR, non-homosexuals should be able to receive additional guidance in coping with adverse consequences, such as a more troubled psychological functioning, or a more critical environment.

In conclusion, our data substantiate findings from mostly retrospective follow-up studies that SR is effective. Some individuals probably need a more thorough diagnostic procedure and more therapeutic support, sometimes even after treatment, than is currently the case. For most transsexuals in this study, the strict eligibility criteria and professional guidance as currently provided appears to be sufficient, as reflected by the overall favourable outcomes of SR. However, alleviation of the gender problem is not equivalent with an easy life. Apparently, clinicians need to be alert for signs that a transsexual applicant will not be able to cope with adversities during treatment.

Another goal was to identify predictors of the course and outcomes of SR. We found that clinicians assessed applicants to be eligible for hormone treatment when they were more gender dysphoric, psychologically more stable, and when the physical appearance better matched the new gender role. Given the nature of the problem, it is not surprising that strong gender dysphoria was one of the main predictors. Since an unfavourable physical appearance could be a risk factor for post-operative regret (Wålinder *et al.* 1978), it is interesting to observe that the clinicians also took this factor into account when deciding upon referral. Furthermore, clinicians greatly valued the applicant's psychological functioning (see also Kuiper & Cohen-Kettenis, 1998). These factors predicted 88% of the starter group. Clearly, clinicians must have had other reasons for referring the remaining 12%, the most likely factor being the diagnosis. They might also have appraised certain risk factors as relatively harmless in view of existing protective factors (e.g. strong social support, adequate coping skills).

We found transsexuals to be more at risk for dropping out of treatment when they were MFs, showed more psychopathology, more GID symptoms in childhood, yet less gender dysphoria at application. The greater vulnerability of MFs to drop out is understandable given that FMs fare better post-operatively.

Unfortunately, our data do not permit us to distinguish during treatment between the impact of psychopathology, on the one hand, and of interactive effects of psychopathology with external forces, on the other. We cannot rule out the possibility that it is not psychopathology *per se* that increases the probability to drop out, but rather a combination of psychological vulnerability and personal circumstances, such as abandonment by a partner. One should also bear in mind that the drop-outs stopped hormone treatment during our data collection; it is possible, however, that they will reapply later in life.

Our finding of an association between more childhood GID symptoms and greater drop out seems puzzling. It is in contrast with the literature on SR risk factors and clinically counter-intuitive. Early gender dysphoria has been associated with early-onset transsexualism and favourable SR outcome (see Lothstein, 1982; Blanchard, 1985; Lindemalm *et al.* 1987; Blanchard *et al.* 1989; Pfäfflin, 1992). Here, it is the combination of factors that is crucial. Still, the contradicting presence of more gender dysphoria in childhood but less at application should alert the clinician when assessing eligibility. This inconsistency may reflect confusion about development, an (unconscious) exaggeration of history if current feelings are not clear-cut, or a conscious effort to mislead the clinician.

Finally, we investigated which assessment factors predicted post-operative functioning. It is important to bear in mind that we applied a continuous scale from good to bad, as opposed to the dichotomy 'no regret'–'regret', because hardly any transsexuals reported regret. A non-homosexual orientation, with more psychopathology and dissatisfaction with secondary sex characteristics predicted unfavourable post-operative functioning. The finding that non-homosexuals and those with more psychological instability are at risk for unfavourable functioning and more dissatisfaction after SR fits with earlier studies (see Introduction; Blanchard *et al.* 1989; Landén *et al.* 1998). We found that two non-homosexuals expressed regret about SR. Finally, dissatisfaction with appearance predicted poor post-operative functioning, either because it directly and adversely affected psychological stability or mood, or it indirectly affected the way they were socially treated (or a combination of both).

Taking all the findings into account, our 'sample' of clinicians appropriately assessed some risk factors that predict the course and outcomes of SR, yet they underestimated others. They particularly recognized the impact of the applicant's psychological functioning and physical appearance on post-operative functioning. However, clinicians might want to take special notice of MFs who report inconsistencies in past and present gender dysphoria, in the presence of psychopathology, and of non-homosexuals with strong dissatisfaction about their appearance and clear psychopathology. They may benefit from additional guidance after SR, while adjusting to their new lives and coping with unexpected or adverse consequences.

The results of this study subscribe to the significance of some of the risk factors described in the literature with more conclusive data. Furthermore, factors were found that could assist clinicians in identifying individuals who might be at risk for poor outcome.

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DECLARATION OF INTEREST

None.

NOTE

An Appendix accompanies this paper on the Journal's website (http//journals.cambridge.org).

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Gender-Affirming Mastectomy Trends and Surgical Outcomes in Adolescents

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Background: There are more than 150,000 transgender adolescents in the United States, yet research on outcomes after gender-affirming mastectomy in this age group is limited. We evaluated gender-affirming mastectomy incidence and postoperative complications, including regret, in adolescents within our integrated health care system.

Methods: Gender-affirming mastectomies performed from January 1, 2013, to July 31, 2020, in adolescents 12 to 17 years of age at the time of referral were identified. The incidence of gender-affirming mastectomy was calculated by dividing the number of patients undergoing these procedures by the number of adolescents assigned female at birth aged 12 to 17 years within our system at the beginning of each year and amount of follow-up time within that year. Demographic information, clinical characteristics (comorbidities, mental health history, testosterone use), surgical technique, and complications, including mention of regret, of patients who underwent surgery were summarized. Patients with and without complications were compared to evaluate for differences in demographic or clinical characteristics using χ^2 tests.

Results: The incidence of gender-affirming mastectomy increased 13-fold (3.7–47.7 per 100,000 person-years) during the study period. Of the 209 patients who underwent surgery, the median age at referral was 16 years (range, 12–17 years) and the most common technique was double incision (85%). For patients with greater than 1-year follow-up (n = 137; 65.6%), at least one complication was found in 7.3% (n = 10), which included hematoma (3.6%), infection (2.9%), hypertrophic scars requiring steroid injection (2.9%), seroma (0.7%), and suture granuloma (0.7%); 10.9% underwent revision (n = 15). There were no statistically significant differences in patient demographics and clinical characteristics between those with and without complications ($P > 0.05$). Two patients (0.95%) had documented postoperative regret, but neither underwent reversal surgery at follow-up of 3 and 7 years postoperatively.

Conclusions: Between 2013 and 2020, we observed a marked increase in gender-affirming mastectomies in adolescents. The prevalence of surgical complications was low, and of more than 200 adolescents who underwent surgery, only 2 expressed regret, neither of which underwent a reversal operation. Our study provides useful and positive guidance for adolescent patients, their families, and providers regarding favorable outcomes with gender-affirming mastectomy.

Key Words: gender affirming, mastectomy, adolescents, complications, regret, revisions, top surgery, incidence

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In a 2017 demographic survey, more than 150,000 adolescents (0.7% of youth) aged 13 to 17 years identified as transgender.[1] Many professional organizations currently provide guidelines and support for gender-affirming health care based on existing scientific evidence.[2] These organizations include the World Professional Association for Transgender Health,[3] American Medical Association,[4] Endocrine Society,[5] American Academy of Pediatrics,[6] American Psychiatric Association,[7] American Psychological Association,[8] Society for Adolescent Health and Medicine,[9] and American Academy of Family Physicians.[10] Despite the growing scientific evidence and support by trans-competent medical experts, there has been a recent wave of state legislation seeking to criminalize health care for transgender adolescents.[11]

Gender-affirming mastectomy, also known as "top surgery," is the most prevalent surgery requested when considering all transgender adolescents,[12] whereas "bottom surgery," which affects genitalia and fertility, is relatively more complex and mostly performed after age 18 years. For many transgender adolescents, hormonal therapy and mental health evaluations may be the first steps in their treatment. In a study of adolescents at our center by Handler et al,[12] referrals consisted of requests for cross-sex hormones and/or blockers (34%), gender-affirming surgery (32%), and mental health (27%). Indeed, transmasculine adolescents who start treatment with puberty suppression and/or mental health support may subsequently request surgery at a later time if gender dysphoria persists, as is the case when the blockers are initiated after there has already been some breast development. However, many transgender individuals (including transgender-nonconforming persons, whom we will collectively refer as "transgender") lack affordable care and access to trans-competent gender-affirmative health care.[13–15] The barriers to their health care, such as state legislation, access to transgender health care, limited access to insurance, and difficulty with insurance approval leading to increased costs, are numerous and complicated.[15–17] Transgender adolescents suffer from mental health issues of depression, anxiety, and suicidal ideation.[18–20] They often have poorer health outcomes that stem from factors such as lack of family and community support, homelessness, poverty, discrimination, and negative health care experiences.[21–23] One study reported that 51% of transmasculine adults bind their chest daily despite 97% who experience back pain, chest pain, skin infection, and even rib fractures.[24] Even when hormonal therapy and chest binding are available, gender dysphoria can still lead to self-harm in adolescents.[25]

Compared with adults, research on gender-affirming surgery in adolescents is more limited. The incidence of referrals or requests for gender-affirming mastectomy in adolescents has risen exponentially over the past decade.[12,26,27] Although studies have evaluated the increase in gender-affirming surgery in adults,[28,29] we know of none that report the incidence of gender-affirming mastectomy in adolescents. Similarly, complications of gender-affirming mastectomy have been described in adults,[30–32] whereas studies in adolescents are limited to self-reported outcomes.[33,34] A few small case series indicated that adolescents who underwent gender-affirming surgeries, including mastectomy, have improvement in their gender dysphoria, which resulted in improved psychological well-being comparable with that of the general population.[33–38] We sought to confirm our favorable clinical experience and hypothesized that the incidence of gender-affirming mastectomies

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in our adolescent population increased over time and that the prevalence of postoperative complications, including regret, was low.

METHODS

We conducted a retrospective cohort study of adolescents who underwent gender-affirming mastectomy within Kaiser Permanente Northern California (KPNC), a large integrated health care system. This study was approved, and informed consent was waived by the Institutional Review Board at KPNC. Clinicians at KPNC provide care in accordance with the World Professional Association for Transgender Health guidelines,[3] which state that gender-affirming mastectomy may be advised for patients younger than 18 years preferably after living in the desired gender role for at least 1 year without hormone therapy as an absolute requirement. Adolescents with gender dysphoria can be referred to the KPNC Multi-specialty Transitions (MST) Department by their pediatrician, endocrinologist, therapist, parents, or self, if 13 years or older. The MST Department comprises a multidisciplinary team of gender specialists in the fields of primary care, mental health, nursing, social work, gynecology, and surgical specialties. Transgender patients are tracked and followed through the MST Department.

Puberty suppression with hormones is complex and is managed through a multidisciplinary pediatric clinic for transgender care within the MST Department: The Proud Clinic. Patients seeking pubertal blockers or hormones are evaluated and treated by this multidisciplinary clinic. If gender dysphoria persists after puberty blockers and/or hormone therapy, adolescent patients seeking gender-affirming chest surgery are triaged and scheduled for an evaluation with a gender therapist who is a licensed mental health provider (psychologist, marriage and family therapist, or clinical social worker) with a specialization in gender health. One of the roles of the gender therapist is to assess the patient for clinically significant gender dysphoria. The therapist works with the family to develop an understanding and acceptance of the youth's gender identity and helps facilitate family communication to enable appropriate informed consent for treatment. They discuss treatment goals and assess patient and family readiness for a referral to a plastic surgeon. During the plastic surgery consultation, both the adolescent and legal guardian meet with the surgeon and readiness for surgery is determined. Surgical techniques are explained, and informed consent is thoroughly reviewed.

We identified all patients younger than 18 years at the time of referral who underwent gender-affirming mastectomy from January 1, 2013, to July 31, 2020, using our institutional database in the MST department. Demographic and clinical characteristics were extracted from the electronic health record (EHR; Epic, Verona, Wisconsin). Demographic variables included age at the time of referral, gender identity (ie, male, nonbinary, other), and race/ethnicity. Clinical variables at the time of surgery included body mass index (BMI), American Society of Anesthesiologists (ASA) physical status classification, mental health history (depression, anxiety, and eating disorder), and social history (tobacco, alcohol, and drug use). Because smoking cessation was a requirement before surgery, tobacco use was classified as "no" or "quit." Testosterone use within 30 days before and after surgery was determined from the medication list in the EHR. All surgeries were performed on an outpatient basis by KPNC plastic surgeons. Operative notes were reviewed, and surgical techniques were categorized into 4 types: double incision, keyhole/infra-areolar, circumareolar/periareolar, and buttonhole.[39] The double-incision technique is ideal for candidates who present with large breast volume, skin excess, and/or poor skin elasticity, and involves elliptical excision of skin excess above the inframammary crease, wide exposure for removal of breast tissue, and nipple-areolar skin graft. In contrast, the keyhole/infra-areolar technique with minimal incisions is suitable for candidates with small breast volumes, good skin elasticity, and no skin excess. It uses a semicircular infra-areolar incision with no skin removal, preserving a small amount of breast tissue deep to the nipple-areolar complex; tissue is removed using liposuction and direct excision with assistance of a lighted retractor. Also suitable for smaller breast volume candidates, the circumareolar/periareolar technique uses 2 concentric, circular incisions through which breast tissue may be removed, and some skin excess may be reduced. The buttonhole technique involves incision design that is similar to the double-incision technique, but the nipple-areolar complex is preserved on an inferior dermal pedicle. The pedicle size must be small in relation to the chest size to avoid chest fullness.

Outcomes included the incidence of gender-affirming mastectomy and the prevalence of complications after it. Surgical complications and revisions were evaluated through chart review. Because most plastic surgeons at our institution offer major revisions 1 year after surgery, we only included patients who had follow-up of at least 1 year for the evaluation of complications and revisions. Complications were defined as hematoma, wound infection, seroma, hypertrophic scar requiring steroid injection, or suture granuloma. The types of revisions were documented and included minor procedures performed under local anesthesia and surgery under general anesthesia. For the entire cohort of 209 patients, manual chart review was performed to search for satisfaction versus regret/dissatisfaction within both postoperative surgical and mental health provider records. After review of notes, an additional search function of key words within the chart was completed to identify notes that may express patient regret not captured with initial review of notes. The key words used were "regret" and multiple synonyms captured by the EHR including "dissatisfaction," "dissatisfied," "unsatisfied," and "unhappy" versus "satisfaction," "satisfied," and "happy." Outcomes were then categorized as satisfaction, regret, or not documented.

The incidence of gender-affirming mastectomy was estimated by dividing the number of patients receiving gender-affirming mastectomies in a year by the product of the number of patients assigned female at birth aged 12 to 17 years who had Kaiser membership at the beginning of each year times the amount of time within that year. Between 2013 and 2019, there was a full 1-year period, whereas for 2020, the time period was 7 months. Because of the COVID-19 pandemic in 2020, elective surgeries were limited from mid-March to mid-May to conserve resources and limit exposure. Postoperative follow-up was censored at the last clinical encounter or KPNC health plan discontinuation. For the overall cohort and among patients with and without complications, frequencies and proportions were calculated for each categorical clinical and demographic variable and mean and SD for normally distributed continuous variables and median and interquartile range (IQR) for nonnormally distributed continuous variables. Associations between clinical and demographic characteristics and complications were assessed using χ^2 tests. Hypothesis tests were 2-sided and considered significant at $P < 0.05$. All statistical analyses were performed with SAS software version 9.4 for Windows (Cary, North Carolina).

RESULTS

A total of 209 patients underwent gender-affirming mastectomy between January 1, 2013, and July 31, 2020. The incidence increased 13-fold (3.7–47.7 per 100,000 person-years; Fig. 1).

The median age at the time of referral was 16 years (IQR, 2 years) and ranged from 12 to 17 years (Fig. 2). Patients had a median postoperative follow-up length of 2.1 years (IQR, 1.69 years). Most patients were White (68%) followed by Hispanic/Latinx (15%), Asian/Pacific Islander (5%), Black (3%), and other (8%). Twelve percent (n = 23) had MediCal insurance. The majority of patients identified as male (87%), and the remaining were nonbinary (10%) or other/questioning (3%). Fifty-two percent of patients had a normal or underweight BMI, whereas the remaining were overweight or obese (BMI >25 kg/m^2). The mean weight of breast tissue removed was 445 ± 338 g for the left breast and 448 ± 358 g for the right breast. The weight of breast tissue removed increased with increasing BMI class ($P < 0.001$). Many patients

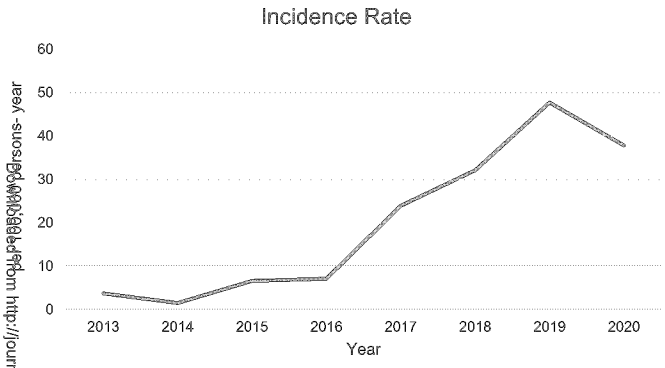

FIGURE 1. Incidence of gender-affirming mastectomy between 2013 and 2020 estimated by dividing the number of gender-affirming mastectomies performed in a year by the product of the number of patients assigned female at birth aged 13 to 17 years who had Kaiser membership at the beginning of each year times the amount of follow-up time in that year. In 2020, elective surgeries were limited to conserve resources and limit exposure during the COVID-19 pandemic, and data were only available through July. full color online

experienced mental health issues preoperatively including depression (50%), anxiety (61%), or an eating disorder (5%). A small number of patients reported substance use: drugs (8%), former tobacco use (4%), or alcohol (2%). The majority of patients received testosterone preoperatively (88%) and postoperatively (84%). Most surgeries (85%) were completed using the double-incision technique, whereas 1% used buttonhole and 14% used limited-incision techniques, keyhole/infra-areolar (8%), and circumareolar/periareolar (6%; Table 1).

For patients with at least 1-year postoperative follow-up (n = 137), the overall prevalence was 7.3% (n = 10) for complications and 10.9% (n = 15) for revisions. Some patients had more than one complication and/or revision. Complications included hematoma (3.6%), wound infection (2.9%), hypertrophic scars requiring steroid injection (2.9%), seroma (0.7%), and suture granuloma (0.7%; Fig. 3). The types of revisions consisted of scar (52%), contour (18%), nipple-areolar complex (18%), combination of areas (12%), and axillary (6%; Fig. 4). Patients with complications did not differ significantly from patients without complications in terms of demographics and clinical characteristics ($P > 0.05$; Table 2).

After a median follow-up of 2.1 years, no adolescents underwent a reversal operation within our system, but 2 adolescents (0.95%) expressed regret. One adolescent identified as nonbinary and underwent surgery at age 16 years. Seven months postoperatively, the patient questioned the timing of their surgery and expressed regret at 1.5 years throughout a follow-up period of 3.7 years. Postoperatively, the patient was in an un-affirming and unsupportive home and social environment.

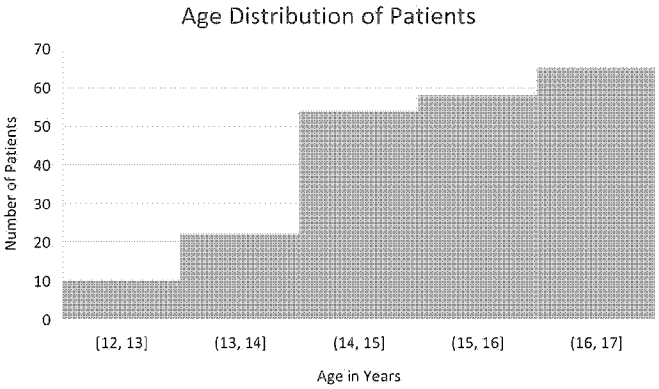

FIGURE 2. Histogram distribution of the age of adolescents at the time of referral who underwent gender-affirming mastectomy between January 2013 and July 2020. full color online

TABLE 1. Demographic and Clinical Characteristics of Adolescents Who Underwent Gender-Affirming Mastectomy From January 2013 to July 2020

	All (n = 209)
Age at referral, median (IQR), y	16 (2)
Gender identity, no. (%)	
Male	182 (87)
Nonbinary	21 (10)
Other	6 (3)
Race/ethnicity, no. (%)	
White	143 (68)
Hispanic/Latino	32 (15)
Asian/Pacific Islander	11 (5)
Black	7 (3)
Other	16 (8)
BMI, no. (%)	
<20 kg/m^2	23 (11)
20–24.9 kg/m^2	86 (41)
25–29.9 kg/m^2	71 (34)
≥30 kg/m^2	29 (14)
ASA classification, no. (%)	
1	107 (51)
2	102 (49)
History of depression, no. (%)	126 (60)
History of anxiety, no. (%)	128 (61)
History of eating disorder, no. (%)	11 (5)
Tobacco use, no. (%)	
No	200 (96)
Quit	9 (4)
Alcohol use, no. (%)	
No	111 (53)
Yes	4 (2)
Missing	94 (45)
Illicit drug use, no. (%)	
No	105 (50)
Yes	16 (8)
Missing	88 (42)
Testosterone use in 30 d before surgery, no. (%)	183 (88)
Testosterone use in 30 d after surgery, no. (%)	175 (84)
Surgery technique, no. (%)	
Double Incision	177 (85)
Keyhole	17 (8)
Circumareolar/periareolar	13 (6)
Buttonhole	2 (1)
Weight of breast tissue removed, mean (SD), g	
Left	445 (338)
Right	448 (358)
Satisfaction/regret, no. (%)	
Satisfaction	190 (91)
Regret	2 (1)
Not documented	17 (8)

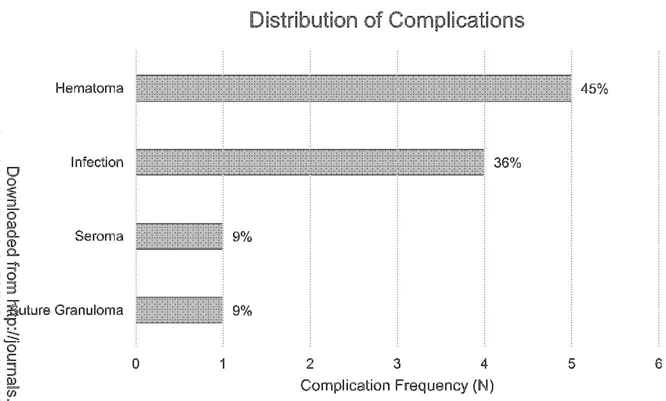

FIGURE 3. Distribution of complications types among patients who underwent gender-affirming mastectomy and had at least one complication between 2013 and 2020. A total of 10 patients experienced 15 complications. full color online

The second adolescent identified as nonbinary and underwent surgery at age 16 years. The patient mentioned regret 11 months after surgery and expressed interest for reversal with the mental health provider but ultimately did not pursue reversal surgery (ie, breast reconstruction) throughout a follow-up period of 6.5 years within our system. Both patients had normal BMI, had well-managed psychiatric anxiety and depression, and underwent the double-incision technique, and neither had a complication or desire for revision.

DISCUSSION

In this retrospective cohort study evaluating gender-affirming surgery in adolescents within a large integrated health care system, we found that the incidence of gender-affirming mastectomy increased 13-fold from January 1, 2013, to July 31, 2020. The overall prevalence of any postoperative complication was 7.3%, and the revision rate was 10.9% for those with at least 1-year postoperative follow-up. No patients underwent a reversal surgery with a median follow-up of 2.1 years. Among the 209 adolescents who underwent gender-affirming mastectomy, only 2 expressed regret. To our knowledge, our study is the largest cohort evaluation of gender-affirming mastectomies in the adolescent population.

Several studies have discussed methods for preoperative evaluation and multidisciplinary care programs for gender-affirming surgical treatment, which are similar to ours in terms of a multidisciplinary team

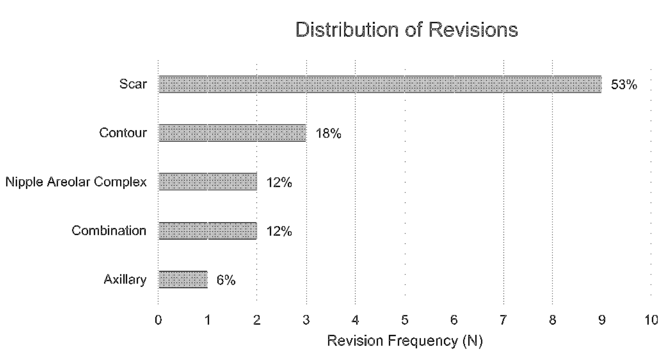

FIGURE 4. Distribution of revisions among patients who underwent gender-affirming mastectomy and had at least one revision between 2013 and 2020 with at least 1-year follow-up. A total of 15 patients experienced 17 revisions. full color online

TABLE 2. Clinical and Demographic Characteristics and Complications of Adolescents Who Underwent Gender-Affirming Mastectomy Between January 2013 to July 2020 With at Least 1-Year Follow-Up

	All (*n* = 137), No. (%)	No Complications (*n* = 127), No. (%)	Complications (*n* = 10), No. (%)	*P**
Age at referral, y				0.918
12	2 (1)	2 (2)	0 (0)	
13	6 (4)	6 (5)	0 (0)	
14	12 (9)	11 (9)	1 (10)	
15	35 (26)	33 (25)	3 (30)	
16	41 (30)	37 (29)	4 (40)	
17	41 (30)	39 (31)	2 (20)	
Gender identity				0.068
Male	121 (88)	114 (90)	7 (70)	
Nonbinary	14 (10)	12 (9)	2 (20)	
Other/questioning	2 (1)	1 (1)	1 (10)	
Race/ethnicity				0.798
White	88 (64)	82 (65)	6 (60)	
Hispanic/Latino	24 (18)	22 (17)	2 (20)	
Asian/Pacific Islander	9 (7)	9 (7)	0 (0)	
African American	6 (4)	5 (4)	1 (10)	
Other	10 (7)	9 (7)	1 (10)	
BMI, kg/m^2				0.739
<20	17 (12)	16 (13)	1 (10)	
20–24.9	52 (38)	47 (37)	5 (50)	
25–29.9	47 (34)	45 (35)	2 (20)	
≥30	21 (15)	19 (15)	2 (20)	
Surgery ASA rating				0.468
1	81 (59)	74 (58)	7 (70)	
2	56 (41)	53 (42)	3 (30)	
History of depression	83 (61)	76 (60)	7 (70)	0.527
History of anxiety	80 (58)	74 (58)	6 (60)	0.915
History of eating disorder	6 (4)	6 (5)	0 (0)	0.482
Tobacco use				0.482
No	131 (96)	121 (95)	10 (100)	
Quit	6 (4)	6 (5)	0 (0)	
Alcohol use				0.748
No	96 (70)	88 (69)	8 (80)	
Yes	2 (1)	2 (2)	0 (0)	
Missing	39 (28)	37 (29)	2 (20)	
Illicit drug use				0.237
No	90 (66)	81 (64)	9 (90)	
Yes	7 (5)	7 (6)	0 (0)	
Missing	40 (29)	39 (31)	1 (10)	
Testosterone use before surgery	120 (88)	113 (89)	7 (70)	0.080
Testosterone use after surgery	126 (92)	118 (93)	8 (80)	0.148
Surgery technique				0.850

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TABLE 2. *(Continued)*

	All (n = 137), No. (%)	No Complications (n = 127), No. (%)	Complications (n = 10), No. (%)	*P**
Double incision	116 (85)	107 (84)	9 (90)	
Circumareolar/ Periareolar	12 (9)	11 (8)	1 (10)	
Keyhole	9 (7)	9 (7)	0 (0)	
Satisfaction/regret				0.132
Satisfaction	127 (93)	119 (94)	8 (80)	
Regret	2 (1)	2 (2)	0 (0)	
Not documented	8 (6)	6 (5)	2 (20)	

**P* values from χ^2 test for the association between each variable and complications. Some patients had more than one complication.

approach.[25,27,40,41] At our center, before meeting with a member of the plastic surgery team, adolescents and their families were well-informed and received extensive education about the risks, benefits, and outcomes. In a case series by Sood et al,[25] they recommended "multiple preoperative consults, as needed, and support from trusted, trans-competent mental health professionals to ensure readiness and facilitate informed consent within a comprehensive care-team model." Importantly, the authors described the case of a 16 year-old patient who presented to the emergency department after attempting to remove his own breasts, thus highlighting the risks when care is not achieved in a timely manner.[25] Similarly, we believe that a multidisciplinary approach helps support adolescents and their families as they consider risks, benefits, and timing of gender-affirming mastectomy.

Although there have been studies reporting the increasing incidence of gender-affirming surgeries in adults[28,29] and referrals in adolescents,[12,26,27] the incidence of gender-affirming mastectomy surgeries performed within the adolescent population has not been reported, to our knowledge. We found a 13-fold increase in the incidence among our adolescent population, which is a greater increase than what was previously reported in the adult population.[28,29] In 2013, the California Department of Managed Health Care banned insurance discrimination against transgender adolescents.[42] After the end of a ban on Medicare coverage for transgender surgery in 2014, there was a marked increase in 2016 to 2017 corresponding to the establishment of a more robust top surgery program within our system.[43] The decline in mastectomies in January to July 2020 was secondary to the COVID-19 pandemic, whereby nonemergent surgeries were not performed to conserve resources and limit the spread of COVID-19. In a large study with nearly 38,000 adult transgender patients in the National Inpatient Sample, Canner et al[28] found a 3-fold increase in patients who were seeking any gender-affirming surgery from 2000 to 2014. However, because the study was limited to inpatient gender-affirming surgeries, it may not be inclusive of all chest and breast surgeries, which are frequently performed on an outpatient basis. Lane et al[29] found a 5-fold increase in mastectomies from 2009 to 2015 among adult transgender patients identified from an administrative claims database. Within the pediatric population, Handler et al[12] evaluated referral trends to our MST Department from 2015 to 2018 and found a 5-fold increase in average monthly referrals for gender-affirming mastectomy. Spack et al[44] also documented an increase in referrals after the expansion of a Gender Management Service clinic in Boston to include pediatric and adolescent patients, with a 4-fold annual increase in referrals. We believe that greater understanding and acceptance of transgender adolescents in our society, along with growing awareness of timely care for this population, has contributed to the increase in requests for gender-affirming mastectomy. We anticipate that the number of adolescents seeking gender-affirming mastectomy may continue to increase until it reaches a steady state, at which time patients seeking surgical care, including those who have not undergone treatment with puberty blockers before the development of breast tissue, would ideally have reasonable and timely access to treatment. On the other hand, if puberty suppression is initiated earlier during adolescence than what our cohort has experienced, breast growth may be successfully suppressed such that fewer patients may experience gender dysphoria, and thus, the requests for mastectomies could decline.

The prevalences of complications (7.3%) and revisions (10.9%) within our adolescent cohort were comparable with those reported in the literature for adults.[30–32,45–49] Complication rates for gender-affirming mastectomy in adults range widely from 5% to 29% and are difficult to compare because of variable definitions of complications, varying lengths of follow-ups, and a variety of techniques.[30–32,45–49] In our adolescent cohort, for those with a follow-up of at least 1 year, the overall prevalence of complications including all major and minor complications was 7.3%, with hematoma (3.6%) as the most common. In a review of 948 adults from our center, with a mean age of 29 years and follow-up of >30 days, Rothenberg et al[31] found a complication rate of 9%, with 2% requiring surgical evacuation for a hematoma and 1% requiring antibiotics for wound infection. Bluebond-Langner et al[32] evaluated complications in 295 transgender adults who underwent mastectomy, using either double-incision (63%) or circumareolar (37%) techniques. They found a complication rate of 18%, consisting of hematoma (6.8%), seroma (5.1%), infection (1.7%), and partial nipple necrosis (3.1%).[32] We attribute our low rate of complications to our use of the double-incision technique, which is most suitable for larger breast sizes with excess skin and has been shown to have the fewest complications and revisions.[31,32,50,51] The prevalence of revision in our study (10.9%) was lower than that of transmasculine adults reported by both Rothenberg et al (19.7%; mean follow-up, 1.9 years) and Bluebond-Langer et al (39.1%; mean follow-up, 0.81 years). In one study evaluating chest dysphoria in 68 transmasculine youth aged 13 to 25 years, Olson-Kennedy et al[34] described the self-reported complications of loss of nipple sensation (59%), postoperative hematoma (10%), and anesthetic complications (7%) in their postsurgical cohort.

Experienced gender surgeons report that "regret after gender-affirming surgery is considered a rare outcome."[52] Danker et al used an anonymous survey to plastic surgeons to study how frequently they were confronted with patients seeking reversal surgery. Of an estimated number of 22,725 patients, they reported 62 patients who expressed regret or sought detransition care, with the most common reason being a change in gender identity. In a survey of 68 patients aged 13 to 25 years who underwent gender-affirming mastectomy with a median follow-up of 2 years, Olson-Kennedy et al[34] reported a regret rate of 1.5% (n = 1) in which one patient answered "sometimes" to the survey statement, "It was a good decision to undergo chest reconstruction." Dhejne et al[53] examined the incidence and prevalence of all requests for adult surgical sex reassignment in Sweden from 1960 to 2010. They defined a regret rate as the number of sex reassigned for reversal to the original sex. In 681 patients, they found 5 female-to-male individuals corresponding to an overall regret rate of 2%.[53] Van de Grift et al[54] assessed satisfaction after any gender-affirming surgery with standardized questionnaires in 201 adult patients. They found that postoperative satisfaction was high, ranging from 94% to 100%, and that only 6% reported dissatisfaction or regret after 5 years from the first gender clinic contact. In our cohort, 2 patients (0.95%) expressed regret; one inquired about reversal surgery, but neither had undergone reversal surgery within follow-up periods of 3.7 and 6.5 years. Among adult transgender patients, common reasons identified for regret were reported as a change in gender identity, rejection or alienation from support system, or difficulty in romantic relationships.[52] Further studies are needed to improve insight into adolescent

experiences and other potential contributors to regret, including but not limited to the un-affirming environment, minority stress, and discrimination.

Our study has several limitations. First, its retrospective design meant we were unable to measure patient satisfaction and quality-of-life outcomes. Complications and any mention of regret were obtained from provider notes, which may be variable, and thus, both may be underreported. In addition, although an integrated health care system allows for continuity of care, some members may have transferred care or changed their insurance status, and thus, subsequent complications, or reversal operations, would not have been captured. Next, our study was conducted at KPNC in an insured cohort of individuals with access to gender-affirming medical and surgical care. Therefore, our outcomes may not be representative of the general population, many of whom lack similar access to care. Finally, the time to develop postoperative regret and/or dissatisfaction remains unknown and may be difficult to discern given that regret is quite rare. Currently, validated patient-reported-outcomes for transgender patients are lacking.[55] Therefore, future studies on patient-reported-outcome and prospective studies evaluating long-term surgical and mental health outcomes are necessary. Continuing to monitor for overall well-being, including patient satisfaction and/or regret, is especially imperative in this adolescent population as they continue to age.

In conclusion, our study demonstrates the rising rate of gender-affirming mastectomy in the adolescent population within our integrated health care system. We found a low prevalence of complications and minimal short-term regret in adolescents after gender-affirming mastectomy. State legislative attempts, which do not take into account the existing guidelines for transgender care, could potentially create additional barriers to gender-affirming surgery in adolescents. However, our study provides additional guidance that gender-affirming mastectomy in adolescents is safe, successful, and increasing in need.

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Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care

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Abstract

IMPORTANCE Transgender and nonbinary (TNB) youths are disproportionately burdened by poor mental health outcomes owing to decreased social support and increased stigma and discrimination. Although gender-affirming care is associated with decreased long-term adverse mental health outcomes among these youths, less is known about its association with mental health immediately after initiation of care.

OBJECTIVE To investigate changes in mental health over the first year of receiving gender-affirming care and whether initiation of puberty blockers (PBs) and gender-affirming hormones (GAHs) was associated with changes in depression, anxiety, and suicidality.

DESIGN, SETTING, AND PARTICIPANTS This prospective observational cohort study was conducted at an urban multidisciplinary gender clinic among TNB adolescents and young adults seeking gender-affirming care from August 2017 to June 2018. Data were analyzed from August 2020 through November 2021.

EXPOSURES Time since enrollment and receipt of PBs or GAHs.

MAIN OUTCOMES AND MEASURES Mental health outcomes of interest were assessed via the Patient Health Questionnaire 9-item (PHQ-9) and Generalized Anxiety Disorder 7-item (GAD-7) scales, which were dichotomized into measures of moderate or severe depression and anxiety (ie, scores ≥10), respectively. Any self-report of self-harm or suicidal thoughts over the previous 2 weeks was assessed using PHQ-9 question 9. Generalized estimating equations were used to assess change from baseline in each outcome at 3, 6, and 12 months of follow-up. Bivariate and multivariable logistic models were estimated to examine temporal trends and investigate associations between receipt of PBs or GAHs and each outcome.

RESULTS Among 104 youths aged 13 to 20 years (mean [SD] age, 15.8 [1.6] years) who participated in the study, there were 63 transmasculine individuals (60.6%), 27 transfeminine individuals (26.0%), 10 nonbinary or gender fluid individuals (9.6%), and 4 youths who responded "I don't know" or did not respond to the gender identity question (3.8%). At baseline, 59 individuals (56.7%) had moderate to severe depression, 52 individuals (50.0%) had moderate to severe anxiety, and 45 individuals (43.3%) reported self-harm or suicidal thoughts. By the end of the study, 69 youths (66.3%) had received PBs, GAHs, or both interventions, while 35 youths had not received either intervention (33.7%). After adjustment for temporal trends and potential confounders, we observed 60% lower odds of depression (adjusted odds ratio [aOR], 0.40; 95% CI, 0.17-0.95) and 73% lower odds of suicidality (aOR, 0.27; 95% CI, 0.11-0.65) among youths who had initiated PBs or GAHs compared with youths who had not. There was no association between PBs or GAHs and anxiety (aOR, 1.01; 95% CI, 0.41, 2.51).

(continued)

Key Points

Question Is gender-affirming care for transgender and nonbinary (TNB) youths associated with changes in depression, anxiety, and suicidality?

Findings In this prospective cohort of 104 TNB youths aged 13 to 20 years, receipt of gender-affirming care, including puberty blockers and gender-affirming hormones, was associated with 60% lower odds of moderate or severe depression and 73% lower odds of suicidality over a 12-month follow-up.

Meaning This study found that access to gender-affirming care was associated with mitigation of mental health disparities among TNB youths over 1 year; given this population's high rates of adverse mental health outcomes, these data suggest that access to pharmacological interventions may be associated with improved mental health among TNB youths over a short period.

+ Invited Commentary

+ Supplemental content

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Abstract (continued)

CONCLUSIONS AND RELEVANCE This study found that gender-affirming medical interventions were associated with lower odds of depression and suicidality over 12 months. These data add to existing evidence suggesting that gender-affirming care may be associated with improved well-being among TNB youths over a short period, which is important given mental health disparities experienced by this population, particularly the high levels of self-harm and suicide.

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Introduction

Transgender and nonbinary (TNB) youths are disproportionately burdened by poor mental health outcomes, including depression, anxiety, and suicidal ideation and attempts.[1-5] These disparities are likely owing to high levels of social rejection, such as a lack of support from parents[6,7] and bullying,[6,8,9] and increased stigma and discrimination experienced by TNB youths. Multidisciplinary care centers have emerged across the country to address the health care needs of TNB youths, which include access to medical gender-affirming interventions, such as puberty blockers (PBs) and gender-affirming hormones (GAHs).[10] These centers coordinate care and help youths and their families address barriers to care, such as lack of insurance coverage[11] and travel times.[12] Gender-affirming care is associated with decreased rates of long-term adverse outcomes among TNB youths. Specifically, PBs, GAHs, and gender-affirming surgeries have all been found to be independently associated with decreased rates of depression, anxiety, and other adverse mental health outcomes.[13-16] Access to these interventions is also associated with a decreased lifetime incidence of suicidal ideation among adults who had access to PBs during adolescence.[17] Conversely, TNB youths who present to care later in adolescence or young adulthood experience more adverse mental health outcomes.[18] Despite this robust evidence base, legislation criminalizing and thus limiting access to gender-affirming medical care for minors is increasing.[19,20]

Less is known about the association of gender-affirming care with mental health outcomes immediately after initiation of care. Several studies published from 2015 to 2020 found that receipt of PBs or GAHs was associated with improved psychological functioning[21] and body satisfaction,[22] as well as decreased depression[23] and suicidality[24] within a 1-year period. Initiation of gender-affirming care may be associated with improved short-term mental health owing to validation of gender identity and clinical staff support. Conversely, prerequisite mental health evaluations, often perceived as pathologizing by TNB youths, and initiation of GAHs may present new stressors that may be associated with exacerbation of mental health symptoms early in care, such as experiences of discrimination associated with more frequent points of engagement in a largely cisnormative health care system (eg, interactions with nonaffirming pharmacists to obtain laboratory tests, syringes, and medications).[25] Given the high risk of suicidality among TNB adolescents, there is a pressing need to better characterize mental health trends for TNB youths early in gender-affirming care. This study aimed to investigate changes in mental health among TNB youths enrolled in an urban multidisciplinary gender clinic over the first 12 months of receiving care. We also sought to investigate whether initiation of PBs or GAHs was associated with depression, anxiety, and suicidality.

Methods

This cohort study received approval from the Seattle Children's Hospital Institutional Review Board. For youths younger than age 18 years, caregiver consent and youth assent was obtained. For youths ages 18 years and older, youth consent alone was obtained. The 12-month assessment was funded via a different mechanism than other survey time points; thus, participants were reconsented for the

12-month survey. The study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study Procedures

We conducted a prospective observational cohort study of TNB youths seeking care at Seattle Children's Gender Clinic, an urban multidisciplinary gender clinic. After a referral is placed or a patient self-refers, new patients, their caregivers, or patients with their caregivers are scheduled for a 1-hour phone intake with a care navigator who is a licensed clinical social worker. Patients are then scheduled for an appointment at the clinic with a medical provider.

All patients who completed the phone intake and in-person appointment between August 2017 and June 2018 were recruited for this study. Participants completed baseline surveys within 24 hours of their first appointment and were invited to complete follow-up surveys at 3, 6, and 12 months. Youth surveys were used to assess most variables in this study; caregiver surveys were used to assess caregiver income. Participation and completion of study surveys had no bearing on prescribing of PBs or GAHs.

Measures

Mental Health Variables

We assessed 3 internalizing mental health outcomes: depression, generalized anxiety, and suicidality. Depression was assessed using the Patient Health Questionnaire 9-item scale (PHQ-9), and anxiety was assessed using the Generalized Anxiety Disorder 7-item scale (GAD-7). We dichotomized PHQ-9 and GAD-7 scores into measures of moderate or severe depression and anxiety (ie, scores ≥10).[26,27] Self-harm and suicidal thoughts were assessed using PHQ-9 question 9 (eTable 1 in the Supplement).

Pharmacological Interventions

Participants self-reported if they had ever received GAHs, including estrogen or testosterone, or PBs (eg, gonadotropin-releasing hormone analogues) on each survey. We conducted a medical record review to capture prescription of androgen blockers (eg, spironolactone) and medications for menstrual suppression or contraception (ie, medroxyprogesterone acetate or levonorgestrel-releasing intrauterine device) during the study period.

Covariates

We a priori considered potential confounders hypothesized to be associated with our exposures and outcomes of interest based on theory and prior research. Self-reported gender was ascertained on each survey using a 2-step question that asked participants about their current gender and their sex assigned at birth. If a participant's self-reported gender changed across surveys, we used the gender reported most frequently by a participant (3 individuals identified as transmasculine at baseline and as nonbinary on all follow-up surveys). We collected data on self-reported race and ethnicity (available response options were Arab or Middle Eastern; Asian; Black or African American; Latinx; Native American, American Indian, or Alaskan Native or Native Hawaiian; Pacific Islander; and White), age, caregiver income, and insurance type. Race and ethnicity were assessed as potential covariates owing to known barriers to accessing gender-affirming care among transgender youth who are members of minority racial and ethnic groups. For descriptive statistics, Asian and Pacific Islander groups were combined owing to small population numbers. We included a baseline variable reflecting receipt of ongoing mental health therapy other than for the purpose of a mental health assessment to receive a gender dysphoria diagnosis. We included a self-report variable reflecting whether youths felt their gender identity or expression was a source of tension with their parents or guardians. Substance use included any alcohol, marijuana, or other drug use in the past year. Resilience was measured by the Connor-Davidson Resilience Scale (CD-RISC) 10-item score developed to measure change in an individual's state resilience over time.[28] Resilience scores were

dichotomized into high (ie, ≥median) and low (ie, <median). Prior studies of young adults in the US reported mean CD-RISC scores ranging from 27.2 to 30.1.[29,30]

Statistical Analysis

We used generalized estimating equations to assess change in outcomes from baseline at each follow-up point (eFigure 1 in the Supplement). We used a logit link function to estimate adjusted odds ratio (aOR) for the association between variables and each mental health outcome. We initially estimated bivariate associations between potential confounders and mental health outcomes. Multivariable models included variables that were statistically significant in bivariate models. For all outcomes and models, statistical significance was defined as 95% CIs that did not contain 1.00. Reported *P* values are based on 2-sided Wald test statistics.

Model 1 examined temporal trends in mental health outcomes, with time (ie, baseline, 3, 6, and 12 months) modeled as a categorical variable. Model 2 estimated the association between receipt of PBs or GAHs and mental health outcomes adjusted for temporal trends and potential confounders. Receipt of PBs or GAHs was modeled as a composite binary time-varying exposure that compared mean outcomes between participants who had initiated PBs or GAHs and those who had not across all time points (eTable 2 in the Supplement). All models used an independent working correlation structure and robust standard errors to account for the time-varying exposure variable.

We performed several sensitivity analyses. Because our data were from an observational cohort, we first considered the degree to which they were sensitive to unmeasured confounding. To do this, we calculated the E-value for the association between PBs or GAHs and mental health outcomes in model 2. The E-value is defined as the minimum strength of association that a confounder would need to have with both exposure and outcome to completely explain away their association (eTable 4 in the Supplement).[31] Second, we performed sensitivity analyses on several subsets of youths. We separately examined the association of PBs and GAHs with outcomes of interest, although we a priori did not anticipate being powered to detect statistically significant outcomes owing to our small sample size and the relatively low proportion of youths who accessed PBs. We also conducted sensitivity analyses using the Patient Health Questionnaire 8-item scale (PHQ-8), in which the PHQ-9 question 9 regarding self-harm or suicidal thoughts was removed, given that we analyzed this item as a separate outcome. Lastly, we restricted our analysis to minor youths ages 13 to 17 years because they were subject to different laws and policies related to consent and prerequisite mental health assessments. We used R statistical software version 3.6.2 (R Project for Statistical Computing) to conduct all analyses. Data were analyzed from August 2020 through November 2021.

Results

A total of 169 youths were screened for eligibility during the study period, among whom 161 eligible youths were approached. Nine youths or caregivers declined participation, and 39 youths did not complete consent or assent or did not complete the baseline survey, leaving a sample of 113 youths (70.2% of approached youths). We excluded 9 youths aged younger than 13 years from the analysis because they received different depression and anxiety screeners. Our final sample included 104 youths ages 13 to 20 years (mean [SD] age, 15.8 [1.6] years). Of these individuals, 84 youths (80.8%), 84 youths, and 65 youths (62.5%) completed surveys at 3, 6, and 12 months, respectively.

Our cohort included 63 transmasculine youths (60.6%), 27 transfeminine youths (26.0%), 10 nonbinary or gender fluid youths (9.6%), and 4 youths who responded "I don't know" or did not respond to the gender identity question on all completed questionnaires (3.8%) (**Table 1**). There were 4 Asian or Pacific Islander youths (3.8%), 3 Black or African American youths (2.9%); 9 Latinx youths (8.7%); 6 Native American, American Indian, or Alaskan Native or Native Hawaiian youths (5.8%); 67 White youths (64.4%); and 9 youths who reported more than 1 race or ethnicity (8.7%). Race and ethnicity data were missing for 6 youth (5.8%).

Table 1. Participant Characteristics

Characteristic	Participants, No. (%) (N = 104)
Gender	
Male or transgender male	63 (60.6)
Female or transgender female	27 (26.0)
Nonbinary or gender fluid	10 (9.6)
Don't know or missing	4 (3.8)
Race and ethnicity[a]	
Asian or Pacific Islander	4 (3.8)
Black or African American	3 (2.9)
Latinx	9 (8.7)
Native American, American Indian, or Alaskan Native or Native Hawaiian	6 (5.8)
White	67 (64.4)
More than 1 race or ethnicity chosen	9 (8.7)
Missing	6 (5.8)
Age at baseline, y	
13	8 (7.7)
14	20 (19.2)
15	18 (17.3)
16	22 (21.2)
17	22 (21.2)
18	8 (7.7)
19	5 (4.8)
20	1 (1.0)
Pharmacological intervention	
PBs[b]	19 (18.2)
GAHs[b]	64 (61.5)
Androgen blockers[c]	17 (51.5)
Menstrual suppression or contraception[d]	25 (35.2)
Depression at baseline (using PHQ-9)	
0-4 (minimal)	14 (13.5)
5-9 (mild)	27 (26.0)
10-14 (moderate)	22 (21.2)
15-19 (moderately severe)	11 (10.6)
≥20 (severe)	26 (25.0)
Missing	4 (3.8)
Anxiety at baseline (using GAD-7)	
0-4 (minimal)	20 (19.2)
5-9 (mild)	28 (26.9)
10-14 (moderate)	20 (19.2)
≥15 (severe)	32 (30.8)
Missing	4 (3.8)
Self-harm or suicidal thoughts at baseline	45 (43.2)
Receiving mental health therapy	65 (62.5)
Tension with caregiver about gender identity or expression	36 (34.6)
Any substance use	34 (32.7)
Resilience at baseline (using CD-RISC 10)	
0-10	8 (7.7)
10-20	35 (33.7)
21-30	15 (14.4)
30-40	34 (32.7)
Missing	12 (11.5)

Abbreviations: CD-RISC 10, Connor-Davidson 10-item Resilience Scale; GAD-7, Generalized Anxiety Disorder 7-item scale; GAH, gender-affirming hormone; PB, puberty blocker; PHQ-9 Patient Health Questionnaire 9-item scale.

[a] Available response options for race and ethnicity were Arab or Middle Eastern; Asian or Pacific Islander; Black or African American; Latinx; Native American, American Indian, or Alaskan Native or Native Hawaiian; Pacific Islander; and White. Asian and Pacific Islander groups were combined owing to small population sizes.

[b] Self-reported receipt ever of PBs or GAHs at baseline or through the end of the study period.

[c] Includes androgen blockers received during the study period; percentage is among 33 youths assigned male sex at birth.

[d] Includes pharmacological interventions for menstrual suppression or contraception received during the study period; percentage is among 71 youths assigned female sex at birth.

At baseline, 7 youths had ever received PBs or GAHs (including 1 youth who received PBs, 4 youths who received GAHs, and 2 youths who received both PBs and GAHs). By the end of the study, 69 youths (66.3%) had received PBs or GAHs (including 50 youths who received GAHs only [48.1%], 5 youths who received PBs only [4.8%], and 14 youths who received PBs and GAHs [13.5%]), while 35 youths had not received either PBs or GAHs (33.7%) (eTable 3 in the Supplement). Among 33 participants assigned male sex at birth, 17 individuals (51.5%) had received androgen blockers, and among 71 participants assigned female sex at birth, 25 individuals (35.2%) had received menstrual suppression or contraceptives by the end of the study.

A large proportion of youths reported depressive and anxious symptoms at baseline. Specifically, 59 individuals (56.7%) had baseline PHQ-9 scores of 10 or more, suggesting moderate to severe depression; there were 22 participants (21.2%) scoring in the moderate range, 11 participants (10.6%) in the moderately severe range, and 26 participants (25.0%) in the severe range. Similarly, half of participants had a GAD-7 score suggestive of moderate to severe anxiety at baseline (52 individuals [50.0%]), including 20 participants (19.2%) scored in the moderate range, and 32 participants (30.8%) scored in the severe range. There were 45 youths (43.3%) who reported self-harm or suicidal thoughts in the prior 2 weeks. At baseline, 65 youths (62.5%) were receiving ongoing mental health therapy, 36 youths (34.6%) reported tension with their caregivers about their gender identity or expression, and 34 youths (32.7%) reported any substance use in the prior year. Lastly, we observed a wide range of resilience scores (median [range], 22.5 [1-38], with higher scores equaling more resiliency). There were no statistically significant differences in baseline characteristics by gender.

In bivariate models, substance use was associated with all mental health outcomes (**Table 2**). Youths who reported any substance use were 4-fold as likely to have PHQ-9 scores of moderate to severe depression (aOR, 4.38; 95% CI, 2.10-9.16) and 2-fold as likely to have GAD-7 scores of moderate to severe anxiety (aOR, 2.07; 95% CI, 1.04-4.11) or report thoughts of self-harm or suicide in the prior 2 weeks (aOR, 2.06; 95% CI, 1.08-3.93). High resilience scores (ie, ≥median), compared with low resilience scores (ie, <median), were associated with lower odds of moderate or severe anxiety (aOR, 0.51; 95% CI, 0.26-0.999).

There were no statistically significant temporal trends in the bivariate model or model 1 (Table 2 and **Table 3**). However, among all participants, odds of moderate to severe depression increased at 3 months of follow-up relative to baseline (aOR, 2.12; 95% CI, 0.98-4.60), which was not a significant increase, and returned to baseline levels at months 6 and 12 (**Figure**) prior to adjusting for receipt of PBs or GAHs.

We also examined the association between receipt of PBs or GAHs and mental health outcomes in bivariate and multivariable models (eFigure 2 in the Supplement). After adjusting for temporal trends and potential confounders (**Table 4**), we observed that youths who had initiated PBs or GAHs had 60% lower odds of moderate to severe depression (aOR, 0.40; 95% CI, 0.17-0.95) and 73% lower odds of self-harm or suicidal thoughts (aOR, 0.27; 95% CI, 0.11-0.65) compared with youths who had not yet initiated PBs or GAHs. There was no association between receipt of PBs or GAHs and moderate to severe anxiety (aOR, 1.01; 95% CI, 0.41-2.51). After adjusting for time-varying exposure of PBs or GAHs in model 2 (Table 4), we observed statistically significant increases in moderate to severe depression among youths who had not received PBs or GAHs by 3 months of follow-up (aOR, 3.22; 95% CI, 1.37-7.56). A similar trend was observed for self-harm or suicidal thoughts among youths who had not received PBs or GAHs by 6 months of follow-up (aOR, 2.76; 95% CI, 1.22-6.26). Lastly, we estimated E-values of 2.56 and 3.25 for the association between receiving PGs or GAHs and moderate to severe depression and suicidality, respectively (eTable 4 in the Supplement). Sensitivity analyses obtained comparable results and are presented in eTables 5 through 8 in the Supplement.

Discussion

In this prospective clinical cohort study of TNB youths, we observed high rates of moderate to severe depression and anxiety, as well as suicidal thoughts. Receipt of gender-affirming interventions, specifically PBs or GAHs, was associated with 60% lower odds of moderate to severe depressive symptoms and 73% lower odds of self-harm or suicidal thoughts during the first year of multidisciplinary gender care. Among youths who did not initiate PBs or GAHs, we observed that depressive symptoms and suicidality were 2-fold to 3-fold higher than baseline levels at 3 and 6 months of follow-up, respectively. Our study results suggest that risks of depression and suicidality may be mitigated with receipt of gender-affirming medications in the context of a multidisciplinary care clinic over the relatively short time frame of 1 year.

Our findings are consistent with those of prior studies finding that TNB adolescents are at increased risk of depression, anxiety, and suicidality[1,11,32] and studies finding long-term and short-term improvements in mental health outcomes among TNB individuals who receive gender-affirming medical interventions.[14,21-24,33,34] Surprisingly, we observed no association with anxiety scores. A recent cohort study of TNB youths in Dallas, Texas, found that total anxiety symptoms improved over a longer follow-up of 11 to 18 months; however, similar to our study, the authors did not observe

Table 2. Baseline Factors Associated With Mental Health Outcomes in Bivariate Models

	Moderate or severe depression (PHQ-9 ≥10)[a]		Moderate or severe anxiety (GAD-7 ≥10)[b]		Any self-harm or suicidal thoughts[c]	
Factor	aOR (95% CI)	*P* value	aOR (95% CI)	*P* value	aOR (95% CI)	*P* value
PBs or GAHs	0.67 (0.33-1.34)	.25	0.90 (0.49-1.66)	.74	0.47 (0.26-0.86)	.01
Time, mo						
0 (baseline)	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
3	1.96 (0.99-3.90)	.05	1.46 (0.71-2.97)	.30	1.00 (0.49-2.06)	.99
6	1.01 (0.46-2.19)	.99	0.77 (0.39-1.52)	.45	1.22 (0.64-2.34)	.54
12	1.42 (0.55-3.66)	.47	0.95 (0.43-2.06)	.89	1.02 (0.41-2.52)	.97
Gender						
Male or transgender male	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
Female or transgender female	1.07 (0.51-2.24)	.87	3.15 (0.92-10.8)	.07	1.20 (0.55-2.64)	.64
Nonbinary or gender fluid	2.40 (0.84-6.87)	.10	1.35 (0.67-2.72)	.40	2.17 (0.73-6.41)	.16
Race or ethnicity						
White	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
Member of minority race or ethnic group[d]	1.08 (0.51-2.28)	.84	0.86 (0.45-1.66)	.66	0.92 (0.53-1.61)	.77
Age, y						
13-15	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
16-17	1.79 (0.82-3.88)	.14	0.63 (0.29-1.39)	.25	0.86 (0.44-1.68)	.66
18-20	0.78 (0.24-2.51)	.68	1.17 (0.43-3.17)	.76	0.79 (0.36-1.74)	.55
Mental health and substance use at baseline						
Moderate or severe depression (PHQ-9 ≥10)	27.2 (13.4-55.4)	<.001	1.91 (0.85-4.29)	.12	1.06 (0.50-2.24)	.88
Moderate or severe anxiety (GAD-7 ≥10)	4.90 (2.27-10.6)	<.001	14.3 (7.31-27.9)	<.001	1.44 (0.76-2.72)	.27
Self-harm or suicidal thoughts	1.32 (0.61-2.85)	.48	1.49 (0.73-3.06)	.28	18.9 (10.4-34.1)	<.001
Receiving mental health therapy	1.46 (0.69-3.08)	.32	0.65 (0.31-1.38)	.26	0.75 (0.36-1.56)	.45
Tension with caregivers about gender identity or expression	1.93 (0.90-4.14)	.09	1.06 (0.52-2.15)	.87	1.55 (0.88-2.74)	.13
Any substance use	4.38 (2.10-9.16)	<.001	2.07 (1.04-4.11)	.04	2.06 (1.08-3.93)	.03
Resilience at baseline (CD-RISC 10 ≥22.5)[e]	0.85 (0.42-1.74)	.67	0.51 (0.26-1.00)	.05	0.74 (0.39-1.44)	.38

Abbreviations: aOR, adjusted odds ratio; CD-RISC 10, Connor-Davidson 10-item Resilience Scale; GAD-7, Generalized Anxiety Disorder 7-item scale; GAH, gender-affirming hormone; NA, not applicable; PB, puberty blocker; PHQ-9, Patient Health Questionnaire 9-item scale.

[a] Bivariate models are adjusted for baseline PHQ-9.

[b] Bivariate models are adjusted for baseline GAD-7.

[c] Bivariate models are adjusted for self-harm or suicidal thoughts reported at baseline.

[d] Owing to small sample sizes, this group includes Asian or Pacific Islander; Black or African American; Latinx; and Native American, American Indian, Alaskan Native, or Native Hawaiian youths and youths who reported more than 1 race or ethnicity.

[e] The median (range) CD-RISC score for the cohort was 22.5 (1-38).

statistically significant improvements in generalized anxiety.[22] This suggests that anxiety symptoms may take longer to improve after the initiation of gender-affirming care. In addition, Olson et al[35] found that prepubertal TNB children who socially transitioned did not have increased rates of depression symptoms but did have increased rates of anxiety symptoms compared with children who were cisgender. Although social transition and access to gender-affirming medical care do not always go hand in hand, it is noteworthy that access to gender-affirming medical care and supported social transition appear to be associated with decreased depression and suicidality more than anxiety symptoms.

Time trends were not significant in our study; however, it is important to note that we observed a transient and nonsignificant worsening in mental health outcomes in the first several months of care among all participants and that these outcomes subsequently returned to baseline by 12 months. This is consistent with findings from a 2020 study[36] in an academic medical center in the northwestern US that observed no change in TNB adolescents' GAD-7 or PHQ-9 scores from intake to first follow-up appointment, which occurred a mean of 4.7 months apart. Given that receipt of PBs or GAHs was associated with protection against depression and suicidality in our study, it could be that delays in receipt of medications is associated with initially exacerbated mental health symptoms that subsequently improve. It is also possible that mental health improvements associated with receiving these interventions may have a delayed onset, given the delay in physical changes after starting GAHs.

Few of our hypothesized confounders were associated with mental health outcomes in this sample, most notably receipt of ongoing mental health therapy and caregiver support; however, this is not surprising given that these variables were colinear with baseline mental health, which we adjusted for in all models. Substance use was the only variable associated with all mental health outcomes. In addition, youths with high baseline resilience scores were half as likely to experience moderate to severe anxiety as those with low scores. This finding suggests that substance use and resilience may be additional modifiable factors that could be addressed through multidisciplinary gender-affirming care. We recommend more granular assessment of substance use and resilience to better understand support needs (for substance use) and effective support strategies (for resilience) for TNB youths in future research.

This study has a number of strengths. This is one of the first studies to quantify a short-term transient increase in depressive symptoms experienced by TNB youths after initiating gender-affirming

Table 3. Temporal Trends in Mental Health Outcomes in Multivariable Model 1[a]

	Moderate or severe depression (PHQ-9 ≥10)		Moderate or severe anxiety (GAD-7 ≥10)		Any self-harm or suicidal thoughts	
Factor	aOR (95% CI)	*P* value	aOR (95% CI)	*P* value	aOR (95% CI)	*P* value
Time, mo						
0 (baseline)	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
3	2.12 (0.98-4.60)	.06	1.50 (0.71-3.15)	.29	0.99 (0.48-2.06)	.98
6	0.99 (0.42-2.35)	.98	0.78 (0.38-1.59)	.49	1.22 (0.63-2.36)	.56
12	1.27 (0.44-3.67)	.66	0.96 (0.43-2.11)	.91	0.98 (0.39-2.48)	.97
Mental health and substance use at baseline						
Moderate or severe depression (PHQ-9 ≥10)	18.5 (8.44-40.5)	<.001	NA	NA	NA	NA
Moderate or severe anxiety (GAD-7 ≥10)	3.63 (1.83-7.19)	<.001	12.4 (6.25-24.7)	<.001	NA	NA
Self-harm or suicidal thoughts	NA	NA	NA	NA	19.9 (10.9-36.1)	<.001
Any substance use	3.35 (1.56-7.18)	.002	2.21 (1.09-4.49)	.03	2.07 (1.09-3.93)	.03
Resilience at Baseline (CD-RISC 10 ≥22.5)[b]	NA	NA	0.48 (0.24-0.95)	.04	NA	NA

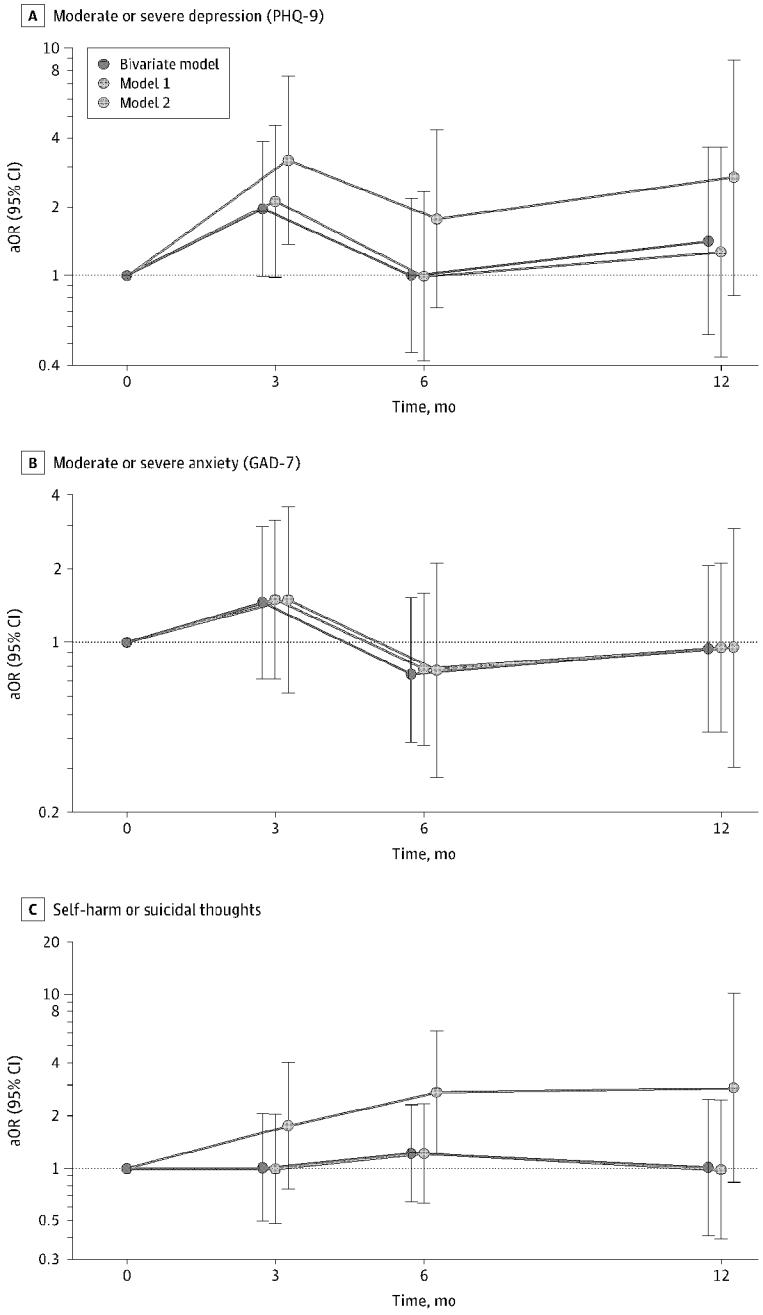
Abbreviations: aOR, adjusted odds ratio; CD-RISC 10, Connor-Davidson 10-item Resilience Scale; GAD-7, Generalized Anxiety Disorder 7-item scale; NA, not applicable; PHQ-9, Patient Health Questionnaire 9-item scale.

[a] Model 1 includes categorical temporal variables (ie, months 3, 6, and 12 relative to baseline) and covariates that were statistically significant in bivariate models (such that 95% CIs did not contain 1.00) (see Table 2). Covariates that were not significant in bivariate models are marked NA.

[b] The median (range) CD-RISC score for the cohort is 22.5 (1-38).

care, a phenomenon observed clinically by some of the authors and described in qualitative research.[37] Although we are unable to make causal statements owing to the observational design of the study, the strength of associations between gender-affirming medications and depression and suicidality, with large aOR values, and sensitivity analyses that suggest that these findings are robust to moderate levels of unmeasured confounding. Specifically, E-values calculated for this study suggest that the observed associations could be explained away only by an unmeasured confounder that was associated with both PBs and GAHs and the outcomes of interest by a risk ratio of 2-fold to 3-fold each, above and beyond the measured confounders, but that weaker confounding could not do so.[31]

Figure. Temporal Trends in Mental Health Outcomes



Outcomes are estimated from bivariate and multivariable generalized estimating equation models. aOR, indicates adjusted odds ratio; GAD-7, Generalized Anxiety Disorder 7-item scale; PHQ-9, Patient Health Questionnaire 9-item scale; whiskers, 95% CIs.

Limitations

Our findings should be interpreted in light of the following limitations. This was a clinical sample of TNB youths, and there was likely selection bias toward youths with supportive caregivers who had resources to access a gender-affirming care clinic. Family support and access to care are associated with protection against poor mental health outcomes, and thus actual rates of depression, anxiety, and suicidality in nonclinical samples of TNB youths may differ. Youths who are unable to access gender-affirming care owing to a lack of family support or resources require particular emphasis in future research and advocacy. Our sample also primarily included White and transmasculine youths, limiting the generalizability of our findings. In addition, the need to reapproach participants for consent and assent for the 12-month survey likely contributed to attrition at this time point. There may also be residual confounding because we were unable to include a variable reflecting receipt of psychotropic medications that could be associated with depression, anxiety, and self-harm and suicidal thought outcomes. Additionally, we used symptom-based measures of depression, anxiety, and suicidality; further studies should include diagnostic evaluations by mental health practitioners to track depression, anxiety, gender dysphoria, suicidal ideation, and suicide attempts during gender care.[2]

Conclusions

Our study provides quantitative evidence that access to PBs or GAHs in a multidisciplinary gender-affirming setting was associated with mental health improvements among TNB youths over a relatively short time frame of 1 year. The associations with the highest aORs were with decreased suicidality, which is important given the mental health disparities experienced by this population, particularly the high levels of self-harm and suicide. Our findings have important policy implications, suggesting that the recent wave of legislation restricting access to gender-affirming care[19] may have significant negative outcomes in the well-being of TNB youths.[20] Beyond the need to address antitransgender legislation, there is an additional need for medical systems and insurance providers to decrease barriers and expand access to gender-affirming care.

Table 4. Association Between GAHs or PBs and Mental Health Outcomes in Multivariable Model 2[a]

	Moderate or severe depression (PHQ-9 ≥10)		Moderate or severe anxiety (GAD-7≥10)		Any self-harm or suicidal thoughts	
Factor	aOR (95% CI)	*P* value	aOR (95% CI)	*P* value	aOR (95% CI)	*P* value
PBs or GAHs	0.40 (0.17-0.95)	.04	1.01 (0.41-2.51)	.98	0.27 (0.11-0.65)	.003
Time, mo						
0 (baseline)	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
3 mo	3.22 (1.37-7.56)	.007	1.49 (0.62-3.59)	.37	1.77 (0.76-4.13)	.19
6 mo	1.77 (0.72-4.37)	.21	0.77 (0.28-2.11)	.61	2.76 (1.22-6.26)	.02
12 mo	2.71 (0.82-8.95)	.10	0.95 (0.31-2.93)	.93	2.93 (0.83-10.4)	.10
Mental health & substance use at baseline						
Moderate or severe depression (PHQ-9 ≥10)	19.4 (8.64-43.4)	<.001	NA	NA	NA	NA
Moderate or severe anxiety (GAD-7 ≥10)	3.82 (1.87-7.82)	<.001	12.4 (6.25-24.7)	<.001	NA	NA
Self-harm or suicidal thoughts	NA	NA	NA	NA	23.9 (12.9-44.5)	<.001
Any substance use	3.20 (1.49-6.84)	.003	2.21 (1.09-4.50)	.03	2.00 (1.08-3.73)	.03
Resilience at baseline (CD-RISC 10 ≥22.5)[b]	NA	NA	0.48 (0.24-0.95)	.04	NA	NA

Abbreviations: aOR, adjusted odds ratio; CD-RISC 10, Connor-Davidson 10-item Resilience Scale; GAD-7, Generalized Anxiety Disorder 7-item scale; GAH, gender-affirming hormone; NA, not applicable; PB, puberty blocker; PHQ-9, Patient Health Questionnaire 9-item scale.

[a] Model 2 includes a time-varying exposure variable measuring the receipt of PBs or GAHs adjusted for temporal trend (ie, categorical variable for months 3, 6, and 12 relative to baseline) and covariates that were statistically significant in the bivariate models (such that 95% CIs did not contain 1.00) (see Table 2). The unadjusted bivariate associations between PBs or GAHs and mental health outcomes are reported in Table 2. Covariates that were not significant in bivariate models are marked NA.

[b] The median (range) CD-RISC score for the cohort is 22.5 (1-38).

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SUPPLEMENT.

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eReferences

Endocrinology of Transgender Medicine

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ABSTRACT Gender-affirming treatment of transgender people requires a multidisciplinary approach in which endocrinologists play a crucial role. The aim of this paper is to review recent data on hormonal treatment of this population and its effect on physical, psychological, and mental health. The Endocrine Society guidelines for transgender women include estrogens in combination with androgen-lowering medications. Feminizing treatment with estrogens and antiandrogens has desired physical changes, such as enhanced breast growth, reduction of facial and body hair growth, and fat redistribution in a female pattern. Possible side effects should be discussed with patients, particularly those at risk for venous thromboembolism. The Endocrine Society guidelines for transgender men include testosterone therapy for virilization with deepening of the voice, cessation of menses, and increases of muscle mass and facial and body hair. Owing to the lack of evidence, treatment of gender nonbinary people should be individualized. Young people may receive pubertal suspension, consisting of GnRH analogs, later followed by sex steroids. Options for fertility preservation should be discussed before any hormonal intervention. Morbidity and cardiovascular risk with cross-sex hormones is unchanged among transgender men and unclear among transgender women. Sex steroid–related malignancies can occur but are rare. Mental health problems such as depression and anxiety have been found to reduce considerably following hormonal treatment. Future studies should aim to explore the long-term outcome of hormonal treatment in transgender people and provide evidence as to the effect of gender-affirming treatment in the nonbinary population. ***(Endocrine Reviews 40: 97 – 117, 2019)***

The acceptance by society, reflected in the media, that gender identity may not always match the assigned sex at birth has provided the option and permission for individuals to question their gender identity more freely. Consequently, in some countries, transgender health services have expanded and developed so that gender-diverse people wanting physical change are able to access gender-affirming medical interventions. Hormone treatment, pivotal for those who wish to transition into their affirmed gender that differs from their sex that is assigned at birth, is ideally prescribed under the supervision of endocrinologists. However, many endocrinologists may feel uneasy and unskilled when working with the transgender population because the field of transgender medicine is relatively new. This review aims to summarize the endocrine treatment of transgender people wishing to undergo gender-affirmation therapies. The review first describes the terminology used in the field of transgender medicine, followed by a critical review of the diagnostic criteria currently in use, and it summarizes the mental health difficulties that transgender people may present with and the benefits of gender-affirming treatment on well-being. Finally, the major focus of this paper is to provide a critical review of the published literature on the hormonal treatment and long-term monitoring for transgender children and adults.

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ESSENTIAL POINTS

- Transgender people before gender-affirming treatment present with higher levels of mental health problems, particularly depression, anxiety, and self-harm, than do cisgender people
- Gender-affirming treatment has been found to reduce mental health problems in transgender people
- Long-term estrogen and androgen-lowering medications may be associated with increased risk of thromboembolism, which can be mitigated by changing the formulation and route of estrogen therapy
- Testosterone treatment in transgender men is seen as safe regarding cardiovascular and oncological disease in the short-term and mid-term, but long-term effects need to be elucidated
- The endocrine treatment of adolescents with gender dysphoria consists of two phases, first pubertal suppression followed by the addition of hormones
- The few somatic data available in adolescents are favorable and hitherto support the fact that the proven psychological benefits of early medical intervention outweigh the potential medical risks
- In well-informed transgender people regrets of gender-confirming treatment are very rare

Terminology

The term "gender nonconforming" is used to describe individuals whose gender identity, role, or expression differs from what is normative for their assigned sex at birth in a given culture and historical period (1). Transgender is used as an umbrella term to describe individuals whose gender identity differs from the assigned sex at birth. Transgender males are people assigned female at birth but who self-identify as male. Transgender females are people assigned male at birth, but who self-identify as female. When a person's identity matches the sex assigned at birth, the term "cisgender" is used. The term "nonbinary" describes people whose gender identity, role, or expression does not conform to the binary understanding of gender (male or female). This can be used as an umbrella term to include people with no gender (agender), two genders (bigender), multiple genders (pangender), or with a fluid gender (gender fluid) (2, 3), among others. Nonbinary people prefer for people to use the pronouns of "they" and "them" when addressing them (3).

Terminology changes all the time, and terms used in the past may become outdated and can be perceived as pejorative. For example, the term transsexual, which has been used since 1949 (4), is largely now confined to the legal and medical literature. The 10th edition of the International Classification of Diseases and Related Health Problems (ICD-10) (5) still uses the term "transsexualism" as a diagnostic term to describe individuals whose sex assigned at birth does not match their gender identity and want gender-affirming treatment. This term is likely to change to "gender incongruence" in the forthcoming 11th edition of the ICD (ICD-11) (6). Other terms still used but considered outdated (although they can still be found in the literature) are "FtM" (female to male) to describe transgender men or "MtF" (male to female) to describe transgender women.

Gender dysphoria refers to a profound distress or discomfort caused by the discrepancy between a person's assigned sex at birth and gender identity (1). Not every transgender person suffers from gender dysphoria, and the urgency for medical intervention among transgender people may vary (1). For some people, social change may be enough without the need for further physical intervention. For others, owing to their personal circumstances, physical intervention may not be opportune or appropriate. Many, however, will access transgender health services to obtain gender-affirming treatment whether in the form of hormone treatment and/or through gender-affirming surgery. Research in the field of transgender medicine has primarily focused on transgender people accessing transgender health services (7). Owing to the requirement in certain countries to provide funded health services only to those with a medical diagnosis, terms describing the gender-related suffering of transgender people have remained part of current diagnostic criteria (5, 8). In this review, the term transgender is used throughout to describe individuals who seek access to medical treatment in order for their bodies to become more congruent to their identified gender. A summary of some of the terms used in transgender health can be found in Table 1.

Methodology

Eligibility criteria

Studies were selected only when participants were described as transgender (whether self-identified or diagnosed by health professionals) and they had empirical data relating to the hormonal treatment in

Table 1. Terminology Used in Transgender Health

Terms and Definitions
Cisgender: A person whose identity matches the sex assigned at birth.
Gender-affirming treatment: Physical treatment that some transgender people access in order for their bodies to be adapted to the bodies of their experienced gender or gender identity by means of hormones and/or surgery.
Gender dysphoria: A profound distress or discomfort caused by the discrepancy between assigned sex at birth and gender identity. This is the same term as the current diagnostic term of the DSM-5.
Gender expression: The external manifestations of someone's gender, which can include name, pronouns, clothing, haircut, behavior, voice, or body characteristics.
Gender identity disorder: Diagnostic term used in previous versions of the DSM. The term is still used for the child diagnosis in the ICD-10, but the proposed name for ICD-11 is gender incongruence of childhood. Currently this term is not preferred given the term "disorder."
Gender identity/experienced gender: A person's internal sense of gender. Unlike gender expression, gender identity is not visible to others.
Gender incongruence: The proposed diagnostic term to be used in the new edition of the ICD-11. Not all individuals with gender incongruence have gender dysphoria or seek gender-affirming treatment.
Gender reassignment: Previously used term to describe what is known now as gender-affirming treatment.
Gender role: The behaviors, attitudes, and personality traits that a society, in a historical period, designates as masculine or feminine.
Natal sex: The term "sex assigned at birth," which is usually based on genital anatomy, is more appropriate.
Sex: Attributes that characterize biological maleness or femaleness. They can include the sex-determining genes, the sex chromosomes, the H-Y antigen, the gonads, sex hormones, internal and external genitalia, and secondary sex characteristics.
Sexual orientation: An individual's physical and emotional attraction to another person. Gender identity and sexual orientation are not the same. Irrespective of their gender identity, transgender people may be attracted to women (gynephilic), attracted to men (androphilic), or be bisexual, asexual, pansexual, and so forth.
Transgender *(adj.):* An umbrella term to describe individuals whose gender identity differs from the sex assigned at birth based on their sexual characteristics.
Transgender female: A person who self-identifies as female, but whose sex was assigned male at birth.
Transgender male: A person whose sex was assigned female at birth (based on sexual characteristics) but self-identifies as male.
Transition: The process during which transgender people change their physical, social, and/or legal characteristics consistent with their gender identity.
Transsexual *(adj.):* A diagnostic term used in the ICD-10. The term is currently used in some of the medical literature when discussing diagnoses. The term transgender should now be used instead except when referring to the current ICD-10 diagnosis.

this population. Only studies in English published in peer-reviewed journals and with >10 participants were selected. This is a critical review with a focus on recent and original data. This paper describes and reviews the available literature since the last published review study by one of the coauthors of the current review (9).

Information sources and search

An electronic literature search included the period between January 1999 and November 2017 used Medline/PubMed, PsycINFO, and Embase. Additionally, reference sections of identified articles and Google Scholar were examined for further relevant publications. The search used keywords for terms referring to transgender people (transsexualism, transgender, gender dysphoria, gender identity disorder, trans*) or hormonal treatment (cross-sex hormones, testosterone, estrogen, blockers, GnRH agonist). Every term used for transgender people was combined using the "OR" and "AND" operators with every term used for hormonal treatment. Articles of interest were those that included the transgender population and had empirical data relating to hormonal treatment within this population. Articles describing the effects of treatment, side effects, risk, and long-term outcome were also collected and reviewed to help with the discussion in this review. If information was only to be retrieved from case reports, such as oncology, both the case reports and recent reviews on the specific topic were examined. The results of the present review are presented by describing the treatment in adults

(transgender women and men) first, followed by the treatment in adolescents.

Diagnosis

Currently the ICD-10 includes the diagnosis of transsexualism as part of the diagnostic category of "gender identity disorders" (F64). It is expected that the new edition of the ICD (ICD-11) will change this term and move it out of the mental health chapter. It is likely that the new term to be used will be "gender incongruence of adolescence and adulthood" (or GIAA) (6, 10, 11).

The desire to de-pathologize being transgender and the importance of securing access to health care has been a dilemma in both the development of the current edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) and the ICD-11. The American Psychiatric Association's diagnosis in the DSM-5 addresses the distress caused by the incongruence between assigned sex at birth and experienced gender as gender dysphoria. This diagnosis aims to classify the symptoms (dysphoria) and not the individual. For an individual to fulfill the diagnostic criteria for gender dysphoria they need to present with a marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months duration (8).

If reaching a consensus to develop terms to classify transgender adults has been complicated, creating criteria for children has been even more complex. The ICD-11 is proposing the diagnosis of gender incongruence in children (10) whereas the DSM-5 uses the diagnosis of gender dysphoria in children.

Prevalence

More than 20 studies have sought to investigate prevalence rates of transgender people. Although more recently prevalence rates of transgender identities have been reported using population studies, most of the available literature has extrapolated prevalence rates from people attending transgender health clinics (7).

Some of the first epidemiological studies, which focused on individuals seeking services to undergo gender-affirming genital surgery (12), found prevalence rates of 0.40 per 100,000 people. The ratio between male assigned at birth and female assigned at birth was found to be 4 to 1 (11). Other European studies, based on people attending transgender health services, provide different prevalence rates over time: 1.22 per 100,000 (1976 to 1980), 1.58 per 100,000 (1976 to 1983), and 2.77 per 100,000 (1976 to 1986) (13). Once again, rates of male assigned at birth transgender people have been found to be higher than female assigned at birth transgender people at a ratio of 3 to 1. Studies looking at more recent periods (between 1972 and 1996) provide higher prevalence rates of 3.42 per 100,000 with ratios between birth-assigned females and males being more similar (1.4 to 1) (14).

Studies have also examined the number of people who have petitioned governmental agencies to change their gender status legally. Those studies have described prevalence rates ranging from 2.1 (15) to 16.6 (16) per 100,000 people. A recent meta-analysis found an overall prevalence for transsexualism (as this is the diagnosis and term used in the published papers) of 4.6 in 100,000 individuals: 6.8 for transgender women and 2.6 for transgender men, with an increase in reported prevalence during the last 50 years (7).

However, not every transgender person wants and/or seeks medical care to affirm gender (1). To identify the overall prevalence of transgender people (including those not accessing services) population studies may be more representative of the transgender community. Population-based studies have found a considerably higher prevalence rate than those reported in clinical studies. For example, a study asking a sample of community participants in the United States (28,045 aged 18 to 64 years) as to whether they considered themselves transgender found a prevalence rate of 0.5% (17). Studies from the Netherlands and Belgium described that 0.7% (18) and 1.1% (19) of people assigned male at birth and 0.6% (18) and 0.8% (19) of people assigned female at birth reported an incongruent gender identity.

Most of the epidemiological studies have been conducted in Western countries, particularly in Europe and the United States. Societies that are more egalitarian and open will facilitate the expression of gender diversity, and hence prevalence rates in those countries may be reported higher than in more restrictive societies. Low prevalence rates in certain societies may need to be regarded with caution, as they may reflect a symptom of repression. A ban on gender identity expression for personal, cultural, or religious reasons may manifest itself as distress and profound unhappiness and may lead to the development of mental health problems (20).

Mental Health in Transgender People and the Effect of Hormonal Treatment

Overall prevalence of mental health diagnoses

Studies investigating rates of mental health diagnoses in the transgender population, once again, have focused on those attending transgender health services (21). Most of the studies have been cross-sectional and report high rates of affective disorders (38%) (22) such as depression (23) and adjustment disorders (24), as well as anxiety disorders (17%) (25, 26). Rates of nonsuicidal self-injuries have also been found to be very high, particularly among young people (46%) as well as suicide attempts (27–29). The few studies that compared their findings to the general cisgender population (controlled by age and sex) found certain mental health diagnoses, such as anxiety disorders, are

threefold more prevalent among transgender people compared with cisgender people (25).

Differences in prevalence according to gender

There are some discrepancies as to whether mental health diagnoses are more common among transgender men or among transgender women. Some studies have found that mental health diagnoses were not related to assigned or identified gender (30, 31), whereas other studies have demonstrated higher rates of mood disorders (23, 32), anxiety disorders (32), adjustment disorders (18), and substance abuse (24) among transgender women than among transgender men. Most of those studies are biased by not controlling for factors known to influence mental health diagnoses, particularly hormone treatment. This means that people have been recruited for studies independently as to whether they are on hormone treatment or not, although research has confirmed that such treatment reduces mental health problems. Interestingly, more recent large controlled studies involving only transgender people not on treatment have found that anxiety disorders were more prevalent among transgender men than among transgender women (25). A similar study also found levels of self-harm were also higher among the same group (28).

Predictors of mental health problems

Several factors have been found to predict mental health issues among the transgender population attending transgender health services, such as experiences of victimization (or transphobic experiences), low self-esteem (27), and interpersonal problems (28, 33). Lack of hormone treatment of those wanting physical change has been found to be the strongest predictor of mental health diagnoses (21, 25, 31).

The role of hormone treatment in mental health

A number of longitudinal studies have explored the role of hormonal treatment in mental health and quality of life among transgender people wanting gender-affirmation treatment. These studies, which have mainly been conducted in Europe [Sweden (34), Italy (35), Belgium (36), and Germany (37)], have all demonstrated that people's mental health (levels of depression and anxiety) significantly improved following hormone treatment. Long-term follow-up studies and studies involving large groups of people are needed to evaluate whether these improvements remain. Hence, hormone treatment of those wanting physical change needs to be accessible, as this will reduce morbidity and improve quality of life of transgender people.

Posttreatment regrets

The literature on posttreatment regret is complex to interpret. Overall satisfaction after gender-affirming treatment is high. A study from >20 years ago found 2% of transgender women and 1% of transgender men later regretted their decision to undergo hormonal and/or surgical treatment (38). There are many causes of regret. Frequently dissatisfaction following gender-affirming surgery has been interpreted as regret regarding social and medical transition. To distinguish those people who express dissatisfaction following gender-affirming treatment from those who wish to detransition and return to their sex assigned at birth, Pfäfflin (39) in 1992 differentiated minor from major regrets. In one of the largest gender clinics (Amsterdam), 2034 individuals received treatment between 1975 and 1998. Ten of these people subsequently indicated that they regretted their decision to have undergone the treatment (nine transgender women and one transgender man) (39). The reason for those regrets varied from identifying with the sex assigned at birth and wanting detransition (n = 6) (classified as major regrets) to dissatisfaction of the outcome of surgery or loss of support following gender-affirming treatment (n = 4) (minor regrets). Upon review in 2005, the number of major and minor regrets increased by 5 out of a total of 3090 subjects. In 2015 the total number of subjects treated had risen to 6793, but there was no further increase in those expressing regret. The fact that fewer people have been having doubts about their treatment decisions over time may reflect the much-improved understanding of gender incongruence both by transgender people themselves and by the medical profession, as well as much greater acceptance of transgender people in society (39).

"The medical professional provides a more patient-centered approach to care and understands the needs of the person rather than making a diagnosis of the patient."

Summary

Mental health diagnoses are common in the transgender population, possibly owing to negative societal values, but they do improve once gender-affirming treatment is initiated. This highlights the importance of hormone treatment and access to adequate transgender health care. Although state-funded health services, which are primarily available in Europe, may develop services where the needs of the transgender population can be provided for, including assessment, psychological support (when needed), hormonal treatment, and gender-affirming surgery, other health care systems may not be so fortunate and transgender people may find themselves searching for professionals who are able to confidently prescribe and monitor hormone treatment.

Results

Hormonal treatment in transgender women

Initial evaluation of transgender women

Transgender women seek hormone therapy to change their physical appearance to better match their gender identity and expression (40, 41). Furthermore,

transgender women experience improved quality of life and a decrease in gender dysphoria upon initiation of hormone therapy (42, 43). In the United States, Canada, and most of Europe, transgender women must seek medical professionals for hormone therapy because these medications are available only by prescription, but there is a black market also particularly for oral contraceptives. For non-Western countries, hormone therapy is often self-prescribed without supervision by a medical professional. Available evidence from the United States and Europe suggests that hormone therapy initiated and monitored under the supervision of a medical professional is associated with very low rates of adverse events (44, 45).

The Endocrine Society guidelines recommend that a medical professional confirm the diagnosis of gender dysphoria and/or gender incongruence in transgender women prior to the initiation of hormone therapy. Medical professionals should document that the gender dysphoria has been persistent and that the individual is able to make an informed decision and consent for treatment (40). However, there are no validated psychological tests or imaging studies that have been clinically useful to diagnose gender dysphoria (46), which is likely because people with gender nonconforming expression and behaviors represent a very large and heterogeneous population. There is no demonstrable biological substrate for gender incongruence. In this regard, medical professionals have been moving toward a more gender-affirmative model whereby the medical professional provides a more patient-centered approach to care and understands the needs of the person rather than making a diagnosis of the patient (47, 48).

Screening for conditions prior to initiation of hormone therapy

Medical professionals should evaluate transgender women for conditions that can be exacerbated by hormone therapy. Patients with a history of thromboembolic diseases such as deep vein thrombosis and pulmonary embolism should undergo evaluation and treatment prior to the initiation of hormone therapy (40). Additionally, risk factors that can increase the risk of thromboembolic conditions should be modified such as smoking, obesity, and sedentary lifestyle. In patients with modifiable risk factors such as known thrombophilia, past history of thrombosis, or a strong family history of thromboembolism, treatment with transdermal estrogen and/or concomitant treatment with anticoagulation therapy may need to be considered, although there are limited data to guide treatment decisions (49, 50). Other diseases such as hormone-sensitive cancers, coronary artery disease, cerebrovascular disease, hyperprolactinemia, hypertriglyceridemia, and cholelithiasis should be evaluated prior to the initiation of estrogen therapy, as these conditions can be exacerbated by estrogen.

Modalities of hormonal therapy in transgender women

There are two main classes of medications used in transgender women: (1) estrogen therapies and (2) androgen-lowering hormone therapies.

Estrogen therapies. The synthetic estrogen ethinyl estradiol was a widely used estrogen in Europe prior to 2003. However, given recent safety concerns about its prothrombotic potential and its potential role in cardiovascular disease, most clinics have now switched to oral, cutaneous, or IM estradiol (51). A few commonly used estrogen regimens in transgender women have been reported [see appendix B of Ref. (40)]; however, there are very few head-to-head studies comparing the efficacy and safety of estrogen regimens. In a large multinational cohort study (titled European Network for the Investigation of Gender Incongruence) of four European countries (Belgium, Netherlands, Italy, and Norway), >300 transgender women were prescribed oral estradiol valerate at 4 mg daily or estradiol valerate at 20 mg IM every 2 weeks or an estradiol patch (100 μg daily), each with cyproterone acetate (CPA) at 50 mg daily (52). In the short term (<5 years), these regimens are associated with mild elevations of prolactin (53) and improvements in bone mineral density (BMD) after 1 year of therapy (54). No short-term or long-term adverse events have been published from this cohort using this hormone regimen.

In a German cohort, transgender women were treated with a regimen of estradiol valerate at 10 mg IM every 10 days. The authors also reported short-term gains in bone density after 24 months of therapy along with higher body mass index (BMI) with an increase of fat mass and decrease of lean body mass (55).

In the United Kingdom, transgender women were previously prescribed ethinyl estradiol or conjugated equine estrogen, but they are now changed to oral estradiol at a dose of ~4 mg daily (56). In a retrospective review of transgender women in the United Kingdom, transgender women prescribed oral conjugated equine estrogens had increased risk of thromboembolism compared with transgender women taking oral estradiol valerate or ethinyl estradiol. In this cohort, 4.4% of transgender women on oral conjugated equine estrogen experienced a thromboembolic event compared with <1% in transgender women on estradiol or ethinyl estradiol ($P = 0.026$).

In the United States, estrogen therapy can be prescribed as oral tablets, IM injections, and transcutaneous preparations (41). Most commonly published in the United States is the prescription of oral estradiol at 4 to 5 mg daily (57, 58). Studies that compare the long-term safety and effectiveness among the different formulations of estrogen are lacking. The Endocrine Society guidelines recommend that the

doses of estradiol be titrated to serum estradiol levels at ~200 pg/mL (734 pmol/L) (40).

Androgen-lowering therapies. Transgender women will often require the addition of a medication to lower testosterone levels into the female range (59). In most European countries, the most commonly prescribed androgen-lowering medication is oral CPA 50 mg daily (44, 52, 60). Cyproterone acts primarily as an androgen receptor blocker but also has some progesterone-like activity (61). However, given reports of increased risk of meningiomas (62–64), association with depression (56), and increased risk of hyperprolactinemia (53) with CPA use, in the United Kingdom, transgender women are now prescribed GnRH agonists to lower testosterone concentrations (65). In contrast to the rest of Europe and the United States, GnRH agonists are provided free of charge to transgender women by the National Health Service in the United Kingdom (56).

Spironolactone is the most commonly prescribed testosterone-lowering medication in the United States (57, 58). Spironolactone is classically known as an antagonist of the mineralocorticoid receptor and a potassium sparing diuretic. It also has antiandrogen properties by directly lowering testosterone synthesis and testosterone action at the androgen receptor (40). One US cohort of ~100 transgender women found estrogen therapy in combination with oral spironolactone at 200 mg daily was effective in lowering serum testosterone levels to the cisgender female range for serum testosterone after ~1 year of therapy (66).

Peripheral androgen receptor blockers such as flutamide or dutasteride have not been recommended for use in transgender women because these agents do not lower serum testosterone levels and there are limited published studies in this population (40).

Other second-line hormonal therapies. Progesterone: Progesterone therapies such as medroxyprogesterone have been used as a second agent to lower testosterone concentrations in transgender girls and women (57). Some transgender women may request progesterone to enhance breast development; however, there are no clinical studies to support a positive effect of progesterone on breast development (67). Furthermore, there are concerns regarding potential increased risk of thromboembolism and stroke found in cisgender women taking progesterone (68, 69). Therefore, progesterone therapy is not a routinely used medication in transgender women.

5α-Reductase inhibitors: Some transgender women may experience male pattern hair loss and may seek treatments to arrest hair loss and/or restore hair. In general, lowering serum testosterone levels into the cisgender female range is often adequate to arrest hair loss in most transgender women; however, there are still some transgender women who experience hair loss despite lowered serum testosterone levels. A few case series in transgender women with androgenetic alopecia have demonstrated finasteride therapy to be effective to improve hair loss without significant side effects (70, 71). The routine use of 5α-reductase inhibitors has been limited over previous concerns of long-term sexual dysfunction and depression reported to be found in cisgender men (72, 73).

Feminization in transgender women

Treatment with estrogen and testosterone-lowering medications will induce feminine and reduce masculine physical characteristics Fig. 1 (41). The most studied physical change in transgender women is the development of breast tissue. An Italian cohort study found increases in breast size were the only physical feature that was significantly associated with improvement in body uneasiness scores (43). However, <20% of transgender women reach Tanner breast stage 4 to 5 after 24 months of hormone therapy and thus often seek mammoplasty. Early studies in transgender women indicated breast development reached a maximum size by 2 years (74). However, a more recent study of 229 transgender women participating in the European Network for the Investigation of Gender Incongruence cohort found that breast development reached a plateau within the first 6 months of therapy and half of the transgender women had a AAA cup size or less (75). Fisher *et al.* (43) also found that testicular volume decreased by ~60% after 24 months of transfeminine hormone therapy.

"All transgender women should be aware of the potential fertility preservation options such as sperm cryopreservation."

Body composition. In a meta-analysis of studies published prior to 2015, transfeminine hormone therapy was associated with increased body fat and a decrease in lean body mass in 171 transgender women (76). More recent studies from Europe have documented that BMI increases in transgender women after transfeminine hormone therapy (43, 77). Klaver *et al.* (78) also demonstrated increases in body weight in 179 transgender women, and transfeminine hormone therapy was associated with an increase in body fat, specifically in the android, leg, and gynoid regions. However, recent studies from the United States have demonstrated that important changes in BMI in transgender girls and women do not occur during a short term (<6 months) (56, 79).

Voice. Transgender women will have an improved self-perceived feminine quality in their voice after the initiation of hormone therapy (80). However, many transgender women still have difficulty with their voice quality and are misperceived in the wrong gender by others (81). Transgender women may undergo voice training exercises to improve their voice quality (82). Laryngeal surgical treatment has been described as an option for transgender women to improve voice quality; however, a meta-analysis failed to demonstrate a significant benefit of surgical techniques to improve the quality of the voice (83).

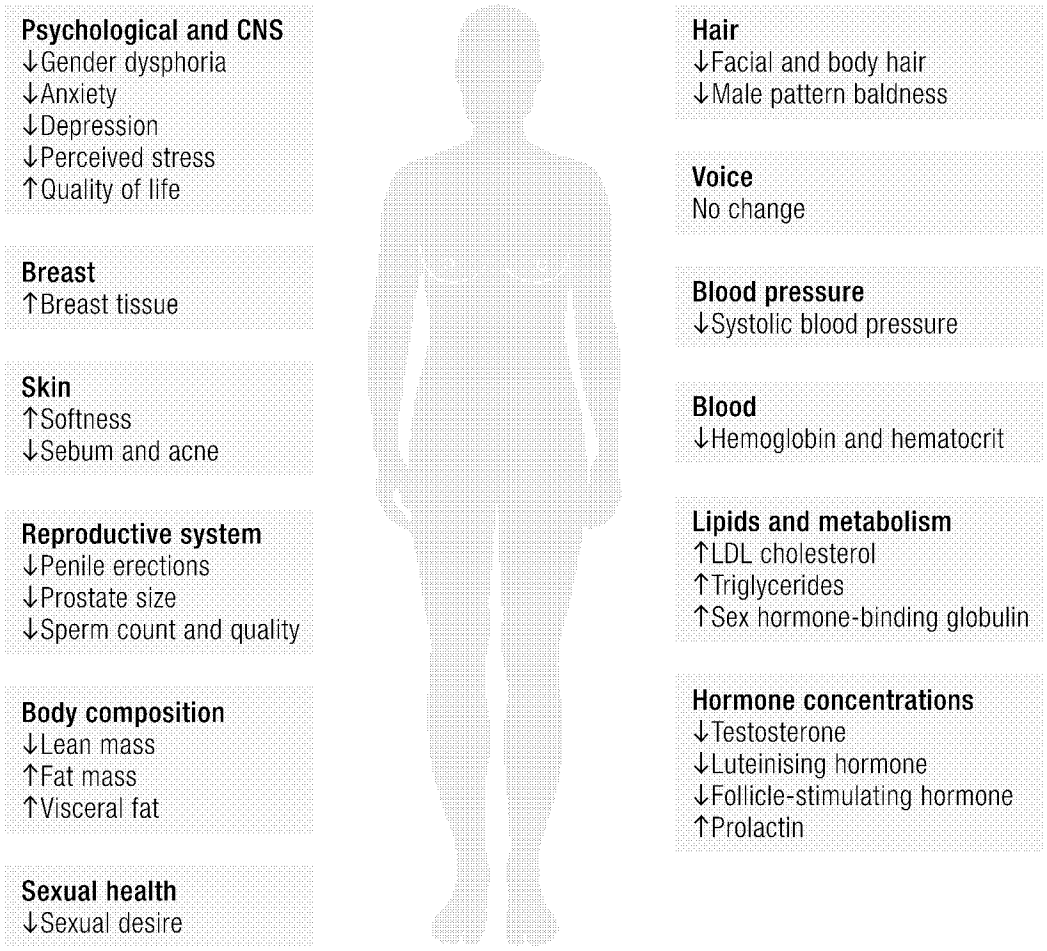

Figure 1. Effects of estrogen and antiandrogen treatment in transgender women. [Reproduced with permission from Tangpricha V, den Heijer M. Estrogen and antiandrogen therapy for transgender women. Lancet Diabetes Endocrinol 2017;5:291–300. (41); ©2019 Illustration Presentation ENDOCRINE SOCIETY].

Skin and hair. Transgender women will also experience reduction in facial hair after transfeminine hormone therapy. Fisher *et al.* (43) reported that Ferriman–Gallwey scores improved after 2 years of transfeminine hormone therapy. Transfeminine hormone therapy may arrest male pattern hair loss (71). A survey of transgender women reported interest in having facial hair removal procedures; however, few data on the effectiveness of such procedures have been published (84).

Safety data specific to transgender women

Cardiovascular and thromboembolic safety. There have been some concerns about long-term effects of transfeminine hormone therapy on cardiovascular outcomes. A single-center study of >200 transgender women from Belgium reported increased rates of myocardial infarction, venous thrombosis, and cerebrovascular disease compared with cisgender men and women (85). A recently commissioned systematic review and meta-analysis of cardiovascular outcomes in transgender individuals did not find an increased risk of myocardial infarction, stroke, or venous thrombosis in transgender women owing to lack of reported outcomes from 29 eligible studies (86). This systematic review also found that transfeminine hormone therapy was associated with increased serum triglyceride levels of 31.9 mg/dL (95% CI, 3.9 to 59.9) in transgender women treated for >24 months with no changes in serum low-density lipoprotein or high-density lipoprotein. Thrombosis risk in transgender women is likely increased given the known prothrombotic actions of estrogen. However, under medical supervision, the risks of transfeminine hormone therapy appear to be safer than self-prescribed transfeminine hormone therapy (45). A large study conducted in 162 transgender women treated with transdermal estrogen in Austria found that only 19 had a genetic mutation associated with venous thrombosis (1 with protein C deficiency and 18 with activated protein C resistance) and none developed a thrombotic event, suggesting that estrogens that avoid the hepatic first-pass effect may have less prothrombotic risk (87). Furthermore, given the low frequency of genetic mutations associated with thrombosis (19 out of 162), the authors do not recommend routine screening for thrombophilia. There have been reports of transgender women who developed

a thrombotic event and were successfully treated with anticoagulation therapy (50, 88). However, there are no long-term studies to guide treatment of transgender women following a thrombotic event.

Bone health. The fracture rate associated with transfeminine hormone therapy is unknown. Estrogen is critically important for preserving BMD in postmenopausal women and in men who lack estrogen action at the bone (*e.g.*, mutations in the estrogen receptor or aromatase enzyme) (89, 90). A recent meta-analysis of 392 transgender women found a significant increase in lumbar spine BMD but no changes in hip BMD. The rates of fracture were found to be low, with no fractures found in 53 transgender women after 12 months in this review (91). A recent multicenter study of 231 transgender women in Europe treated with transfeminine hormone therapy found a 3.67% increase in lumbar spine bone density and a 0.97% and 1.86% increase in total hip and femoral neck bone density, respectively, after 1 year of therapy (54).

Transgender women have been found to have lower BMD even prior to the start of hormone therapy (92). Van Caenegem *et al.* (92) found that 16% of transgender women had T-scores at the lumbar spine below −2.5 and approximately one third had T-scores between −1 and −2.5 at the lumbar spine or total hip. The reasons why transgender women had lower bone density than expected for age are not clear, but the authors hypothesized decreased outdoor physical activity as an explanation, as vitamin D status was found to be low in 72% of the cohort.

Oncological data and mortality. The prevalence of hormone-sensitive cancers such as breast and prostate cancer appears to be low among transgender women. Initial studies from a cohort of >2000 transgender women reported no increase in breast cancer incidence compared with the expected rate of breast cancer in cisgender women (93). A large cohort of >5000 transgender military veterans in the United States reported only nine cases of breast cancer in transgender veterans, two in transgender women, and seven in transgender men (94). All of the transgender women presented with late-stage breast cancer that proved to be fatal, whereas the transgender men before or after breast ablation presented with earlier disease (95). One the largest studies examining cancer risk in transgender women in the United States used data from one large health care system (Kaiser Permanente: Georgia and Northern and Southern California (96). Using an electronic database method to identify transgender women in this cohort, they identified 2791 transgender women subjects. Based on ICD-9 codes, the investigators found no increased risk of breast cancer or any cancer when comparing transgender women to matched cisgender women. However, there was an increased risk of breast cancer and endocrine gland cancers in transgender women compared with matched cisgender men. Furthermore, there was a decreased risk of prostate cancer compared with matched cisgender men. Other studies have reported a low risk of prostate cancer in transgender women. A recent review of literature of prostate cancer in transgender women only found 10 cases reported (97).

Other considerations. Fertility: All transgender women should be aware of the potential fertility preservation options such as sperm cryopreservation. Transgender women report that they are interested in having their own biologic children but very few transgender women use fertility preservation technologies (98, 99), possibly due to the lack of funding for fertility preservation in many countries. Because sperm production will decline after the initiation of hormone therapy, the Endocrine Society guidelines recommend that all transgender women discuss fertility options with their health care team prior to the initiation of hormone therapy (40).

Monitoring of feminizing hormone therapy: Transgender women who take hormone therapy under medical supervision experience very low rates of complications (44, 45). Transgender women should maintain serum estradiol and testosterone concentrations within the expected physiologic female range (40). The Endocrine Society recommends hormone measurements every 3 months in the first year of initiating hormone therapy until the hormone concentrations reach the desired concentrations. Once the hormone dose is achieved, the hormone concentrations of both testosterone and estrogen can be measured once yearly or when there is a dose change to ensure that levels remain in the range expected for cisgender females (40). Transgender women taking spironolactone should have measurement of potassium and kidney function on a regular basis. Following surgery, transgender women can have a final measurement of serum testosterone to confirm that levels in the male range are eliminated.

Measurement of prolactin levels during the course of gender-affirming hormone therapy has been suggested by the Endocrine Society guidelines. However, recent reports indicate that elevated prolactin levels seem to occur in transgender women on CPA and not on spironolactone. Defreyne *et al.* (53) demonstrated that prolactin levels increased in transgender women receiving cyproterone but decreased after discontinuation. Furthermore, a recent study by Fung *et al.* (100) demonstrated that transgender women treated with cyproterone had significantly higher prolactin levels compared with those treated with spironolactone (41).

Hormonal treatment in transgender men

Initial evaluation of transgender men

During the first outpatient consultation, the same principles apply as described for transgender women above.

Screening for conditions prior to initiation of hormone therapy

Transgender men must be informed of the possibilities, consequences, limitations, and risks of testosterone treatment. Fertility preservation options are to be discussed before starting a medical intervention. Pregnancy is an absolute contraindication for testosterone therapy, and relative contraindications include severe hypertension, sleep apnea, and polycythemia (40). Conditions that can be exacerbated by testosterone therapy are presence of erythrocytosis, baseline high hematocrit levels (*e.g.*, secondary to smoking or chronic obstructive pulmonary disease), sleep apnea, and congestive heart failure. Knowledge on the presence of menstruation problems prior to initiation of testosterone treatment and on sexual practices will guide the need for follow-up procedures such as pelvic ultrasounds and pap smears.

Modalities of hormonal treatment in transgender men

Testosterone. The principal hormonal treatment used to induce virilization is testosterone. Under medical supervision, testosterone therapy is safe based on short-term and longer-term safety studies (44, 101, 102). Different testosterone formulations may be available depending on geographical location. Most commonly prescribed are injectable testosterone esters (40). More recently, subcutaneous administration of testosterone was shown to be effective and preferred by transgender men at a median dosage 75 mg weekly in 63 transgender men (103, 104), confirming an earlier intervention study (104). Long-acting testosterone undecanoate is also being used for treatment of transgender men (105). However, in the United States, the prescription of testosterone undecanoate is limited owing to the potential risk of oil pulmonary embolus, and both patient and provider must undergo Risk Evaluation and Mitigation Strategy training to receive this therapy. Other intervention studies [see appendix A of Ref. (40)] have also used topical androgen gel or transdermal patches. The use of oral testosterone (testosterone undecanoate), axillary solutions, patches, nasal sprays, buccal tablets, or pellets is rarely reported for treatment in transgender men. In one study the effects of three different testosterone formulations were evaluated at baseline and after 12 months of treatment and no differences were found regarding short-term safety, compliance, body composition, metabolic parameters, and general life satisfaction (106). Androgen therapy will need to be continued lifelong to maintain the achieved virilization and to avoid symptoms of hypogonadism such as vasomotor symptoms or osteoporosis.

Progestational agents. If menstrual bleeding does not stop after initiation of testosterone, a progestational agent, such as oral lynestrenol at 5 to 10 mg daily or medroxyprogesterone at 5 to 10 mg, might be considered. This occurs frequently with the use of transdermal or oral testosterone undecanoate, which are both associated with lower testosterone levels compared with injectable testosterone. GnRH analogs to halt menses are theoretically possible, but they are rarely reported in adults given the costs of therapy. If ovariectomy is performed, the progestational medication can be discontinued (107–109).

Virilization in transgender men

Treatment in transgender men is intended to induce virilization. This includes cessation of menses, development of male physical contours, a deepening of the voice, clitoral growth, increased sexual desire, and increased facial and body hair (Fig. 2) (108, 110, 111). Male pattern baldness may also occur. Changes in body composition, with redistribution of body fat and increased muscle mass and strength, have been described extensively (40, 44, 112). The time period before cessation of menses may vary from 1 to 12 months after testosterone initiation, sometimes requiring the addition of a progestational agent (40, 113). Mean clitoral length may reach 3.83 ± 0.42 cm after 2 years of testosterone therapy (43)

It is important that transgender men understand the possibilities but also the limitations of testosterone treatment. Height and bone structure (broader hips) and the larger degree of subcutaneous fat remain largely unchanged when therapy is started after puberty (108). Most of the published guidelines have been developed with the white transgender person in mind, but ethnic differences may warrant tailoring of standard doses (114). Recommendations based on clinical experience are in favor of continuing testosterone treatment of elderly transgender men (115).

Body composition. Testosterone therapy will enhance a more masculine musculature, body shape, and body fat distribution. Testosterone therapy will result in changes in body composition. A meta-analysis of 10 studies examining body composition changes in response to testosterone during 12 months found body weight increased by 1.7 kg (0.7 to 2.7), body fat decreased by 2.6 kg (−3.9 to −1.4), and lean body mass increased by 3.9 kg (3.2 to 4.5) (76). Another systematic review, focusing among other parameters on BMI, revealed an increase in BMI from 1.3% to 11.4% (116). Grip strength increased with 18% in a study with 23 participants and 1-year parenteral testosterone undecanoate treatment (92).

Voice. Testosterone therapy at doses in the physiological range for men will induce acoustic changes occurring from effects on the larynx (117). In a cross-sectional study of 38 transgender men, acoustic voice variables and voice quality were similar between the transgender men and cisgender controls. However, 10% of the transgender men experienced issues with pitch quality, needing voice therapy and sometimes pitch-lowering surgery (118). Transgender

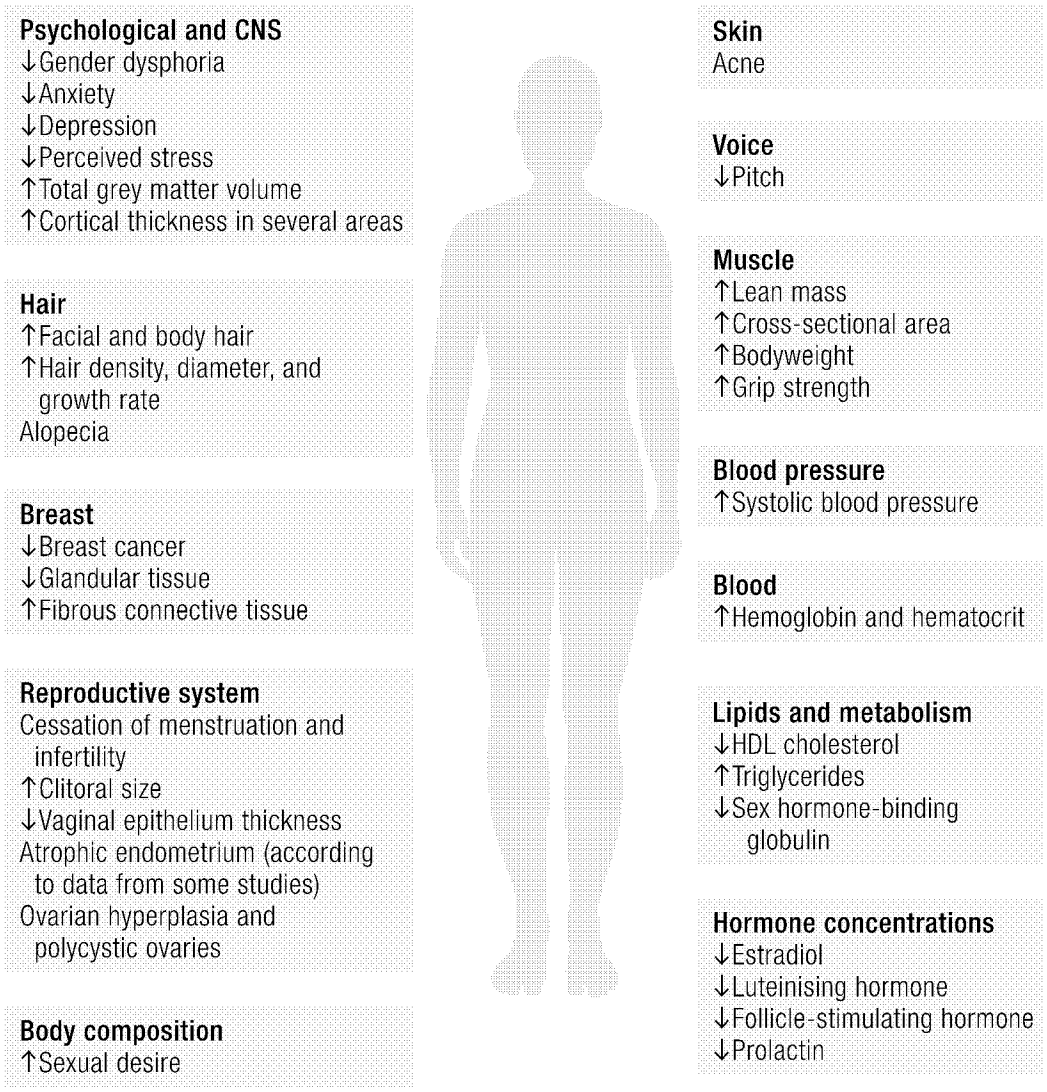

Figure 2. Effects of testosterone treatment in transgender men. [Reproduced with permission from Irwig MS. Testosterone therapy for transgender men. *Lancet* Diabetes Endocrinol 2017;5: 301–311. (110); ©2019 Illustration Presentation ENDOCRINE SOCIETY].

men (n = 77) whose voices sounded more congruent with their experienced gender reported greater well-being than did those with less gender-congruent voices (119). There are very few prospective data on the voice changes in transgender men upon testosterone treatment. Seven transgender men on IM testosterone esters all reached a cisgender male mean fundamental frequency within 6 months of testosterone therapy. A mean decrease of 49 Hz was measured (120). In the largest longitudinal study to date (n = 50, with 36 having data for baseline and 12-months follow-up), acoustic analysis of fundamental frequency of the habitual voice showed a significant decrease after 3 months (−37 Hz), up to 12 months (−67 Hz), with group data congruent with cisgender male reference data. In 24% of participants additional voice therapy was necessary. When using an adapted version of the Transsexual Voice Questionnaire (121) for transgender men looking at self-perception of voice prospectively during IM testosterone undecanoate therapy in 80 participants, improvements during the first 3 months were attributed to the hormonal intervention (80).

Skin and hair. Both androgens and estrogens are known to affect the pilosebaceous unit of the skin, as in the sebocytes and hair follicle dermal papilla androgen and estrogen receptors are expressed. In a study of 17 transgender men, IM testosterone therapy was associated with increases in the Ferriman–Gallwey hirsutism scores (122). After 12 months, facial and abdominal hair had not yet reached diameters found in cisgender males. An increase in acne on the face and back was present in 94% and 88%, respectively, after 4 months. Data on both the shorter-term and longer-term dermatological effects of IM testosterone undecanoate were available from a prospective intervention study in 20 hormone-naive transgender men, combined with a cross-sectional part with 50 transgender men with an average of 10 years on various testosterone treatments (101). The Ferriman–Gallwey

score (in cisgender women usually <8) increased in a time-dependent manner from a median of 0.5 to 12 after 1 year, whereas long-term testosterone treatment resulted in a median score of 24. The presence and severity of acne based on the Gradual Acne Grading Scale increased during the first year and peaked at 6 months; facial acne was present in 82%, and back acne was present in 88%. Long-term data from this study showed that 94% of transgender men had no to mild acne. In a study with 45 transgender men, 16% developed troublesome acne when treated with testosterone undecanoate for 2 years (123).

In a retrospective, observational study, 81 transgender men treated with testosterone esters or testosterone undecanoate self-assessed the degree of male pattern baldness using a five-point scale [*i.e.*, type I (no hair loss) to type V (complete hair loss)]. The authors found that 38% of transgender men had male pattern baldness types II to V. Thinning of hair was related to the duration of androgen administration and present in half of the transgender men after 13 years (124). Wierckx *et al.* (44) reported that 17% of participants developed androgenic alopecia based on the Norwood–Hamilton classification after 1 year of treatment. Longer-term (10 years on average) testosterone treatment was associated with 32% of mild frontotemporal hair loss and 31% moderate to severe androgenetic alopecia (101). In 10 transgender men with androgenetic alopecia, treatment with oral finasteride at 1 mg daily for 12 months induced improvement with one grade on the Norwood–Hamilton scale after a mean of 5.5 months since the start of treatment (70).

Safety data specified for transgender men

Cardiovascular safety. Adult cisgender men have higher cardiovascular mortality rates than do women, which has been attributed to differences in sex hormone levels. However, the available cardiovascular outcome data in transgender men show that testosterone treatment does not result in adverse cardiovascular outcomes (125). Four different recent review papers (86, 116, 126, 127) summarized the effects of testosterone on surrogate risk factors of cardiovascular disease. These reviews demonstrated that despite a perceived negative impact on a number of risk factors, including an increase in hematocrit, a decrease in high-density lipoprotein cholesterol, an increase in triglycerides, low-density lipoprotein cholesterol levels, and inflammation parameters (128), a small increase in systolic blood pressure (44, 123), and a decrease in adiponectin and leptin (129), no significant increase in cardiovascular outcomes was found (77). Furthermore, there have been no elevated rates of cardiovascular deaths when compared with cisgender men and women at short and medium follow-up in the larger studies [except for one study (30)]. However, data on cardiovascular outcomes in older (65+ years of age) transgender men are mostly lacking (86). In a cross-sectional study of 50 transgender men on testosterone treatment of an average of 10 years, no subject had experienced myocardial infarction, stroke, or deep venous thrombosis (130). In a similar case-control study, 138 transgender men on testosterone therapy for an average of 7.4 years showed a low cardiovascular morbidity (85). In a prospective study with 43 transgender men who were treated with testosterone esters every 3 weeks, there was an increased incidence of previously absent metabolic syndrome after 1 (16.3%) and 2 years (18.6%), especially in those with psychiatric comorbidity (131). Furthermore, most studies in transgender men report no adverse impact of testosterone treatment on fasting glucose or insulin sensitivity (44, 106, 129, 131).

Many studies report an association between testosterone therapy and increased Hb (range, +4.9% to 12.5%) and hematocrit (range, +4.4%–17.6%) during the first year of treatment, which then plateaus after the initial year of treatment (105, 123). Clinically significant erythrocytosis has been reported but is likely very uncommon (116). In such cases, practitioners sometimes advise change of the testosterone route of administration or reduction of dosage, despite the absence of outcome data showing risk reduction of thrombotic events. In one study, use of testosterone gel showed smaller increases in Hb (+4%) and hematocrit (+2%) compared with injectable testosterone (106).

A prospective study of 89 transgender men treated with parenteral testosterone undecanoate and lynestrenol for ~4 years found no cases of venous thromboembolic disease despite five subjects who had the activated protein C mutation. The authors concluded that general screening for thrombophilic defects is not recommended (87). In a similar study, 50 transgender men followed for ~10 years found no cases of venous thromboembolism (130)

Importantly, note that most transgender men are still relatively young, at an age when the risk of cardiovascular events is low. Long-term data and data from older transgender men are needed.

Bone health. Sex steroid hormones play important roles in bone growth and maintenance. Men develop larger, longer, and stronger bones during puberty, explained through the combination of sex steroids and mechanical loading. Testosterone therapy in transgender men preserves bone density with adequate dosing due to aromatization of testosterone to estradiol (132). There are very limited data on the risk of osteoporotic fractures in transgender men (91). Transgender men have similar BMD compared with cisgender females prior to testosterone therapy (92, 133, 134).

Following ovariectomy, testosterone substitution therapy appears to prevent short-term (<2 years) (54, 92, 106, 123, 133, 135–137) and long-term (10+ years) (138–141) bone loss due to estrogen deficiency.

Transgender men had larger cortical bone size compared with cisgender females in a cross-sectional study (140). An additional study confirmed the higher cortical thickness by histomorphometric bone biopsy study (142) and higher areal BMD at cortical sites (136, 139). This reflects the effect of androgens on the periosteal circumference of cortical bone. The androgen-induced higher muscle mass also induces a higher mechanical load on the bone, possibly stimulating bone formation according to the mechanostat theory (143). Higher bone formation was observed in transgender men on testosterone (92, 133, 138, 140), and both muscle mass and strength were positively associated with trabecular and cortical parameters and bone size. Nearly all studies reported a maintained areal BMD, which argues against bone loss (91). However, in transgender men who underwent ovariectomy, bone loss has been described when they irregularly used or stopped androgen therapy or when dosage was inadequate (134, 135, 138).

Oncological data and mortality. Both practitioners and transgender men express concern around carcinogenicity of long-term hormonal therapy, although these concerns are not supported by the available data. Recently, the published cancer case reports in transgender men were summarized (144): one vaginal, one cervical, seven breast, one endometrial, and three ovarian cancers have been described to date. The association to risk factors such as smoking and alcohol use, sexually transmitted infections, and lack of adequate access to screening programs has to be acknowledged and included in future research (144). In transgender men on testosterone treatment and not undergoing surgical interventions, breast and cervical cancer screening protocols are advised, but timing and frequency of monitoring of female internal organs in transgender men are a matter of debate.

The available data on cancer mortality are limited and based on studies on four different populations (Belgium, Sweden, Netherlands, and United States). Despite low statistical power, these reviews demonstrate very few cancer events in the population of transgender men (30, 85, 93, 102, 130, 145, 146). The data on overall mortality in transgender men, specifically related to testosterone treatment, are scarce, and the few available studies are underpowered (30). A study from the Dutch cohort with 122 transgender men (145), with a later follow-up on 293 (146) and 364 transgender men (102), reported mortality to be similar to those of the general population. The lack of cancer outcome data underlines the need for studies of a large and inclusive sample size and long-term follow-up from multiple specialized centers.

Other considerations. Fertility: There is a clear need to discuss reproductive options with transgender men before starting testosterone treatment (98). From a study based on a questionnaire, 54% of the transgender men desired to have children and 37% would have banked oocytes had this been possible (147). Genital reconstructive surgery results in an irreversible loss of natural reproductive capacities, whereas testosterone therapy has an important but partially reversible impact on fertility. In theory, embryo and oocyte cryopreservation as established techniques, and ovarian tissue cryopreservation more experimentally can be mentioned as examples of fertility preservation options (148). The necessary hormonal stimulations with multiple endovaginal ultrasound monitoring are likely to be perceived as physically and emotionally difficult, making oocyte cryopreservation not the preferred fertility preservation technique in this group, and some wish to postpone this toward the time of hysterectomy and oophorectomy. A strong suppression of anti-Müllerian hormone has been described in 22 transgender men treated with a GnRH agonist, combined with testosterone gel and an aromatase inhibitor (149). Reassuringly, androgen treatment did not deplete the primordial follicles in the ovarian cortex strips, and a normal distribution of cortical follicles in the ovaries remained intact in 40 transgender men after >1 year of testosterone treatment (150). However, the use of *in vitro* maturation without the use of xenotransplantation is far from implementation in a clinical setting (151). Once a mature oocyte is obtained, the use of partner sperm or donor sperm and a recipient uterus upon thawing of the oocytes, or a female partner or surrogate mother, will enable conception.

"Treatment can generally start when the adolescent is in Tanner stages 2 to 3."

Based on an online survey in 41 transgender men who had been pregnant, of which 25 had used testosterone, 80% reported resuming menstruation within 6 months upon interrupting testosterone treatment, whereas 20% experienced no menses before pregnancy. Of note, exogenous testosterone is not an adequate means of birth control. Testosterone has teratogen effects on the fetus; therefore, transgender men should avoid pregnancy while on testosterone therapy. This is included in preconception counseling that addresses stopping testosterone while trying to conceive and during pregnancy, with the possibility of increasing gender dysphoria during and after the pregnancy. Postpartum, the options for breast feeding and when to reinitiate testosterone have to be discussed (152).

Monitoring of virilizing hormone therapy: Monitoring is advised three to four times in the first year of treatment and once or twice per year thereafter, according to the Endocrine Society guidelines (40). Aiming at testosterone levels in the physiologic normal male range and measuring hematocrit or Hb to avoid erythrocytosis are the most important parameters. Bone densitometry in transgender men should be performed when risk factors (smoking, excessive alcohol use, family history of osteoporosis, history of fracture, use of glucocorticoids, anorexia nervosa) for

osteoporosis exist, and more specifically in those who stop or temporarily interrupt hormone therapy after gonadectomy. Screening for breast and cervical cancer in transgender men who do not undergo surgical interventions is advised (40).

Hormonal treatment in adolescents

The endocrine treatment of transgender adolescents consists of two phases: pubertal suspension or gonadal suppression followed by the addition of hormones. During the first phase, pubertal development is halted and adolescents can further explore their gender identity and prepare for the next phase.

Gonadal suppression in adolescents

Gonadal suppression using GnRH analogs. To achieve gonadal suppression generally, GnRHa analogs (GnRHas) are used (153). GnRHas have been used since 1981 in the treatment of central precocious puberty (154, 155), and their benefits are well established and the use of GnRHa is regarded as both safe and effective, with no long-term adverse effects (156).

Treatment can generally start when the adolescent is in Tanner stages 2 to 3. In clinical practice, transgender boys usually can start when in Tanner breast stage 2 and transgender girls when they have a testicular volume of 6 to 8 mL. Also, adolescents who have already physically matured can use GnRHas to inhibit unwanted pubertal development, such as breast formation and menses in girls or further male phenotype development and erections in boys, until the adolescent's gender identity is more stable (40).

The general safety and efficacy of GnRHas have been studied (157, 158). Anthropometry and body development, hormonal status, and metabolic parameters were followed prospectively in 49 transgender girls (median age at start, 13.6 years; Tanner genital stage 4) and 67 transgender boys (median age, 14.2 years; Tanner breast stage 4) during 12 months of GnRHa monotherapy. Puberty was adequately suppressed with a decrease of testicular volume from 13.9 (±6.5) mL to 8.6 (±4.7) mL in 33 transgender girls. In transgender boys who initiated GnRHas early in puberty at Tanner breast stage 2 and early menarche, breast tissue fully regressed to stage 1 (n = 4) and menses ceased. Effective gonadal suppression was also reflected in a decrease in gonadotropin levels after a period of 3 months to nearly undetectable levels and a coinciding decrease in sex hormones. Testosterone decreased from 262 ng/dL (9.1 nmol/L) to <29 ng/dL (1.0 nmol/L) in transgender girls. In transgender boys, estradiol decreased from a median of 123 pmol/L to 29 pmol/L. As for anthropometry, height velocity decreased in both transgender boys and transgender girls whereas BMI SD score calculated for sex assigned at birth increased significantly. Body composition and the lean body mass percentage decreased and fat percentage increased significantly. Regarding safety monitoring, glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, and creatinine levels did not significantly change from baseline to 12 months of treatment, but alkaline phosphatase decreased, most likely reflecting the decrease in growth velocity (157).

GnRHas are generally well tolerated with the exception of hot flushes early in treatment (158). However, hypertension in transgender adolescents under triptorelin treatment was reported in three transgender boys in a cohort of 138 subjects. Hypertension was reversible upon cessation of triptorelin, but in one case increased intracranial pressure occurred, requiring the temporary use of acetazolamide (159). GnRHa-induced hypertension is an uncommon side effect and has only been reported incidentally in children (160, 161).

Gonadal suppression in adolescents using other regimes. When resources cannot provide for GnRHa alternative treatment, regimens should be considered such as progestagens in transgender boys or CPA in transgender girls (40). Similar to transgender women, endogenous androgen production can be suppressed using antiandrogens such as CPA or spironolactone in late pubertal girls. The effects of prolonged CPA monotherapy were studied retrospectively in 27 transgender girls who were in Tanner genital stage 4. After 6 months of CPA at 50 mg once daily, testosterone decreased from 432 ng/dL (15.8 nmol/L) to 248 ng/dL (8.6 nmol/L) and remained stable at 226 ng/dL (7.8 nmol/L). LH and FSH, however, were not suppressed at 5.0 IU/L and 5.1 IU/L during this period. Prolactin increased from 318.2 pmol/L to 760.8 pmol/L, but none developed galactorrhea. Clinically more than half of the subjects reported reduced shaving frequency and approximately one third had breast development (Tanner breast stages 2 to 3). There was no increase in BMI SD scores. Fatigue was the only reported side effect. As for safety monitoring, only a transient increase of liver enzymes was seen in 15% of the study subjects. The levels remained under the threshold of three times the upper limit and therefore treatment was not stopped. Metabolic parameters such as lipid profile and glucose homeostasis were not negatively affected (162).

In postmenarche adolescent transgender boys an alternative for GnRHas to stop or decrease menses frequency may be the use of progestagens. A cohort of 42 transgender boys (mean age of 15 years and in Tanner breast stage 4) was retrospectively studied during 11.6 months of lynestrenol monotherapy. After 6 months, metrorrhagia occurred in 50% but reduced to 18% in the following 6 months. Subjects reported headache (12%) and hot flushes (10%). Serum LH decreased from 7.56 IU/L to 2.58 IU/L, but levels of FSH and estradiol remained unchanged. Weight increased during the first 6 months but returned to baseline value after 12 months. Regarding safety

monitoring, Hb and hematocrit increased but remained in the normal male range. Liver enzymes, lipid profile, and glucose homeostasis were not negatively affected (163).

The addition of gender-affirming hormones to GnRHa monotherapy

Hormone therapy in adolescents generally has two treatment regimes. In the case when GnRHa treatment is initiated in the early stages of pubertal development, the "new" puberty is induced with a dosage scheme that is also common in hypogonadal patients. Alternatively, when GnRHa treatment is initiated in late puberty and thus the duration of the hypogonadal state was limited, hormones can be given at a higher initial dose and more rapidly increased until the expected adult dose. An additional advantage of GnRHa treatment is that hormones do not have to be administered in supraphysiological dosages, which would otherwise be needed to suppress endogenous sex steroid production (40).

The timing of starting sex hormones in transgender adolescents continues to be an issue of debate. The recommended age of 16 years (40) is based on local jurisdiction, and not on cognitive maturation or pubertal development. In most countries at age 16 one is considered to be legally adult and one can make medical decisions. Indeed, when the first studied cohort was started in the Netherlands the age of 16 was chosen for this very reason. As a consequence there are few data available on starting GnRHa at an earlier age. The Endocrine Society guidelines make a recommendation to allow hormone therapy to be initiated at ages younger than 16 when the transgender child is evaluated by a multispecialty team with expertise in gender identity development in children. However, the need for re-evaluating the recommended age for starting GnRHa may shift in the future (1).

Transgender girls. For a pubertal induction, it is recommended to start 17β-estradiol at a dosage of 5 mg/kg/d, followed by six monthly increments of 5 mg/kg until a maintenance dosage of 2 mg is reached. The second treatment regimen is more suitable for transgender girls who initiated gender-affirming treatment when at least 15.5 years old. After a period of gonadal suppression varying from 3 to 6 months, estrogens can be given at a daily start dosage of 1 mg and increased to 2 mg after 6 months (40).

The effects of the addition of 17β-estradiol were studied prospectively in 28 transgender girls (155). Estrogen treatment was started at a median age of 16.0 years after a median duration of 24.8 months of GnRHa monotherapy. Breast development had started within 3 months, and after 1 year median Tanner breast stage was 3 progressing to 5 after 3 years (n = 16) with a variability of all breast stages. With respect to body shape, hip circumference increased and waist circumference decreased. Although BMI increased, BMI SD scores did not. When bone age was <15 years at the start of estradiol, median height gain was 6.8 cm after 3 years of estrogen therapy. Overall final height was 182.7 cm, corresponding to +1.9 SD for Dutch adult women. When the adult dose of 2 mg of estradiol daily was used during a median duration of 2 years, the median serum estradiol was 27 pg/mL (100 pmol/L) [range, 6.5 to 103 pg/mL (24 to 380 pmol/L)]. A change in prolactin levels was not seen. Additionally, Hb, hematocrit, HbA1c, liver enzymes, and creatine remained unchanged (164).

Transgender boys. For pubertal induction the use of testosterone ester injections is recommended. The initial dose is 25 mg/m^2 every 2 weeks IM and is increased with 25 mg/m^2 every 6 months. The maintenance dosages vary from 200 mg per 2 weeks for testosterone monoesters, such as testosterone enanthate, to 250 mg per 3 to 4 weeks for testosterone ester mixtures. For transgender boys who started treatment in late puberty, testosterone can be started at 75 mg IM every 2 weeks, followed by the maintenance dosage after 6 months (40). It is advised to continue GnRHa at least until maintenance dosage of testosterone is reached and preferred to continue until gonadectomy. With androgens, virilization of the body occurs, including lowering of the voice, more muscular development, particularly in the upper body, facial and body hair growth, and clitoral growth (40, 158).

Other considerations. Bone health in transgender adolescents: During puberty, the bone mass increases and peak bone mass is only achieved at the age of 20 to 30 years (165, 166). Bone mass accrual is regulated by genetic factors, gonadal hormones, and environmental factors such as physical activity and adequate supply of nutrients (calcium, vitamin D). During the hypogonadal state induced by GnRHa monotherapy, BMD is affected (167, 168). In transgender girls BMD of the lumbar spine remained stable but z score decreased during 1.5 to 2 years of gonadal suppression. In the femoral region, BMD and z score decreased but not significantly. In contrast, in transgender boys the BMD of lumbar spine and femoral region decreased together with the corresponding z scores (168).

When sex steroids are added, bone mass accrual reassumes. In transgender girls, absolute BMD and z scores in the lumbar spine but not the hip increased (167, 168), but after 2 years of estrogen their z scores were still below those of age- and sex assigned–matched norms (168). In transgender boys (150, 151), the bone density and z scores of the lumbar spine and the femoral region increased (n = 42) after 2 years of testosterone therapy but were still not at pretreatment levels (168).

When BMD development was assessed until young adulthood, however, it was found that the loss in z score was still partially present at the age of 22

"GnRHa treatment in adolescents is both clinically and biochemically effective in suppressing the hypothalamic-pituitary-gonadal axis and appears to be well tolerated and safe."

implying a possible delay in or loss of peak bone mass (167). To this date only one case report has been published on long term BMD development and it was shown that absolute BMD and *z* scores of a transgender man, treated with GnRHa in his adolescence was in the normal range at age 35. However pretreatment data were not provided (169).

The addition of gender-affirming hormones to other methods of gonadal suppression: For transgender girls, two retrospective studies reported on the addition of estrogens to antiandrogen therapies in transgender adolescents. In one study the subjects received CPA (163), and in the other study spironolactone (79) was used. The addition of estrogens to CPA monotherapy in transgender girls resulted in either the initiation or further progression of breast development. Oral 17β-estradiol was started at 0.5 mg daily and increased to 0.75 mg after 6 months. After 12 months of estrogen therapy, 66.7% reached Tanner breast stage 3 and 9.5% reached Tanner breast stage 4. After 12 months, both testosterone and LH decreased significantly to 168 ng/dL (5.8 pmol/L) and 3.2 IU/L, respectively, and FSH demonstrated a declining trend to 2.8 IU/L. The mean 17β-estradiol level was 33 pg/mL (121.1 pmol/L). The most common adverse event reported by the transgender girls was fatigue but resolved in almost all. BMI SD scores remained stable. In addition metabolic parameters, lipid profile and glucose homeostasis did not change (162).

In a study of 44 transgender girls (mean age, 18 years; range, 14 to 25 years) of whom 38 received spironolactone (dosage, 50 to 200 mg daily), oral estrogen was added in three routes: oral (dosage between 1 and 8 mg daily), IM (dosage 20 to 80 mg monthly), or transdermal (dosage 0.025 to 0.200 mg weekly). There were no changes reported in BMI, metabolic parameters, lipid profile, and prolactin and there were no differences in the methods of administration. Among the 38 subjects taking spironolactone, potassium levels did not change (79).

For transgender boys, testosterone can be added to progestagens as previously described (40) The clinical effects and effects on metabolic parameters in adolescent transgender boys have been investigated retrospectively in two studies, one single-center study (n = 42) (163) and one multicenter study center (n = 72) (79); however, in the latter study, seven subjects had received GnRHas prior to the testosterone therapy. Only the single-center study reported on side effects, which were fatigue and acne. Clinically, there was a weight gain as both BMI (79) and BMI SD scores increased (163). Although testosterone preparation and dosing differed, both studies reported an increase in both Hb and hematocrit. With a testosterone ester mixture on a biweekly frequency, values remained within the normal male range (163), whereas when treated with testosterone ester on a weekly base, hematocrit increased to supraphysiological levels of >50% in 3% of the cohort (two cases) with no adverse events reported (79). Alanine aminotransferase, aspartate aminotransferase, and creatinine increased but remained in the normal range. Lipid profile was more unfavorable with an increase of cholesterol and low-density lipoprotein and a decrease of high-density lipoprotein. Glucose homeostasis parameters HbA1c (79, 163) and insulin, glucose, or homeostatic model assessment index (154) were not affected.

Final considerations. Knowledge regarding the treatment of gender dysphoria and nonconforming has steadily advanced during the past 10 years (170). Although the psychological benefits of gender-affirming treatment of young adolescents with gender dysphoria using GnRHas have been established (171, 172), data on long-term health outcome are still sparse. GnRHa treatment in adolescents is both clinically and biochemically effective in suppressing the hypothalamic–pituitary–gonadal axis and appears to be well tolerated and safe (157). However, transgender boys may be more susceptible to the development of arterial hypertension (159). Studies regarding treatment with estrogen on pubertal development and short-term safety demonstrate feminization of the body without adverse events (164). In transgender boys, data on combined GnRHas and androgens is lacking. Retrospective reports on BMD development demonstrated a loss of *z* scores in transgender boys and transgender girls during gonadal suppression, followed by an increase after the addition of hormones, but at the age of 22 years *z* scores were still under pretreatment levels. Other long-term follow-up data are not available. Also, the aforementioned studies mainly describe a relatively older and mature group, mid-teens and Tanner stage 4 and up, which coincides with a relatively shorter duration of an induced hypogonadal state. There are currently no publications available focusing on treatment of the young and less matured (Tanner stages 2 or 3) adolescents with gender dysphoria, and therefore the effects of prolonged gonadal suppression (*i.e.*, 3 to 4 years) for the short term or long term are unknown. There needs to be investigation when the initiation of sex steroid hormones before the recommended age of 16 may prevent the negative sequelae of hypogonadism on the skeleton. Finally, when GnRHas are not available, alternative methods to suppress puberty can be used in the more sexually matured adolescent. Short-term data on the uses of antiandrogens in transgender girls and progestagens in transgender boys demonstrated their efficacy and safety (162, 163).

Key Conclusions and Recommendations for Future Clinical Research

The current available research is based mostly on cross-sectional studies, with limited longitudinal data.

There is also a paucity of information on diverse ethnic and socioeconomic populations and studies on treatment outcome in adolescents. The current literature comes from mostly Western European and from higher income countries, where many participants undergo surgical procedures, and has at best intermediate duration follow-up. Limited data exist on hormonal treatment in gender nonbinary persons. For specific analyses such as outcome or mortality, no single center has a sufficiently large patient base to study the population with statistical rigor.

An important barrier to better care is the diversity of training and practice across providers. Health care professionals continue to face challenges in providing optimal care for the transgender population, also due to a lack of education on the topic. The improvement of formal transgender education in medical schools and among health care providers in the broadest sense is timely (173). Professionals working in health services need to understand that patient gender identity is important and needs to be considered during any consultation. Treating people with respect requires a good understanding of people's identity regarding their gender. Transgender health care has to be included in national and international conferences of all involved specialties. We feel strongly about the fact that involving the transgender community at all stages of research is vital. This patient-centered research will progressively lead toward more studies where transgender community involvement is crucial in identifying research priorities, research design, helping recruitment, and dissemination of study results. Patient-centered outcome priorities in endocrinology are breast development in transgender women, time to menstrual cessation in transgender men, dose-related responses to hormonal interventions, and effect on sexual function and fertility, among many others (174).

Transgender medicine research is finally moving away from case reports and small series. Many efforts have gone into summarizing available data in numerous recent systematic reviews, from which we have to internalize the findings, avoid repeating the same research, and take the investigations further. The collection and reporting of original good quality data through networks has to be higher on the agenda. Innovative and patient-centered long-term research with randomized controlled trials if possible, to advance of the safety and efficacy of hormonal interventions, is a priority. In doing so, clinicians and academics must listen to the voices of transgender people, recognizing and respecting the internal diversity within the transgender community.

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Abbreviations

BMD, bone mineral density; BMI, body mass index; CPA, cyproterone acetate; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; GnRHa, gonadotropin releasing hormone analog; ICD, International Classification of Diseases and Related Health Problems. .

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ORIGINAL PAPER

Alterations in Body Uneasiness, Eating Attitudes, and Psychopathology Before and After Cross-Sex Hormonal Treatment in Patients with Female-to-Male Gender Dysphoria

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Abstract
Body dissatisfaction plays an important role in the development of psychiatric problems such as eating disorders as well as gender dysphoria (GD). Cross-sex hormonal treatment (CHT) alleviates the dissatisfaction by making various changes in the body. We examined the alteration of body uneasiness, eating attitudes and behaviors, and psychological symptoms longitudinally in Turkish participants with female-to-male gender dysphoria (FtM GD) after CHT. Thirty-seven participants with FtM GD and 40 female controls were asked to complete the Body Uneasiness Test to explore different areas of body-related psychopathology, the Eating Attitudes Test to assess eating disturbances, and the Symptom Checklist-90 Revised to measure psychological state, both before CHT and after 6 months of CHT administration. The baseline mean body weight, BMI scores, body uneasiness scores, and general psychopathological symptoms of participants with FtM GD were significantly higher than female controls, whereas baseline eating attitudes and behaviors were not significantly different. Over time, FtM GD participants' mean body weight and BMI scores increased, body uneasiness and general psychopathological symptoms decreased, and eating attitudes and behaviors had not changed at 24th weeks following CHT administration compared to baseline. CHT may have a positive impact on body uneasiness and general psychopathological symptoms in participants with FtM GD. However, CHT does not have an impact on eating attitudes and behaviors.

Keywords Body image · Body uneasiness · Cross-sex hormonal treatment · Eating attitudes · Gender dysphoria

Introduction

Gender dysphoria (GD) is characterized by the distress resulting from incongruence between an individual's expressed/experienced gender and their sex as assigned at birth (American Psychiatric Association, 2013). Body image problems and body dissatisfaction are important components of GD (Jones, Haycraft, Murjan, & Arcelus, 2016; Zucker, Lawrence, & Kreukels, 2016), and it has been argued that concerns about the body are the primary source of distress (Bandini et al., 2013). The distress is related to the fact that the physical characteristics of the person are not of the biological sex he/she desires (van de Grift et al., 2016a), and becomes much more salient with the onset of puberty and the emergence of secondary sex characteristics (Zucker et al., 2016). To reduce this distress and to eliminate dysphoria, most people with GD desire to quell their existing primary and/or secondary bodily sex characteristics and instead obtain those of the opposite sex (Fisher et al., 2014; Vocks, Stahn, Loenser, & Legenbauer, 2009), often through the use of cross-sex hormonal treatment (CHT) and/or sex reassignment surgery (SRS; Bandini et al., 2013; Fisher et al., 2014; Gómez-Gil et al., 2012; Kraemer, Delsignore, Schnyder, & Hepp, 2008).

The complex concept of body image involves the perception, imagination, emotion, and behavior with regard to one's physical appearance (Becker et al., 2016; Cash, Ancis, & Strachan, 1997; Cuzzolaro, Vetrone, Marano, & Garfinkel, 2006). It can be examined by assessing body-related

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satisfaction, feelings, ideals, and quality of life (van de Grift et al., 2017). Body dissatisfaction has also been depicted as the negative evaluation of one's appearance (Jones et al., 2016). People with GD, compared to those without, evaluate their own bodies more negatively because of the conflict between their current body and their gender identity (Becker et al., 2016; Couturier, Pindiprolu, Findlay, & Johnson, 2015; Jones et al., 2016; van de Grift et al., 2016a; Vocks et al., 2009; Witcomb et al., 2015). Further, in two recent studies, it has been shown that body image problems of people with GD extend beyond sex characteristics (Becker et al., 2016; van de Grift et al., 2016a).

The literature emphasizes that body dissatisfaction plays an important role in the development of disordered eating as well as in GD (Ålgars, Alanko, Santtila, & Sandnabba, 2012; Jones et al., 2016; Khoosal, Langham, Palmer, Terry, & Minajagi, 2009). Negative body image is closely linked with various forms of psychiatric disorders, including eating disorders (Klemchuck, Hutchinson, & Frank, 1990; Tylka, 2004), among both male-to-female (MtF; Couturier et al., 2015; Ewan, Middleman, & Feldmann, 2014; Hepp & Milos, 2002; Hepp, Milos, & Braun-Scharm, 2004; Winston, Acharya, Chaudhuri, & Fellowes, 2004) and female-to-male (FtM; Couturier et al., 2015; Fernández-Aranda et al., 2000; Turan, Aksoy Poyraz, & Duran, 2015a) individuals with GD. Further, research concerning the interaction between GD and eating disorders (Feder, Isserlin, Seale, Hammond, & Norris, 2017; Vocks et al., 2009) has revealed various reasons for the distorted body image and maladaptive eating-related attitudes observed in GD individuals, including MtF individuals wanting to be "super females" (Hepp & Milos, 2002) and equating slimness with attractiveness, and FtM individuals striving to reduce their body weight in order to suppress female sexual characteristics and menstruation (Hepp & Milos, 2002; Turan et al., 2015a).

However, few studies have explored the relationships among GD, body image, and eating disorders. In one such study, Vocks et al. (2009) found that individuals with MtF GD reported higher levels of disturbed eating behavior compared to both male and female controls, although no significant differences were detected between FtM individuals and female controls. In a study of the relationships among gender identity, body dissatisfaction, and eating behaviors, Ålgars, Santtila, and Sandnabba (2010) found that both women and men with a conflicted gender identity were less satisfied with their bodies than control participants. Further, while women with conflicted gender identity showed more disordered eating than female controls, there were no significant differences between men with a conflicted gender identity and male controls. More recently, Witcomb et al. (2015) assessed the risk of the development of disordered eating by comparing persons with GD, persons with eating disorders, and controls. Overall, those with eating disorders were at a higher risk of eating psychopathology than persons with GD or controls, persons with GD had greater body dissatisfaction than controls, and persons with FtM GD and men with eating disorders had similar levels of body dissatisfaction.

CHT is an essential component of the sex reassignment process (Coleman et al., 2012) and has been reported to have positive effects on the mental and sexual health of most GD individuals (Colizzi, Costa, & Todarello, 2014; Gómez-Gil et al., 2012; Heylens, Verroken, De Cock, T'Sjoen, & De Cuypere, 2014b; Klein & Gorzalka, 2009). Further, body uneasiness and concerns about body dissatisfaction have been found to significantly decrease after receipt of CHT (Fisher et al., 2014; Khoosal et al., 2009; Kraemer et al., 2008). Testosterone is a vital male sex hormone that is administered during FtM CHT, and it plays a key role in the development and maintenance of male attributes. It regulates many physiological processes, including protein, lipid, carbohydrate, and bone metabolism (Corona et al., 2013; Gooren, Giltay, & Bunck, 2008; Traish, 2014), and alters body composition by increasing muscle mass and decreasing fat mass (Bassil, Alkaade, & Morley, 2009; Harman & Blackman, 2003; Van Caenegem et al., 2015). However, the impact of testosterone and other forms of CHT on eating attitudes along with body uneasiness has not been investigated in longitudinal studies in the context of persons with GD.

To fill this gap, the present study investigated longitudinally the short-term impact of how body uneasiness, eating attitudes, and psychopathology change in persons with FtM GD after CHT administration. We hypothesized that body-related uneasiness would diminish, eating attitudes would improve, and psychological symptoms would improve among this group after CHT administration.

Method

Participants and Procedure

A total of 41 persons with FtM GD who had applied for sex reassignment at the Istanbul University Cerrahpaşa Medical Faculty were enrolled. Criteria for inclusion were as follows: (1) aged over 18 years; (2) diagnosis of GD according to the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*; American Psychiatric Association, 2013), and confirmed after several sessions with two different mental health professionals specializing in GD. The exclusion criteria were as follows: (1) the presence of any neurological, metabolic, endocrinological, or intersexual pathology; (2) had previously received CHT or any kind of sex reassignment surgery (SRS); (3) an intellectual disability; and (4) illiteracy.

During initial screening for compliance with the exclusion criteria, one person was excluded because of detection of 5-alpha-reductase deficiency syndrome. All 40 participants

were initially considered eligible for CHT after a multidisciplinary assessment, but two of them were excluded because they had mastectomies and one participant chose not to continue with the process. None of the patients had any intellectual disability according to the diagnostic criteria of *DSM-5*. Consequently, the study protocol was completed by 37 eligible participants, with data collected before CHT began (baseline) and at the 24th week of CHT administration. Clinical diagnostic assessments were conducted over 24 weeks by psychiatrists, psychologists, endocrinologists, and medical geneticists, in accordance with the legal requirements defined for CHT in Turkey. The process of sex reassignment in Turkey is determined by article 40 of the Turkish Civil Code. According to the article, permission can only be given if the person is older than 18 years of age, not married, and has official medical board reports to prove that the operation is psychologically needed and that the ability to reproduce is permanently lost.

The control group comprised 40 age and educational status-matched female volunteers. This was composed of nursing students, hospital staff, and their family members. Informed consent was obtained from all participants included in the study.

The CHT administration practices followed by the Cerrahpaşa Medical Faculty are largely based on the standards of care guidelines of the World Professional Association for Transgender Health (7th version; Coleman et al., 2012). Hormonal treatment for FtM GD persons involves the administration of intramuscular injections of either 250 mg of testosterone esters depot (30 mg testosterone propionate, 60 mg testosterone phenylpropionate, 60 mg testosterone isocaproate, and 100 mg testosterone decanoate) every 3–4 weeks, or 1000 mg of testosterone undecanoate every 12–14 weeks.

Measures

Sociodemographical and clinical variables such as age, level of education, employment status, relationship status, and sexual orientation were collected via a semi-structured sociodemographical and clinical data form. Sexual orientation was assessed by asking participants the following question: "How would you describe your sexual orientation?," with the response choices of "only members of the same biological sex are sexually attractive to me," "only members of the opposite biological sex are sexually attractive to me," "both members of the same biological sex and members of the opposite biological sex are attractive to me," "neither members of the same biological sex nor members of the opposite biological sex are attractive to me," and "others." Body weight and height were measured while participants were wearing lightweight clothing and no shoes.

Body Uneasiness Test

The Body Uneasiness Test (BUT; Cuzzolaro et al., 2006) is a 71-item self-report questionnaire that is used to assess body image disturbances, with responses rated on a 6-point Likert-type scale (1 = *never* to 6 = *always*). It consists of two parts: BUT*A (consisting of 34 items) measures present body uneasiness through calculating a Global Severity Index (GSI). BUT*B (consisting of 37 items) measures the focus of attention on a specific body part or function. BUT*A investigates five factors: weight phobia, body image concerns, avoidance, compulsive self-monitoring, and depersonalization, and a GSI score over 1.2 indicates a high risk of discomfort with one's body. BUT*B scores are combined to form two global measures: the positive symptom total (PST) and the positive symptom distress index (PSDI), with higher scores indicating greater body uneasiness. The BUT has been validated in large samples of both nonclinical and clinical (suffering from eating disorders) participants and shows good psychometric properties (Cuzzolaro et al., 2006). Cronbach's alpha for internal consistency was .72 in the present study.

Eating Attitudes Test

Eating disturbances were assessed using the 40-item Eating Attitudes Test (EAT-40; Garner & Garfinkel, 1979), which is a multidimensional self-report questionnaire that is used to identify abnormal eating attitudes, behaviors, and traits. Responses are scored on a 6-point Likert-type scale (1 = *never* to 6 = *always*). Items 1, 18, 19, 23, and 39 are scored as follows: 6 = 3 points; 5 = 2 points; 4 = 1 point; 3, 2, or 1 = 0 points. The other items are scored as follows: 1 = 3 points; 2 = 2 points; 3 = 1 point; 4, 5, or 6 = 0 points. Total scores ranged from 0 to 120, and higher scores indicate more disordered eating attitudes and behaviors. A score of 30 or above indicates that the respondent is at risk of an eating disorder (Garner, Olmsted, Bohr, & Garfinkel, 1982). The Turkish adaptation of the EAT-40 was developed by Savaşır and Erol (1989).

Symptom Checklist-90-Revised

The Symptom Checklist-90-Revised (SCL-90-R; Derogatis, Rickels, & Rock, 1976) is a 90-item self-report inventory that is designed to measure ten symptoms of psychopathology (Somatization, Obsessive–Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, Psychoticism, and Additional) over a 1-week interval. Responses are made on a 5-point Likert-type scale (0 = *not at all* to 4 = *extremely*). The Global Severity Index (GSI) is the mean of all of the subscale scores and indicates overall psychological distress. The validity and reliability of the Turkish version of the SCL-90-R were assessed by

Dağ (1991), who stated that a GSI score higher than 1.00 is considered to indicate that symptoms exist at a psychopathology level.

Statistical Analysis

Statistical analysis was conducted using SPSS 21 (SPSS Inc., Chicago, IL). We calculated percentages for categorical variables and means and SD for quantitative variables. Initially, the differences in the demographic variables between participants with FtM GD and female controls were evaluated using independent *t* tests. Participants' weight, BMI, EAT-40, adjusted mean scores of the SCL-90-R dimensions, and BUT scores were compared before and after CHT treatment with female controls using independent samples *t* tests. Comparison of the same variables in participants with FtM GD before and after CHT treatment exposition was performed using paired *t* tests. To avoid inflation of the risk of false-positive results by multiple comparisons, alpha levels were adjusted using the conservative Bonferroni method which applies an adjusted alpha level that is calculated based on the number of scales in each questionnaire. Effect sizes were calculated for each variable using Cohen's *d*. The significance level was set at $p < .05$.

The association between the scales (EAT-40, SCL-90-R, and BUT) and biodemographic characteristics (age, level of education, weight, and BMI), and between the scales (EAT-40, SCL-90-R, and BUT) were explored using Spearman rank-order correlations.

Results

Sample Characteristics

The data from 37 participants with FtM GD and 40 female controls were analyzed. Age, level of education, employment status, relationship status, and sexual orientation of the participants included in the study are summarized in Table 1. Participants with FtM GD and female controls did not show any significant differences in their sociodemographical characteristics.

Body Uneasiness

FtM GD participants' baseline scores on all BUT*A subscales (Global Severity Index, Body Image Concern, Avoidance, Compulsive Self-Monitoring, and Depersonalization; all $p < .001$), except for Weight Phobia, were significantly higher than those of female controls. With regard to BUT*B subscales, the baseline scores of participants with FtM GD for BUT*B–II (shape of the head and face, forehead, ears, chin, neck), BUT*B–III (stomach, abdomen, hips, thighs, knees), BUT*B–IV (stature, legs, ankles, feet, hands), BUT*B–V (arms, shoulders, chest, breasts, genitals), BUT*B–VIII (sweating, blushing, noises, odors, buttocks), and PSDI were significantly higher than female controls (all $p < .001$).

FtM GD participants' scores on all BUT*A subscales after CHT (Global Severity Index, Body Image Concern,

Table 1 Sociodemographic characteristics of participants with female-to-male gender dysphoria and female controls

Characteristic	FtM GD participants $n = 37$	Female controls $n = 40$
	$M \pm SD$	
Age (years)	24.59 ± 4.90	22.70 ± 3.50
Level of education (years)	12.30 ± 3.10	12.23 ± 1.31
	Number (%)	
Employment status		
Employed	14 (37.8%)	13 (32.5%)
Student	19 (51.4%)	23 (57.5%)
Unemployed	4 (10.8%)	4 (10.0%)
Relationship status		
Single	17 (45.9%)	19 (47.5%)
In a relationship	20 (54.1%)	21 (52.5%)
Sexual orientation		
Same biological sex	37 (100%)	0 (0%)
Opposite biological sex	0 (0%)	40 (100%)
Bisexual	0 (0%)	0 (0%)
Asexual	0 (0%)	0 (0%)
Others	0 (0%)	0 (0%)

FtM GD female-to-male gender dysphoria

Avoidance, Compulsive Self-Monitoring, and Depersonalization; $p = .001$ for Compulsive Self-Monitoring; $p < .001$ for other subscales), except for Weight Phobia, were significantly higher than female controls as well as the baseline (pre-CHT) scores. The scores of BUT*B subscales after CHT for participants with FtM GD for BUT*B–III ($p < .001$), BUT*B–V ($p < .001$), BUT*B–VIII ($p = .001$), and PSDI ($p < .001$) were significantly higher than those of female controls.

The BUT*A-Global Severity Index ($p = .002$), BUT*A-Body Image Concern ($p = .001$), and BUT*A-Depersonalization ($p = .002$) scores decreased significantly after CHT compared to baseline in participants with FtM GD. With regard to scores for all BUT*B subscales, there were no significant changes after CHT compared with baseline in FtM GD participants' scores. The differences between the groups in relation to BUT*A and BUT*B scores are shown in Table 2.

Weight, BMI, and Eating Attitudes

The baseline mean body weight of participants with FtM GD was higher than that of female controls, and it increased significantly after CHT ($p < .001$). Similarly, in terms of the baseline values for BMI, participants with FtM GD had a higher BMI than female controls, and BMI significantly increased after CHT ($p < .001$). Neither participants with FtM GD nor female controls met the required score for eating disorders (> 30 points) as measured by the EAT-40, and there was no significant change in FtM GD participants' EAT-40 scores after CHT. With regard to EAT-40, there was no significant difference between FtM GD (both who use hormonal treatment and who do not use) and female controls. Comparisons of the groups (baseline, after CHT, and female controls) in terms of EAT-40 are shown in Table 3.

Psychopathology

FtM GD participants' baseline scores for all SCL-90-R subscales (Somatization, Obsessive–Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Paranoid Ideation, Psychoticism, and Additional Symptoms; all $p < .0045$), except for Phobic Anxiety, were significantly higher than those of female controls. After CHT in participants with FtM GD, there were no significant differences for Obsessive–Compulsive, Interpersonal Sensitivity, Depression, and Additional Symptoms subscales compared to female controls. For participants with FtM GD, there was a significant decrease in Interpersonal Sensitivity and Psychoticism scores from before to after CHT. The results concerning the comparisons of the SCL-90-R at baseline of participants with FtM GD to after CHT, and compared to the female controls are presented in Table 4.

No significant correlation was found between age, level of education, weight, BMI, and body uneasiness, eating attitudes and psychopathology. Results of correlation are presented in Table 5.

Discussion

In this short-term longitudinal study, we investigated alterations in body uneasiness, eating attitudes, and psychopathology after the use of CHT in a sample of participants with FtM GD. The main results were as follows: (1) the baseline mean body weight, BMI scores, body uneasiness scores, and general psychopathological symptoms of participants with FtM GD were higher than female controls, but baseline eating attitudes and behaviors were not; (2) compared to baseline, at the 24th week of CHT administration, participants' mean body weight and BMI scores had increased, body uneasiness and general psychopathological symptoms decreased, but eating attitudes and behaviors had not changed.

Previous studies on body image have determined that people with GD are dissatisfied with their bodies and are particularly likely to develop body image disturbances (Ålgars et al., 2010; Becker et al., 2016; Jones et al., 2016; Lindgren & Pauly, 1975; van de Grift et al., 2016a; Vocks et al., 2009). CHT or SRS can help to address this (Bandini et al., 2013; Fisher et al., 2014; Fisher et al., 2016; Khoosal et al., 2009; Kraemer et al., 2008; Kuiper & Cohen-Kettenis, 1988; Pauly & Lindgren, 1976–1977; van de Grift et al., 2016b, 2017). However, as not all body parts are affected by the treatment for GD, it is uncertain whether medical interventions can completely alleviate body dissatisfaction (van de Grift et al., 2017). In their investigation of body uneasiness, Fisher et al. (2014) found that participants with MtF GD who used CHT reported less body uneasiness compared with participants with MtF GD who did not use CHT; however, contrary to their expectations, no significant differences were observed between CHT and no-CHT participants with FtM GD. In a more recent longitudinal study by Fisher et al. (2016), participants with GD were reported to have significantly lower subjective levels of GD and body uneasiness after CHT as compared to those without. In the present study, we found that the body uneasiness of participants with FtM GD was higher than that of female controls at baseline, and this uneasiness was reduced after the CHT administration. This may be because the effects of CHT promote acceptance and appreciation of individuals' ideal body shape by relieving body-related distress through modifying secondary sex characteristics (Fisher et al., 2014).

In our study, Body Image Concern, Avoidance, Compulsive Self-Monitoring, and Depersonalization scores were significantly higher for participants with FtM GD than those for female controls, but Body Image Concern and Depersonalization scores were significantly lower after CHT. The alleviation of Body Image Concern after CHT suggests that

Table 2 Body Uneasiness Test scores at baseline and after cross-sex hormonal treatment for participants with female-to-male gender dysphoria compared with female controls

BUT Scale	FtM GD participants: baseline $n=37$		FtM GD participants: after CHT $n=37$		Female controls $n=40$		Group comparison 1		
	M	SD	*M*	SD	*M*	SD	*df/t*	*p**	Effect size (Cohen's *d*)
BUT*A									
Global severity index[a]	2.52	.84	2.00	.95	.65	.71	75/10.61	< .001	2.40
Weight phobia[a]	2.75	1.04	2.31	1.20	.86	.94	75/− .70	ns	− .16
Body image concern[a]	3.28	1.10	2.52	1.20	.75	.85	75/11.32	< .001	2.57
Avoidance[a]	2.11	1.19	1.63	1.10	.42	.62	53.15/7.72	< .001	1.78
Compulsive self-monitoring[a]	1.60	.95	1.32	.97	.65	.71	66.18/4.93	< .001	1.13
Depersonalization[a]	2.27	.97	1.74	1.08	.45	.56	56.70/9.97	< .001	2.30
BUT*B									
BUT*B–I[a] (eyebrows, eyes, nose, mouth, lips, teeth)	.40	.51	.63	1.39	.34	.36	64.15/.62	ns	.14
BUT*B–II[a] (shape of the head and face, forehead, ears, chin, neck)	.56	.56	.79	1.81	.15	.22	46.39/4.21	< .001	.96
BUT*B–III[a] (stomach, abdomen, hips, thighs, knees)	1.76	1.31	1.85	2.45	.37	.58	48.67/5.95	< .001	1.37
BUT*B–IV[a] (stature, legs, ankles, feet, hands)	.83	1.03	1.10	2.69	.12	.22	39.06/4.14	< .001	.95
BUT*B–V[a] (arms, shoulders, chest, breasts, genitals)	3.00	.96	2.74	2.41	.24	.40	47.63/16.3	< .001	3.75
BUT*B–VI[a] (mustache, beard, facial hair)	.75	1.67	.33	.97	.28	.76	49.47/1.55	ns	.36
BUT*B–VII[a] (hair, skin)	.77	1.13	.88	1.31	.39	.80	75/1.72	ns	.39
BUT*B–VIII[a] (sweating, blushing, noises, odors, buttocks)	1.89	.94	1.68	2.33	.28	.45	50.48/9.47	< .001	2.19
PST[b]	14.89	7.65	13.81	8.17	9.45	11.35	75/2.45	ns	.56
PSDI[a]	3.29	.77	2.96	1.00	.34	.41	53.52/20.8	< .001	4.78

BUT Scale	Group comparison 2			Group comparison 3		
	df/t	*p**	Effect size (Cohen's *d*)	*df/t*	*p**	Effect size (Cohen's *d*)
BUT*A						
Global severity index[a]	75/7.1	< .001	1.61	37/3.42	.002	.58
Weight phobia[a]	75/− .76	ns	− .18	37/2.46	ns	.39
Body image concern[a]	64.16/7.37	< .001	1.70	37/3.70	.001	.66
Avoidance[a]	55.82/5.88	< .001	1.36	37/2.32	ns	.42
Compulsive self-monitoring[a]	75/3.47	.001	.79	37/1.57	ns	.29
Depersonalization[a]	53.19/6.49	< .001	1.50	37/3.27	.002	.52
BUT*B						
BUT*B–I[a] (eyebrows, eyes, nose, mouth, lips, teeth)	40.47/1.24	ns	.29	37/− 1.18	ns	− .22
BUT*B–II[a] (shape of the head and face, forehead, ears, chin, neck)	37.02/2.15	ns	.50	37/− .79	ns	− .17
BUT*B–III[a] (stomach, abdomen, hips, thighs, knees)	39.67/3.58	.001	.83	37/− .24	ns	− .05
BUT*B–IV[a] (stature, legs, ankles, feet, hands)	36.45/2.23	ns	.51	37/− .78	ns	− .13
BUT*B–V[a] (arms, shoulders, chest, breasts, genitals)	37.86/6.21	< .001	1.45	37/.72	ns	.14
BUT*B–VI[a] (mustache, beard, facial hair)	75/.25	ns	.06	37/1.58	ns	.31

Table 2 continued

BUT Scale	Group comparison 2			Group comparison 3		
	df/t	*p**	Effect size (Cohen's *d*)	*df/t*	*p**	Effect size (Cohen's *d*)
BUT*B–VII[a] (hair, skin)	58.76/1.96	ns	.45	37/−.58	ns	−.09
BUT*B–VIII[a] (sweating, blushing, noises, odors, buttocks)	38.44/3.61	.001	.83	37/.59	ns	.12
PST[b]	75/1.92	ns	.44	37/.87	ns	.14
PSDI[a]	46.73/14.8	< .001	3.43	37/2.10	ns	.37

Group comparison 1: FtM GD participant's baseline scores versus female controls' scores; Group comparison 2: FtM GD participant's scores after CHT versus female controls; Group comparison 3: FtM GD participant's baseline scores versus FtM GD participant's scores after CHT

BUT Body Uneasiness Test, *FtM GD* female-to-male gender dysphoria, *CHT* cross-sex hormonal treatment, *PST* positive symptom total, *PSDI* positive symptom distress index, *ns* nonsignificant

*$p < .003$ (Bonferroni corrected p value)

[a]Absolute range, 0–5

[b]Absolute range, 0–37

Table 3 Eating Attitudes Test Scores at baseline and after cross-sex hormonal treatment for participants with female-to-male gender dysphoria compared with female controls

FtM GD participants EAT-40[a] Score: baseline $n = 37$		FtM GD participants EAT-40 Score: after CHT $n = 37$		Female controls EAT-40 Score $n = 40$		Group comparison 1			Group comparison 2			Group comparison 3		
M	SD	*M*	SD	*M*	SD	*df/t*	*p*	Effect size (Cohen's *d*)	*df/t*	*p*	Effect size (Cohen's *d*)	*df/t*	*p*	Effect size (Cohen's *d*)
20.00	10.57	17.59	10.57	19.20	15.14	69.92/.27	ns	.61	75/−.54	ns	.12	36/1.95	ns	.23

Group comparison 1: FtM GD participant's baseline scores versus female controls' scores; Group comparison 2: FtM GD participant's scores after CHT versus female controls; Group comparison 3: FtM GD participant's baseline scores versus FtM GD participant's scores after CHT

EAT-40 Eating Attitudes Test, *FtM GD* female-to-male gender dysphoria, *CHT* cross-sex hormonal treatment, *ns* nonsignificant

[a]Absolute range, 0–120

Table 4 Symptom Checklist-90-Revised Scores at baseline and after cross-sex hormonal treatment for participants with female-to-male gender dysphoria compared with female controls

SCL-90-R Scale	FtM GD participants: baseline $n=37$		FtM GD participants: After CHT $n=37$		Female controls $n=40$		Group comparison 1			Group comparison 2			Group comparison 3		
	M	SD	*M*	SD	*M*	SD	*df/t*	*p*	Effect size (Cohen's *d*)	*df/t*	*p*	Effect size (Cohen's *d*)	*df/t*	*p*	Effect size (Cohen's *d*)
Somatization[a]	46.60	7.50	46.53	10.95	40.01	5.01	75.00/4.60	< .001	− 1.04	49.46/3.34	.002	− .77	37/.046	ns	.01
Obsessive–compulsive[a]	48.35	11.68	44.64	13.83	39.42	6.63	55.85/4.10	< .001	− .94	50.65/2.10	ns	− .48	37/2.02	ns	.29
Interpersonal sensitivity[a]	51.29	14.02	46.46	11.52	41.92	6.22	48.90/3.70	< .001	− .62	54.52/2.08	ns	− .49	37/3.35	.002	.38
Depression[a]	47.69	12.04	43.86	10.48	40.12	6.09	52.38/3.43	.001	− .80	56.92/1.88	ns	− .44	37/2.17	ns	.35
Anxiety[a]	44.79	8.52	43.81	8.01	39.27	4.18	51.32/3.53	.001	− .82	52.99/3.05	.004	− 2.65	37/.69	ns	1.38
Hostility[a]	49.19	11.75	47.08	11.46	39.68	4.34	44.87/4.61	< .001	− .57	45.32/3.66	.001	− .85	37/1.14	ns	.18
Phobic anxiety[a]	49.16	13.49	45.43	7.21	43.22	4.02	41.70/2.60	ns	− .12	54.84/1.69	ns	− .38	37/2.14	ns	.35
Paranoid ideation[a]	50.64	14.91	47.21	13.01	38.70	6.06	47.04/4.52	< .001	− .94	50.31/3.62	.001	− .84	37/1.73	ns	.24
Psychoticism[a]	50.18	9.46	45.36	8.46	39.56	5.22	55.23/6.02	< .001	− 1.33	59.19/3.58	.001	− .82	37/3.90	< .001	.53
Additional Sypmtoms[a]	46.43	9.15	43.83	8.22	40.48	5.13	55.30/3.45	< .001	− .80	59.09/2.09	ns	− .48	37/2.12	ns	.30
Global Severity Index[a]	47.97	11.03	44.33	11.05	38.12	5.02	49.31/4.97	< .001	− 1.16	49.27/3.13	.003	− .72	37/2.40	ns	.88

Group comparison 1: FtM baseline versus female controls; Group comparison 2: FtM after CHT versus female controls; Group comparison 3: FtM baseline versus FtM after CHT

SCL-90-R Symptom Checklist-90 Revised, *FtM GD* female-to-male gender dysphoria, *CHT* cross-sex hormonal treatment

[a]Absolute range, 0–100

Table 5 Correlations between measures of body uneasiness, eating attitudes and psychopathology and age, level of education, weight and Body Mass Index

Variable	Age		Level of education		Weight		BMI	
	FtM GD participants: baseline $n=37$	FtM GD participants: after CHT $n=37$	FtM GD participants: baseline $n=37$	FtM GD participants: after CHT $n=37$	FtM GD participants: baseline $n=37$	FtM GD participants: after CHT $n=37$	FtM GD participants: baseline $n=37$	FtM GD participants: after CHT $n=37$
BUT Scale								
BUT*A								
Global Severity Index								
r	−.73	−.5	−.07	−.31	.25	.27	.30	.25
p	ns	ns	ns	ns	Ns	ns	ns	ns
BUT*B								
PST								
r	−.18	−.21	.10	.32	.21	.25	.23	.25
p	ns	ns	ns	ns	Ns	ns	ns	ns
PSDI								
r	−.07	.07	−.8	−.31	−.12	.00	−.08	.01
p	ns	ns	ns	ns	ns	ns	ns	ns
EAT-40 Scale								
r	.65	.06	−.03	.19	.04	.20	.04	.14
p	ns	ns	ns	ns	ns	ns	ns	ns
SCL-90-R Scale								
Global Severity Index								
r	−.27	−.32	.05	−.01	.08	.15	.08	.14
p	ns	ns	ns	ns	ns	ns	ns	ns

BUT Body Uneasiness Test, *PST* positive symptom total, *PSDI* positive symptom distress index, *EAT-40* Eating Attitudes Test, *SCL-90-R* Symptom Checklist-90 Revised, *BMI* Body Mass Index, *FtM GD* female-to-male gender dysphoria, *CHT* cross-sex hormonal treatment

CHT induces physical changes that are more congruent with GD individuals' gender identity (Fisher et al., 2016; van de Grift et al., 2016a), as our participants' negative body image regarding these factors decreased. Moreover, it has been reported by clinicians to be relatively easier for participants with FtM GD than with MtF GD to make social transitions and develop a more congruent assessment of physical appearance (Fisher et al., 2016; van de Grift et al., 2016a). In society, an individual with FtM GD displaying masculine features is generally more accepted than an individual with MtF GD displaying feminine features (Turan et al., 2015b; van de Grift et al., 2016a). Some studies have reported that persons with GD have higher depersonalization scores (Bandini et al., 2013; Fisher et al., 2013) and that depersonalization scores decrease after CHT administration (Colizzi, Costa, & Todarello, 2015a) and SRS (Kersting et al., 2003; Wolfradt & Neumann, 2001). Further, in their longitudinal study, Colizzi et al. (2015a) reported no significant differences in depersonalization/derealization scores between GD individuals who had received CHT and those who had undergone SRS. Our finding regarding a decrease in depersonalization scores after CHT may be associated with the psychological effects of CHT, in that it helps to reduce feelings of alienation from their own body among persons with GD. However, the lack of change in Compulsive Self-Monitoring and Avoidance after CHT in our study might be attributed to the absence of SRS such as mastectomy or other surgical interventions. In a recent study, it was reported that persons with GD who received both CHT and SRS had more favorable body satisfaction scores compared with persons with GD who used only (van de Grift et al., 2017).

Becker et al. (2016) concluded that the body image concerns of participants with GD are composed of both genital and non-genital body part issues. In addition to this, they found that participants with FtM GD reported dissatisfaction regarding all female body features, unlike participants with MtF GD in which they were dissatisfied with sex-specific body features. Another study has shown that the most central subscales in network analysis are muscularity and posture in individuals with FtM GD (van de Grift et al., 2016c). In accordance with these studies, when participants with FtM GD were compared to female controls, we found that they were also dissatisfied with the body parts outside the sex-specific body parts. Although there were no significant differences in the comparisons between baseline and after CHT in FtM GD participant's scores, the dissatisfaction of shape

of the head and face, forehead, ears, chin, neck (BUT*B–II), stature, legs, ankles, feet, and hands (BUT*B–IV), which differed significantly from female controls before CHT, did not show any significant difference when compared to female controls after CHT. Having a male muscular structure is important to be an ideal male for individuals with FtM GD (Wickman, 2003). In a network analysis of body satisfaction of individuals with FtM GD, it has been reported that the most central body features were arms, figure, and appearance (van de Grift et al., 2016c). Additionally, testosterone therapy induces physical changes that are more congruent with GD individuals' gender identity, such as development of male muscular build and growth in facial and body hair (Coleman et al., 2012). These changes in the shape of the head and face and muscular build that were obtained after CHT might have reduced body dissatisfaction.

A number of studies have demonstrated that testosterone administration in participants with GD results in a marked increase in weight and BMI (Colizzi et al., 2015b; Elbers, Asscheman, Seidell, Megens, & Gooren, 1997; Fisher et al., 2016; Gooren, 2005; Gooren, Wierckx, & Giltay, 2014; Hembree et al., 2009; Quirós et al., 2015), which is supported by our findings of weight gain and higher BMI scores after CHT administration. This may have occurred because all androgens cause some degree of sodium retention and expansion of extracellular fluid volume (Wilson, 1988). Women are more likely to develop subcutaneous fat, whereas men tend to have more visceral fat (Blaak, 2001; Shi, Seeley, & Clegg, 2009; Wajchenberg, 2000), and thus testosterone administration reduces recipients' subcutaneous fat tissue and increases visceral fat (i.e., lean body mass; Elbers, Asscheman, Seidell, & Gooren, 1999; Gooren, 2005). In our study, the increases observed in weight and BMI may be associated with such changes in body composition. On the other hand, we found that the baseline mean body weight and BMI scores of participants with FtM GD were higher than those of female controls. Vocks et al. (2009) reported that participants with FtM GD reported more weight and shape concerns than male controls, and suggested that this group may be unwilling to lose weight, as being overweight makes breasts and hips look smaller relative to abdominal size.

Studies have found higher rates of disturbed eating behaviors and attitudes in participants with GD compared with controls (Ålgars et al., 2010; 2012; Cella, Iannaccone, & Cotrufo, 2013; Diemer, Grant, Munn-Chernoff, Patterson, & Duncan, 2015; Vocks et al., 2009). In our study, eating attitudes scores of participants with FtM GD at baseline did not meet the required score for eating disorders (> 30 points), and there was no significant change in FtM GD participants' EAT-40 scores after CHT. Similarly, Vocks et al. reported that participants with MtF GD show higher levels of disturbed eating attitudes than both male and female controls, although no significant differences were detected between participants with FtM GD and female controls. In a recent study of disordered eating encompassing 200 participants with GD, 200 participants with eating disorders, and 200 controls, there were no significant differences between GD patients and controls (Witcomb et al., 2015). Probably, female controls may still be affected by such sociocultural slimness ideal for females, which may diminish the differences in eating attitudes scores between participants with FtM GD and female controls (Vocks et al., 2009; Witcomb et al., 2015). However, another study reported that biological females with conflicted gender identity reported more disordered eating than female controls, whereas no significant differences were detected between men with conflicted gender identity and male controls (Ålgars et al., 2010). Further, several case reports show that GD is associated with an increased risk of eating disorders among both biological males (Couturier et al., 2015; Ewan et al., 2014; Hepp & Milos, 2002; Hepp et al., 2004; Winston et al., 2004) and females (Couturier et al., 2015; Fernández-Aranda et al., 2000; Turan et al., 2015a).

Some studies have shown that psychiatric problems are more common in patients with GD (a Campo, Nijman, Merckelbach, & Evers, 2003; Hepp, Kraemer, Schnyder, Miller, & Delsignore, 2005; Heylens et al., 2014a). Not surprisingly, we found that FtM GD participants' baseline scores for all SCL-90-R subscales (except for Phobic Anxiety) were significantly higher than female controls. Participants with GD experience high stress due to social rejection and the incongruence between their biological sex and gender identity (Simon, Zsolt, Fogd, & Czobor, 2011), and can develop psychopathological problems in reaction to their incongruent body image (Colizzi et al., 2014). In previous studies, the positive effects of CHT on the mental health of individuals with GD have been highlighted (Colizzi, Costa, Pace, & Todarello, 2013; Colizzi et al., 2014; Costantino et al., 2013; Gómez-Gil et al., 2012; Gorin-Lazard et al., 2013; Heylens et al., 2014a; Turan et al., 2015b). In our study, we observed that in addition to Phobic Anxiety there were no significant differences after CHT in Obsessive–Compulsive, Interpersonal Sensitivity, Depression, and Additional Symptoms in participants with FtM GD compared to female controls. Additionally, one of the most important results of this study is that Interpersonal Sensitivity and Psychoticism scores significantly reduced after CHT. CHT provides desired changes in terms of body and shape for participants with GD, which can reduce self-reported distress (Colizzi et al., 2013; Gómez-Gil et al., 2012). Beginning a new life as one's desired sex may also have positive effects on mood among GD individuals (Costantino et al., 2013); further, some clinical evidence suggests that testosterone has antidepressant effects (McHenry, Carrier, Hull, & Kabbaj, 2014). Depressive symptoms, fatigue, and irritability have been found to be greatly reduced during testosterone replacement therapy (Kanayama, Amiaz, Seidman, & Pope, 2007; Pope, Cohane,

Kanayama, Siegel, & Hudson, 2003; Wang et al., 1996). In our cohort, testosterone may have acted as an antidepressant by reducing general psychopathological symptoms. As noted above, participants with FtM GD have a relatively easier social transition (Fisher et al., 2016; van de Grift et al., 2016a) and are reported to have a more congruent assessment of physical appearance compared to MtF GD (van de Grift et al., 2016a), and these factors may have reduced Interpersonal Sensitivity and Psychoticism in our study.

This study had several limitations. First, the sample size was relatively small, although it can be difficult to recruit large numbers of participants in this field of research. Second, the female controls were only assessed at baseline. The reassessment of the female controls after 24 weeks could have increased the value of the study. Third, we did not examine the long-term effects of CHT. Although the physical impact is better understood, the impact on the outcomes explored here should be investigated in more detail. Further, we used self-report measures that may have been affected by social desirability bias. Collecting data from family members or medical professionals in addition to the participants' reports could counteract the potential bias that is inherent to self-report measures to some extent. However, despite these limitations, the current study provides important information about both the relationships among eating attitudes, body uneasiness, and GD, and alterations in eating attitudes and body uneasiness in persons with FtM GD after CHT administration. In the future, studies with a larger sample size and long-term follow-up are required to better understand the relationships among eating attitudes, body satisfaction, and GD.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This study was approved by the ethics committee of the Cerrahpaşa Medical Faculty at Istanbul University.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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JAMA Psychiatry | Original Investigation

Association Between Recalled Exposure to Gender Identity Conversion Efforts and Psychological Distress and Suicide Attempts Among Transgender Adults

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IMPORTANCE Gender identity conversion efforts (GICE) have been widely debated as potentially damaging treatment approaches for transgender persons. The association of GICE with mental health outcomes, however, remains largely unknown.

OBJECTIVE To evaluate associations between recalled exposure to GICE (by a secular or religious professional) and adult mental health outcomes.

DESIGN, SETTING, AND PARTICIPANTS In this cross-sectional study, a survey was distributed through community-based outreach to transgender adults residing in the United States, with representation from all 50 states, the District of Columbia, American Samoa, Guam, Puerto Rico, and US military bases overseas. Data collection occurred during 34 days between August 19 and September 21, 2015. Data analysis was performed from June 8, 2018, to January 2, 2019.

EXPOSURE Recalled exposure to GICE.

MAIN OUTCOMES AND MEASURES Severe psychological distress during the previous month, measured by the Kessler Psychological Distress Scale (defined as a score ≥13). Measures of suicidality during the previous year and lifetime, including ideation, attempts, and attempts requiring inpatient hospitalization.

RESULTS Of 27 715 transgender survey respondents (mean [SD] age, 31.2 [13.5] years), 11 857 (42.8%) were assigned male sex at birth. Among the 19 741 (71.3%) who had ever spoken to a professional about their gender identity, 3869 (19.6%; 95% CI, 18.7%-20.5%) reported exposure to GICE in their lifetime. Recalled lifetime exposure was associated with severe psychological distress during the previous month (adjusted odds ratio [aOR], 1.56; 95% CI, 1.09-2.24; $P < .001$) compared with non-GICE therapy. Associations were found between recalled lifetime exposure and higher odds of lifetime suicide attempts (aOR, 2.27; 95% CI, 1.60-3.24; $P < .001$) and recalled exposure before the age of 10 years and increased odds of lifetime suicide attempts (aOR, 4.15; 95% CI, 2.44-7.69; $P < .001$). No significant differences were found when comparing exposure to GICE by secular professionals vs religious advisors.

CONCLUSIONS AND RELEVANCE The findings suggest that lifetime and childhood exposure to GICE are associated with adverse mental health outcomes in adulthood. These results support policy statements from several professional organizations that have discouraged this practice.

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Supplemental content

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Transgender persons are those whose sex assigned at birth differs from their gender identity, the inner sense of their own gender.[1] According to a study by the Williams Institute,[1] approximately 1.4 million (0.6%) adults in the United States identify as transgender. Transgender persons in the United States experience a disproportionately high prevalence of adverse mental health outcomes, including a 41% lifetime prevalence of self-reported suicide attempts.[2-4]

Studies[5-7] have shown that gender-affirming models of care are associated with positive mental health outcomes among transgender people. Gender identity conversion therapy refers to psychological interventions with a predetermined goal to change a person's gender identity to align with their sex assigned at birth.[8] Several US states have passed legislation banning conversion therapy for gender identity.[8] Professional organizations including the American Medical Association,[9] the American Psychiatric Association,[10] the American Academy of Child & Adolescent Psychiatry,[11] and the American Academy of Pediatrics[12] have labeled the practice unethical and ineffective. Despite these policy statements, however, the question of whether to ban gender identity conversion therapy remains a contentious policy debate.

State-level conversion therapy bans have been focused on gender identity conversion efforts (GICE) by licensed mental health practitioners. Nonlicensed religious advisors have also advertised GICE, and it is unknown whether GICE by these 2 groups of practitioners are distinct in their effects on mental health.[13]

Because gender identity is thought to be stable after puberty for most transgender persons, few have supported use of GICE after pubertal onset.[4] Some, however, have supported these efforts for prepubescent children, theorizing that gender identity may be more modifiable at this age.[14] Increasingly, this approach has fallen out of favor, with the growing understanding that gender diversity is not a pathologic finding that requires modification.[14] To our knowledge, there have been no studies evaluating the associations between exposure to GICE during either childhood or adulthood and adult mental health outcomes.

The current study used the largest cross-sectional survey to date of transgender adults living in the United States to assess whether recalled lifetime exposure to GICE is associated with adverse mental health outcomes, including suicide attempts. The study also assessed whether recalled childhood exposure to GICE before the age of 10 years is associated with adverse mental health outcomes in adulthood. We hypothesized that there would be associations between exposure to GICE by both secular and religious professionals and worse mental health outcomes.

Key Points

Question Is recalled exposure to gender identity conversion efforts (ie, psychological interventions that attempt to change one's gender identity from transgender to cisgender) associated with adverse mental health outcomes in adulthood?

Findings In a cross-sectional study of 27 715 US transgender adults, recalled exposure to gender identity conversion efforts was significantly associated with increased odds of severe psychological distress during the previous month and lifetime suicide attempts compared with transgender adults who had discussed gender identity with a professional but who were not exposed to conversion efforts. For transgender adults who recalled gender identity conversion efforts before age 10 years, exposure was significantly associated with an increase in the lifetime odds of suicide attempts.

Meaning The findings suggest that lifetime and childhood exposure to gender identity conversion efforts are associated with adverse mental health outcomes.

Methods

Study Design and Data Source

The 2015 US Transgender Survey[15] is a cross-sectional survey that was conducted by the National Center for Transgender Equality (NCTE) between August 19 and September 21, 2015. It is the largest existing survey of transgender adults and was distributed via community-based outreach.[15] The US Transgender Survey protocol was reviewed and approved by the University of California Los Angeles institutional review board, Los Angeles, California. The US Transgender Survey data set was organized and recoded as described in the NCTE report on the survey.[15] The protocol for the present study was reviewed by the Fenway Institute institutional review board and was determined not to comprise human subjects research. Data analysis was performed from June 8, 2018, to January 2, 2019.

Study Population

The data set includes responses from 27 715 transgender adults residing in the United States, with representation from all 50 states, the District of Columbia, American Samoa, Guam, Puerto Rico, and US military bases overseas. The NCTE report on the survey further characterizes recruitment strategies and the sample of respondents.[15] Because the organizations that conducted outreach for the survey did not systematically document the number of individuals reached by their outreach efforts, a response rate could not be calculated.

Exposures

The primary exposure of interest was an affirmative response to the binary survey question, "Did any professional (such as a psychologist, counselor, or religious advisor) try to make you identify only with your sex assigned at birth (in other words, try to stop you being trans)?" This recalled exposure is herein referred to as GICE. Endorsement of lifetime exposure to GICE was examined among all those who confirmed having spoken to a professional about gender identity. Outcomes were compared among respondents who reported exposure to GICE before the age of 10 years with outcomes among those who endorsed lifetime exposure to therapy without GICE. Because the data set does not contain age of exposure to non-GICE therapy, participants with any lifetime exposure to non-GICE therapy were selected as the reference group in the analysis of those exposed to GICE before age 10 years. As

Table 1. Demographics of Participants With and Without Lifetime Exposure to Gender Identity Conversion Efforts[a]

Characteristic	Did any professional try to make you identify only with your sex assigned at birth?[b] No. (%) Yes (n = 3869)	No (n = 15 882)	*P* Value[c]
Sex assigned at birth			
Male	1143 (29.5)	5576 (35.1)	<.001
Female	2726 (70.5)	10 306 (64.9)	
Gender identity			
Cross-dresser	101 (2.6)	721 (4.5)	<.001
Transgender woman (male to female) or woman (birth-assigned male)	2452 (63.4)	8980 (56.5)	<.001
Transgender man (female to male) or man (birth-assigned female)	816 (21.1)	4084 (25.7)	<.001
Nonbinary or genderqueer (birth-assigned female)	327 (8.5)	1454 (9.2)	.11
Nonbinary or genderqueer (birth-assigned male)	173 (4.5)	643 (4.0)	.25
Sexual orientation			
Asexual	339 (8.8)	1034 (6.5)	<.001
Bisexual	753 (19.5)	2570 (16.2)	<.001
Gay, lesbian, or same gender-loving	811 (21.0)	3369 (21.2)	.75
Heterosexual or straight	838 (21.7)	4124 (26.0)	<.001
Pansexual	531 (13.7)	2039 (12.8)	.15
Queer	353 (9.1)	1933 (12.2)	<.001
Other	245 (6.3)	812 (5.1)	.003
Racial/ethnicity			
Alaska Native or American Indian	49 (1.3)	133 (0.8)	.02
Asian, Asian American, Native Hawaiian, or Pacific Islander	62 (1.6)	511 (3.2)	<.001
Biracial, multiracial, or other	79 (2.0)	288 (1.8)	.38
Black or African American	477 (12.3)	1926 (12.1)	.75
Latino, Latina, or Hispanic	609 (15.7)	2219 (14.0)	.005
White, Middle Eastern, or North African	2593 (67.0)	10 805 (68.0)	.23
Census age cohort, y			
18-24	339 (8.8)	1527 (9.6)	.11
25-44	1589 (41.1)	5887 (37.1)	<.001
45-64	1408 (36.4)	6141 (38.7)	.01
≥65	534 (13.8)	2326 (14.6)	.19
Family support of gender identity			
Supportive	1516 (39.2)	8287 (52.2)	<.001
Neutral	672 (17.4)	2659 (16.7)	.46
Unsupportive	1012 (26.2)	2184 (13.7)	<.001
Not asked	549 (14.2)	2752 (17.3)	<.001
Relationship status			
Partnered	1754 (45.3)	7845 (49.4)	<.001
Educational level			
Less than high school	795 (20.5)	1833 (11.5)	<.001
High school graduate or GED	904 (23.4)	4290 (27.0)	<.001
Some college or associate degree	1137 (29.4)	4883 (30.7)	.10
Bachelor degree or higher	1033 (26.7)	4875 (30.7)	<.001
Employment status			
Employed	1957 (50.6)	9890 (62.3)	<.001
Unemployed	532 (13.7)	1332 (8.4)	<.001
Out of the labor force	1346 (34.8)	4578 (28.9)	<.001
Unspecified	35 (0.9)	82 (0.5)	.01

(continued)

Table 1. Demographics of Participants With and Without Lifetime Exposure to Gender Identity Conversion Efforts[a] (continued)

Characteristic	Did any professional try to make you identify only with your sex assigned at birth?[b] No. (%) Yes (n = 3869)	No (n = 15 882)	P Value[c]
Total household income, $			
No income	87 (2.2)	432 (2.7)	.11
1-9999	503 (13.0)	1608 (10.1)	<.001
10 000-24 999	1075 (27.8)	2955 (18.6)	<.001
25 000-49 999	863 (22.3)	3692 (23.2)	.22
50 000-99 999	728 (18.8)	3732 (23.5)	<.001
100 000 or more	430 (11.1)	2468 (15.5)	<.001
Unspecified	184 (4.8)	994 (6.3)	<.001

Abbreviation: GED, general equivalency diploma.

[a] Descriptive statistics for transgender adults who reported receiving any therapy regarding gender identity, with bivariate comparisons of those with and without exposure to conversion efforts.

[b] Professionals included psychologists, counselors, or religious advisors.

[c] Rao-Scott χ^2 tests were used for categorical variables, and the Mann-Whitney test was used for comparison of age because of nonnormality.

data regarding ages of pubertal onset among respondents were not available, younger than 10 years was used as a cutoff to approximate a prepubertal population, with the understanding that there is significant individual variability in the age at onset of puberty.[16,17] Furthermore, we examined whether there was a difference in outcomes between those who reported exposure to GICE from a secular professional compared with those who reported exposure to GICE from a religious advisor.

Outcomes

We compared respondents with and without recalled exposure to GICE with regard to the following binary mental health variables: severe psychological distress during the previous month (defined as a score of ≥13 on the Kessler Psychological Distress Scale, a cutoff that has been previously validated in US samples[18]); binge drinking during the previous month (defined as ≥1 day of consuming ≥5 standard alcoholic drinks on the same occasion, a threshold for which the rationale in alcohol research among transgender persons has been discussed in previous reports[19]); lifetime cigarette and illicit drug use (not including marijuana); suicidal ideation during the previous year; suicidal ideation with plan during the previous year; suicide attempt during the previous year; suicide attempt requiring inpatient hospitalization during the previous year; lifetime suicidal ideation; and lifetime number of suicide attempts (0, 1, or ≥2).

Control Variables

Demographic and socioeconomic variables were collected and analyzed as defined in the US Transgender Survey, including sex assigned at birth, present gender identity, sexual orientation, racial/ethnic identity according to the recoded NCTE categories reflecting those typically reported in the American Community Survey, age (both in integer form and using US census categories to capture cohort effects), family support of gender identity, relationship status (with *partnered* coded by these authors as binary and inclusive of both open and polyamorous relationships), educational achievement, employment status, and total household income. In supplemental analyses, we also controlled for exposure to sexual orientation conversion efforts undertaken by professionals.

Table 2. Outcomes for Those With Lifetime Exposure to Gender Identity Conversion Efforts[a]

Outcome	Adjusted Odds Ratio (95% CI)	P Value
Suicidality in previous 12 mo		
Ideation	1.44 (1.03-2.02)	<.001
Ideation with plan	1.52 (1.09-2.14)	<.001
Attempt	1.49 (0.91-2.46)	.01
Attempt requiring inpatient hospitalization	1.62 (0.75-3.48)	.04
Suicidality in lifetime		
Ideation	1.90 (1.12-3.23)	<.001
Attempts	2.27 (1.60-3.24)	<.001[b]
Mental health and substance use in previous month		
Severe psychological distress[c]	1.56 (1.09-2.24)	<.001
Binge drinking	0.88 (0.59-1.30)	.27
Mental health and substance use in lifetime		
Cigarette use	1.18 (0.83-1.68)	.12
Illicit drug use	1.08 (0.75-1.54)	.50

[a] Mental health outcomes among transgender adults exposed to gender identity conversion efforts compared with those who discussed gender identity with a professional without conversion efforts, adjusting for assigned sex at birth, gender identity, sexual orientation, race/ethnicity, age cohort, family support of gender identity, partnership status, educational attainment, employment status, and total household income.

[b] Ordinal logistic regression with outcome categories: 0, 1, and 2 or more.

[c] Kessler Psychological Distress Scale (defined as a score ≥13).

Statistical Analysis

Analyses were conducted using SAS Studio, version 3.71, Basic Edition (SAS Institute). Participants were excluded from analyses if they did not report ever discussing their gender identity with a professional. Control variables were treated as unordered classification variables. Using the sample weights generated by the NCTE[15] to improve generalizability by addressing sampling biases around age, educational level, and race/ethnicity, we generated descriptive statistics for control and outcome variables. Bivariate analyses comparing responses from transgender adults were conducted based on (1) whether or not they had any lifetime exposure to GICE, (2) whether they had experienced GICE before age 10 years

Table 3. Demographics of Those With and Without Childhood Exposure to Gender Identity Conversion Efforts[a]

Characteristic	No. (%)		P Value[c]
	Reported Exposure to Conversion Efforts Before Age 10 y (n = 206)[b]	Reported Exposure to Any Lifetime Therapy Without Conversion Efforts (n = 15 882)	
Race/ethnicity			
Alaska Native or American Indian	5 (2.4)	133 (0.8)	.04
Asian, Asian American, Native Hawaiian, or Pacific Islander	3 (1.5)	511 (3.2)	.22
Biracial, multiracial, or other	8 (3.9)	288 (1.8)	.05
Black or African American	5 (2.4)	1926 (12.1)	<.001
Latino, Latina, or Hispanic	24 (11.6)	2219 (14.0)	.39
White, Middle Eastern, or North African	161 (78.2)	10 805 (68.0)	.002
Census age cohort, y			
18-24	17 (8.2)	1527 (9.6)	.59
25-44	110 (53.4)	5887 (37.1)	<.001
45-64	76 (36.9)	6141 (38.7)	.65
≥65	3 (1.5)	2326 (14.6)	<.001
Family support of gender identity			
Supportive	59 (28.6)	8287 (52.2)	<.001
Neutral	37 (18.0)	2659 (16.7)	.71
Unsupportive	80 (38.8)	2184 (13.8)	<.001
Not asked	30 (14.6)	2752 (17.3)	.34
Employment status			
Employed	95 (46.1)	9890 (62.3)	<.001
Unemployed	31 (15.0)	1332 (8.4)	<.001
Out of the labor force	77 (37.4)	4578 (28.8)	.01
Unspecified	2 (0.8)	82 (0.5)	.68
Total household income, $			
No income	10 (4.9)	432 (2.7)	.10
1-9999	47 (22.8)	1608 (10.1)	<.001
10 000-24 999	57 (27.7)	2955 (18.6)	.001
25 000-49 999	32 (15.5)	3692 (23.2)	.01
50 000-99 999	32 (15.5)	3732 (23.5)	.01
100 000 or more	14 (6.8)	2468 (15.5)	<.001
Unspecified	14 (6.8)	994 (6.3)	.86

[a] Descriptive statistics for transgender adults who reported receiving any therapy regarding gender identity, with bivariate comparisons for those with and without exposure to conversion efforts before age 10 years.

[b] Individuals with unspecified age of reported exposure to conversion efforts, unspecified exposure to conversion efforts, and unspecified exposure to any therapy (missing data; n = 100) were excluded from this analysis.

[c] Rao-Scott χ^2 tests were used, and the Mann-Whitney test was used for comparison of age because of nonnormality.

vs never, and (3) whether GICE were conducted by a secularvs religious professional. These bivariate analyses were performed to detect potential confounders to control for in subsequent regression analysis. Except for age, all variables were categorical; thus, we used Rao-Scott χ^2 tests for design-adjusted data with 1 *df* for bivariate comparisons. Age as an integer variable was nonnormally distributed; thus, bivariate comparison was performed with the nonparametric Mann-Whitney test. Standard errors and 95% CIs were calculated for the prevalence estimates of exposure to GICE using the aforementioned 1.4 million persons as the total population estimate.[1]

Multivariable logistic regression models were conducted to test whether GICE were associated with the outcomes, adjusted for variables with significant differences between groups in the preceding bivariate analyses. These models also used survey weights generated by the NCTE for age, educational level, and race/ethnicity. Adjusted odds ratios (aORs) with 95% CIs and 2-sided *P* values were reported, with a $P < .001$ threshold for significance.

Approximately 66 comparisons (between bivariate tests and logistic regression models) were made in each analysis. To reduce risk of type I error, a modified Bonferroni correction for multiple comparisons was performed, with resulting $\alpha = .001$ (ie, .05 divided by 50). Using the full number of comparisons yields only a slightly lower $\alpha = .0008$, which ultimately would not have altered the findings. We therefore selected an $\alpha = .001$ for both ease of reading and also the statistical consensus that unmodified Bonferroni correction tends to be maximally conservative, thereby unnecessarily inflating type II error.[20] Thus, hypothesis tests were 2-sided with corrected significance level $P < .001$ for both primary and secondary analyses, and the 95% CIs reported reflect this correction.

Respondents with missing data for exposure and outcome variables comprised less than 2% of the analytic samples and were therefore excluded without compensatory methods, as is widely considered acceptable for this degree of data completeness.[21] Data were missing for less than 9% of each control variable, thereby obviating the need for imputation, which can introduce bias, especially when data are nonrandomly missing. There is debate about the degree of incompleteness that is acceptable without compensatory measures, and al-

though individuals with incomplete data may be of particular interest, thresholds for missingness as high as 10% are considered to be acceptable.[22]

Results

Of the 27 715 US Transgender Survey respondents (mean [SD] age, 31.2 [13.5] years), 11 857 (42.8%) were assigned male sex at birth, and 3869 (14.0%; 95% CI, 13.3%-14.7%) reported exposure to GICE. Of 19 751 respondents who had discussed their gender identity with a professional, 3869 (19.6%; 95% CI, 18.7%-20.5%) reported exposure to GICE in their lifetime. Of these individuals, 1361 (35.2%; 95% CI, 32.7%-37.7%) who reported exposure to GICE stated that these were enacted by a religious advisor.

Demographic variables among exposed and unexposed respondents are shown in **Table 1**. After adjusting for statistically significant demographic variables, lifetime exposure to GICE was significantly associated with multiple adverse outcomes, including severe psychological distress during the previous month (aOR, 1.56; 95% CI, 1.09-2.24; $P < .001$) and lifetime suicide attempts (aOR, 2.27; 95% CI, 1.60-3.24; $P < .001$). (**Table 2**).

Overall, 206 (1.0%; 95% CI, 0.8%-1.2%) of those who reported discussing their gender identity with a professional also reported exposure to GICE before age 10 years. Demographics are shown in **Table 3**. After adjusting for statistically significant demographic variables, exposure to GICE before age 10 years was significantly associated with several measures of suicidality, including lifetime suicide attempts (aOR, 4.15; 95% CI, 2.44-7.69; $P < .001$) (**Table 4**).

Raw frequencies of outcome variables among exposure groups are shown in the **Figure**. There were no statistically significant differences in outcomes between those who were exposed to GICE enacted by religious advisors and those exposed to GICE by secular professionals (all aOR, $P > .001$) (eTable 1 and eTable 2 in the Supplement).

We also repeated all analyses adjusting for lifetime exposure to sexual orientation conversion efforts, defined as a positive response to the survey question, "Did any professional (such as a psychologist, counselor, or religious advisor) ever try to change your sexual orientation or who you are attracted to (such as try to make you straight or heterosexual)?" After this adjustment, both lifetime exposure (aOR, 1.96; 95% CI, 1.38-2.80; $P < .001$) and childhood exposure (aOR, 3.05; 95% CI, 1.55-6.02; $P < .001$) to GICE were associated with increased odds of lifetime suicide attempts but not with the other outcome variables (eTables 3 and 4 in the Supplement). Because this question was unclear regarding the referent gender (sex assigned at birth vs gender identity) when defining sexual orientation conversion efforts, we refer to the models not adjusted for this variable throughout the article.

Table 4. Outcomes for Those With Childhood Exposure to Gender Identity Conversion Efforts[a]

Outcome	Adjusted Odds Ratio (95% CI)	*P* Value
Suicidality in previous 12 mo		
Ideation	2.03 (1.01-4.07)	<.001
Ideation with plan	2.82 (1.42-5.62)	<.001
Attempt	2.40 (0.87-6.62)	.005
Attempt requiring inpatient hospitalization	1.72 (0.26-11.24)	.34
Suicidality in lifetime		
Ideation	1.90 (0.66-5.52)	.05
Attempts	4.15 (2.44-7.69)	<.001[b]
Mental health and substance use in previous month		
Severe psychological distress[c]	1.75 (0.72-4.24)	.04
Binge drinking	0.84 (0.33-2.14)	.54
Mental health and substance use in lifetime		
Cigarette use	1.53 (0.66-3.56)	.09
Illicit drug use	1.76 (0.83-3.75)	.01

[a] Mental health outcomes of transgender adults exposed to gender identity conversion efforts before age 10 years compared with those who discussed gender identity with a professional without conversion efforts in their lifetime, adjusted for age cohort, sex assigned at birth, race/ethnicity, family support of gender identity, employment status, and total household income.

[b] Ordinal logistic regression with outcome categories: 0, 1, and 2 or more.

[c] Kessler Psychological Distress Scale (defined as a score ≥13).

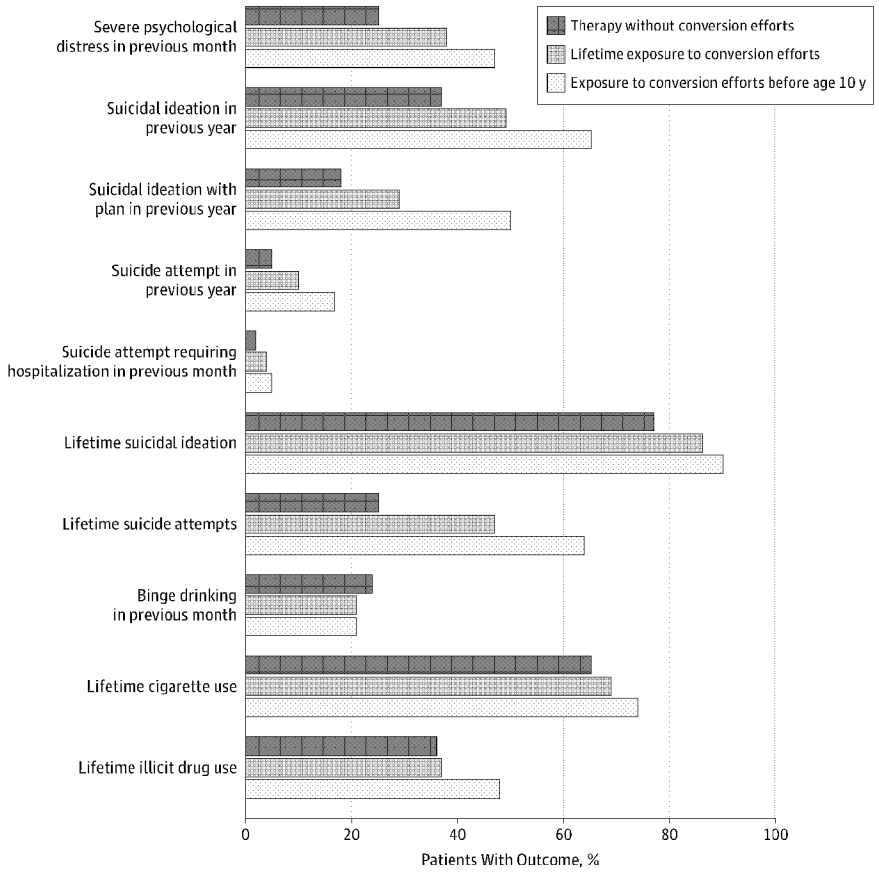
Discussion

This study was the first, to our knowledge, to show an association between exposure to GICE (lifetime and childhood) and adverse mental health outcomes among transgender adults in the United States. We found that recalled lifetime exposure to GICE was highly prevalent among adults: 14.0% of all transgender survey respondents and 19.6% of those who had discussed gender identity with a professional reported exposure to GICE.

The Generations Study[23] by the Williams Institute found that 6.7% of sexual minority group adults in the United States reported lifetime exposure to conversion efforts for sexual orientation.[23] Based on the findings of the current study, it appears that transgender people are exposed to GICE at high rates, perhaps even higher than the percentage of cisgender nonheterosexual individuals who are exposed to sexual orientation conversion efforts, although direct comparisons are not possible. One potential explanation for this is that compared with persons in the sexual minority group, many persons in the gender minority group must interact with clinical professionals to be medically and surgically affirmed in their identities. This higher prevalence of interactions with clinical professionals among people in the gender minority group may lead to greater risk of experiencing conversion efforts.

One study[24] showed that conversion efforts for sexual orientation were associated with an increased risk of depression and suicidal ideation. The current study was the first, to our knowledge, to find associations between any type of conversion efforts and both suicidal ideation and suicide attempts. A plausible association of these practices with poor mental health outcomes can be conceptualized through the minority stress framework; that is, elevated stigma-related stress from

Figure. Mental Health Outcomes Among Those With and Without Exposure to Gender Identity Conversion Efforts



Raw frequencies for outcome variables among those with a lifetime history of non–gender identity conversion efforts therapy, lifetime history of exposure to gender identity conversion efforts, and exposure to conversion efforts before age 10 years. Severe psychological distress in the previous month was defined as a score of 13 or more on the Kessler Psychological Distress Scale, a cutoff that has been previously validated in US samples.[17] Binge drinking was defined as at least 1 or more day of consuming 5 or more standard alcoholic drinks on the same occasion, a threshold for which the rationale in alcohol research among transgender people has been discussed in previous reports.[18] Illicit drug use excludes marijuana use.

exposure to GICE may increase general emotion dysregulation, interpersonal dysfunction, and maladaptive cognitions.[25] Of note, having a lifetime suicide attempt was a more common outcome compared with severe psychological distress during the previous month, a result that was likely attributable to the time frames during which these variables were defined. Although this study suggests that exposure to GICE is associated with increased odds of suicide attempts, GICE are not the only way in which minority group stress manifests, and thus other factors are also likely to be associated with suicidality among gender-diverse people.

Respondents from more socioeconomically disadvantaged backgrounds (eg, low educational attainment or low household income) more commonly reported exposure to GICE. These individuals may have been more likely to receive GICE, or exposure to GICE may have been so damaging that they were impaired in educational, professional, and economic advancement. The cross-sectional nature of this study limits further interpretation. This finding warrants additional attention in the context of nationally representative data showing lower educational attainment and lower income among transgender people in the United States compared with their cisgender counterparts.[26]

Given the considerable debate surrounding the merits of GICE for prepubertal youth,[4] we examined recalled early exposure to GICE (ie, before age 10 years) and found this to be less prevalent, with 1% of those who had ever discussed gender identity with a professional reporting that they had been exposed before age 10 years. Many experts have expressed concern that early exposure to GICE may lead to persistent feelings of shame because of physicians and parents defining gender-expansive experience as unacceptable.[4] A study[27] in Canada found a higher prevalence of shame-related feelings among youth treated with GICE. Both family and peer rejection of a child's gender identity have been associated with adverse mental health outcomes.[27-30] Extending those findings, the current study showed that recalled early exposure to GICE was associated with adverse mental health outcomes, including lifetime suicide attempts, compared with discussion of gender identity with a professional and no exposure to conversion efforts. Although not compared directly, the aOR of lifetime suicide attempts was higher for those exposed to GICE before age 10 years than the aOR for those with lifetime exposure, suggesting that rejection of gender identity may have more profound consequences at earlier stages of development. Further research is needed to better understand the as-

sociations between stage of development at time of exposure to GICE and risk of lifetime suicide attempts.

Our results support the policy positions of the American Academy of Child and Adolescent Psychiatry,[11] the American Psychiatric Association,[10] the American Academy of Pediatrics,[12] and the American Medical Association,[9] which state that gender identity conversion therapy should not be conducted for transgender patients at any age. Our finding of no difference in mental health outcomes between respondents who received GICE from a secular-type professional and those who received it from a religious advisor suggests that any process of intervening to alter gender identity is associated with poorer mental health regardless of whether the intervention occurred within a secular or religious framework.

Strengths and Limitations

Strengths of this study include its sample size, more than 90% completeness in the data set, and participants from a wide geographic area within the United States. Limitations include its cross-sectional study design, which precludes determination of causation. It is possible that those with worse mental health or internalized transphobia may have been more likely to seek out conversion therapy rather than non-GICE therapy, suggesting that conversion efforts themselves were not causative of these poor mental health outcomes. This interpretation, however, would also imply a mechanism whereby societal rejection leads to internalized transphobia and life-threatening adult mental health outcomes.

We also lack data regarding the degree to which GICE occurred (eg, duration, frequency, and forcefulness of GICE, as well as what specific modalities were used). If a sizable proportion of those reporting exposure to GICE in the current study experienced relatively mild or infrequent conversion efforts, this might suggest the findings of this study are even more concerning (ie, even mild or infrequent conversion efforts were associated with adverse mental health outcomes, including suicide attempts). Because the survey question asked about exposure to GICE from professionals, it is possible that exposures to GICE from other people (eg, family members) were not captured. Although the survey included respondents from a wide geographic distribution across the United States, these participants were not recruited via random sampling. The sample may not be nationally representative. Data are also lacking regarding when respondents entered puberty, making it difficult to define a prepubertal sample; we therefore set an approximate prepubertal cutoff at age 10 years. In this study, we compared exposure to GICE before age 10 years with lifetime exposure to non-GICE therapy. Although it would have been ideal to compare the former group with those who experienced non-GICE therapy before age 10 years, we lacked data on the age at which respondents were exposed to non-GICE therapy.

Conclusions

The findings suggest that recalled exposure to GICE is associated with adverse mental health outcomes in adulthood, including severe psychological distress, lifetime suicidal ideation, and lifetime suicide attempts. In this study, exposure to GICE before age 10 years was associated with adverse mental health outcomes compared with therapy without conversion efforts. Results from this study support past positions taken by leading professional organizations that GICE should be avoided with children and adults.

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