Title

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Journal

Journal of Adolescent Health, 67(3)

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Publication Date

2020-09-01

DOI

10.1016/j.jadohealth.2020.03.028

Peer reviewed

HHS Public Access

Author manuscript

J Adolesc Health. Author manuscript; available in PMC 2021 September 01.

Published in final edited form as:

J Adolesc Health. 2020 September ; 67(3): 376–383. doi:10.1016/j.jadohealth.2020.03.028.

Physiologic and metabolic characteristics of a cohort of transgender and gender-diverse youth in the United States

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Abstract

Purpose: The purpose of this study is to describe baseline physical and laboratory characteristics of participants in the largest prospective study of transgender and gender-diverse (TGD) youth in the United States.

Methods: Participants were recruited from four clinics which specialize in the care of TGD youth prior to starting either GnRH analogs for pubertal suppression or gender-affirming hormone treatment. Anthropometric and laboratory measurements were abstracted from the medical chart. Baseline characteristics including height, weight, BMI, blood pressure, and laboratory measurements were compared to age-matched National Health and Nutritional Examination Survey (NHANES) comparison group.

Results: Seventy-eight TGD youth with an median age of 11 years (range 8–14 years) were recruited prior to pubertal suppression, of whom 41 (53%) were designated male at birth, and 296 participants with an median age of 16 years (range 12–20 years) were recruited prior to beginning gender-affirming hormones, of whom 99 (33%) were designated male at birth. The mean HDL-C was lower in study participants when compared to NHANES participants (50.6 ± 12.3 mg/dL vs. 53.3 ± 13.3 mg/dL, p = 0.001). Otherwise, the study cohorts were similar in terms of BMI, proportion of overweight and obesity, blood pressure, and baseline laboratory variables.

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The authors have no relevant financial conflicts of interest to disclose.

Conclusions: Prior to starting gender-affirming treatment, TGD youth are physiologically similar to the general population of children and adolescents in the United States, with the exception of slightly lower HDL-C. Evaluation of this cohort over time will define the physiological effects of pubertal blockade and gender-affirming hormone treatment.

Implications and Contributions: This study describes the baseline metabolic and physiologic characteristics of a large multi-site cohort of transgender and gender-diverse (TGD) youth in the United States. TGD youth had lower HDL-C than the general United States population but were otherwise similar in terms of their anthropometric, metabolic, and physiologic parameters.

Keywords

Transgender; gender-diverse; adolescent; transgender health; gender-affirming hormones

INTRODUCTION

Increasing numbers of transgender/gender-diverse (TGD) youth, individuals whose gender identity does not align with their sex designated at birth, are seeking medical care in the United States.[1] Despite these increasing numbers, there is a paucity of data detailing the risks and benefits of gender-affirming medical treatments, and current guidelines are based primarily on expert opinion.[2,3] Gender-affirming medical care for transgender youth includes gonadotropin-releasing hormone analog (GnRHa) treatment for those in early puberty to halt the further development of secondary sex characteristics discordant with the youth's identified gender, as well as initiation of gender-affirming hormone (GAH) treatment (i.e., estrogen in transfeminine individuals and testosterone in transmasculine individuals) to induce secondary sex characteristics consistent with the youth's affirmed gender.

Sex steroids are believed to have a significant effect on cardiovascular health, and cardiovascular disease (CVD) is more common in cisgender men than cisgender women.[4] There is greater cardiovascular morbidity among transgender adults, with an increased risk of myocardial infarction in both transgender women and transgender men compared to cisgender women.[5,6] However, it is unclear if TGD youth carry increased risk for CVD at baseline, or if cardiovascular morbidity can be attributed to GAH treatment.

Anthropometric and metabolic features are potentially modifiable risk factors for CVD, and changes in these factors have been described in adults treated with GAH. Individuals treated with testosterone have metabolic changes associated with an increased risk of CVD including increased hemoglobin levels, systolic blood pressure and low-density lipoprotein cholesterol (LDL-C), and decreased high-density lipoprotein cholesterol (HDL-C). Individuals treated with combined estrogen and antiandrogens have decreased hemoglobin levels, which are also associated with an increased risk of CVD. Both transwomen and transmen on GAH treatment have higher triglyceride levels, which are associated with an increased risk of CVD. [7,8]

While anthropometric and metabolic changes have been described with GAH treatment in adults, it is unclear if TGD youth have metabolic risk factors at baseline prior to initiating

GnRHa or GAH treatment. For example, transgender men have been reported to have an increased prevalence of polycystic ovary syndrome (PCOS), a condition associated with risk factors such as obesity and dyslipidemia.[9–11] Available studies describing the characteristics of transgender youth in the United States have been small, have focused on older adolescents, and have primarily examined self-reported physical and mental health.[12–14] The few studies exploring metabolic characteristics of adolescent gender-affirming care were conducted in European centers that rarely initiate GAH treatment prior to age 16 years and treat a population that is neither ethnically nor racially representative of the United States.[15–17] There are currently no large published studies describing the anthropometric and metabolic characteristics of this population in the US.

The Trans-Youth Care (TYC) Study is an observational multi-site study among four academic medical centers with multidisciplinary clinics dedicated to serving TGD youth: Children's Hospital Los Angeles/University of Southern California, Boston Children's Hospital/Harvard Medical School, the Ann & Robert H. Lurie Children's Hospital of Chicago/Northwestern University, and the Benioff Children's Hospital/University of California San Francisco.[18]

Here we present the baseline anthropometric and metabolic characteristics of participants in the Trans-Youth Care Study, the largest study of transgender and gender diverse youth in the United States.

METHODS

The TYC Study is a multi-site, longitudinal, observational study of gender-affirming medical care of TGD children and adolescents in the United States. The research protocol was approved by the Institutional Review Boards at all study sites. A full description of the study protocol is published for reference.[18] Briefly, TGD youth seeking treatment for gender dysphoria between July 2016 and September 2018 were recruited into one of two cohorts based on their intent to initiate GnRHa or GAH treatment. Participants were excluded if they could not read or understand English, had serious psychiatric symptoms, or were otherwise unable to provide informed consent or complete the study activities. Participants in the GnRHa and GAH cohorts completed questionnaires evaluating their mental health, psychosocial functioning, and gender identity. Ferriman-Gallwey scores were collected via participant self-report. Anthropometric, physiologic, and laboratory data were collected as part of the routine medical care of the participant and abstracted from the medical record. For the analyses in this report, data from the GnRHa cohort were restricted to participants who were in early puberty (Tanner Stages II and III), and data from the GAH cohort were restricted to those were in mid- to late puberty (Tanner Stages III, IV, V) unless they had prior GnRHa exposure.

Z-scores and percentiles were determined based on the Centers for Disease Control (CDC) growth data for the participants sex designated at birth.[19] Using United States census data, participants' ZIP codes were matched to average median household median incomes.[20] To provide a comparison group, 2015–2016 data from the National Health and Nutrition

Examination Survey (NHANES) were used to create cohorts of participants in the same age range as the study cohorts.[21]

Mean and standard deviation were used to summarize normally distributed variables, median and range were used to summarize non-normally distributed variables, and comparisons were made via Student's t-test and the Mann-Whitney test, respectively. Race, sex designated at birth, and estimated household income as derived by ZIP code (see above) were used as covariates. Pearson's r was used to assess linear correlations, and regression was utilized to adjust for covariates. Proportions were compared using Fisher's exact test. A p value of < 0.05 was considered significant, with no adjustment for multiple testing for this descriptive analysis. Stata Statistical Software: Release 16 (College Station, TX) was used for calculations.

RESULTS

GnRHa Cohort

Demographics—Seventy-eight TGD participants who were Tanner Stage II or III, of whom 41 (53%) were designated male at birth and 37 (47%) were designated female at birth, were included in the analysis (Table 1). Fourteen participants who were recruited prior to starting GnRH analogs for pubertal suppression were in late puberty or post-puberty (i.e., Tanner Stage IV or V) and were excluded from this analysis (Figure 1). The median age was 10 years (range 8–13 years) for participants designated female at birth and 11 years (range 9–14 years) for participants designated male at birth.

Of the participants who were designated male at birth, 18 (43%) identified as female, 20 (49%) identified as transgender female, two (5%) identified as gender fluid, and one (2%) identified as non-binary. Of the participants who were designated female at birth, 20 participants (54%) identified as male, 15 (41%) as transgender male, and 2 (5%) as non-binary. There was no difference in racial/ethnic makeup between birth-designated male and birth-designated female participants. There were a greater proportion of TYC participants who were white compared to the NHANES comparison group (57% vs. 34% , $p < 0.0001$), and there were a smaller proportion of participants with estimated household income < $55,000 (17% vs. 56%, $p < 0.0001$); there was no difference between those designated male and female at birth.

Anthropometric Measurements—There was no difference in mean height, weight, or BMI Z-scores (calculated for birth-designated sex), for blood pressure, or for the prevalence of obesity between participants designated female and male at birth (Table 2). For birth-designated males, there was a significant decrease in height Z-score with increasing participant age (Supplemental Figure 1). Otherwise there was no correlation between participant age and height, weight, or BMI Z-score.

When compared to the NHANES comparison group there was no difference in mean height, height Z-score, weight, or weight Z-score. The participants in the GnRHa cohort did have slightly lower mean BMI Z-scores (0.36 ± 1.06 vs. 0.64 ± 1.11) and a smaller proportion of participants who were classified as obese than the NHANES comparison group (6% vs.

17%), but these differences were not significant once controlled for race and estimated household income (p = 0.5 and 0.2, respectively) (Supplemental Figure 3).

The GnRHa participants had higher systolic and diastolic blood pressure measurements than the NHANES age-matched controls (111 ± 11 mmHg vs. 104 ± 9 mmHg, p < 0.001; 63 ± 8 mmHg vs. 54 ± 9 mmHg, p < 0.001 when controlled for sex designated as birth, race, and estimated household income), and there were a greater proportion who would be classified as hypertensive based on systolic blood pressure measurement (12% vs. 3%, p = 0.002).

Gender-Affirming Hormone Cohort

Demographics—One participant recruited prior to starting GAH was in early puberty (Tanner II) and was excluded, leaving two hundred and ninety-six participants for analysis in this cohort(Figure 1); 99 (33%) were designated male at birth, and 197 (67%) were designated female at birth (Table 1). Of these, thirteen (4%) designated male participants and seven (2%) designated female participants had previously used a GnRHa for pubertal blockade. The median age of participants was 16 years (range 12–20 years) and similar to those designated male and female at birth. Of the participants who were designated male at birth, 44 (44%) identified as female, 50 (50%) identified as transgender female, 1 (1%) identified as gender queer, and 3 (3%) identified as non-binary. Of the participants who were designated female at birth, 82 participants (42%) identified as male, 103 (53%) as transgender male, 2 (1%) identified as gender fluid, 1 (0.5%) as gender queer, and 9 (5%) as non-binary. The racial and ethnic distribution was similar between both designated-sex groups.

Similar to the GnRHa cohort, the GAH cohort had a greater proportion of participants who were white when compared to NHANES (63% vs. 36%, p < 0.0001) and a smaller proportion of participants with estimated household income < $55,000 (21% vs. 58%, p < 0.001). The rate of current tobacco use (defined as daily, weekly, or monthly use in the past three months) was 9% in the GAH cohort, similar to the published rate for 8^{th}, 10^{th}, and 12^{th} grade students (5.4%, p = 0.4).[22]

Anthropometric Measurements—For the analysis of anthropometric measurements, GAH cohort participants who had previously used GnRHa were excluded. With these participants excluded, there was no difference in height Z-score between those designated male and those designated female at birth (Table 2); however when compared to the NHANES age-matched comparison group TGD participants who were designated female at birth were taller (height Z-score 0.15 ± 1.03 vs. −0.17 ± 1.08, p = 0.006 when controlled for race and estimated household income).

There was a difference in weight and BMI Z-scores between designated sex groups, with those designated female at birth having significantly higher weight Z-score and BMI Z-score than those designated male at birth (0.78 ± 1.05 vs 0.42 ± 1.25, p = 0.013; 0.74 ± 1.07 vs. 0.34 ± 1.26, p = 0.02, respectively). The majority of participants had BMIs in the normal weight category (56%); 24% were overweight and 18% were obese. This distribution was not different between participants designated female and male at birth (p = 0.5).

Participants who were designated male at birth had higher BMI Z-scores (0.34 ± 1.26 vs. − 0.23 ± 0.44) than the NHANES comparison group ($p < 0.001$ controlled for race and estimated household income). Those designated female at birth had weight and BMI Z-scores comparable to those of the NHANES comparison group ($p = 0.6$ and $p = 0.7$ respectively). Despite the difference in BMI Z-scores in those designated male at birth, the distribution of obesity categories of the TGD participants was similar to those in the NHANES cohort, with the majority classified as normal weight (62%), 25% overweight, and 12% obese ($p = 0.4$) (Supplemental Figure 3).

As was seen in the GnRHa cohort, the mean systolic and diastolic blood pressures were higher in the TGD participants than in the NHANES group, (116 ± 11 mmHg vs. 111 ± 10 mmHg, $p < 0.001$; 65 ± 9 mmHg vs. 61 ± 11 mmHg, $p < 0.001$) when controlled for sex designated at birth, race, and estimated household income. Likewise, there was a greater proportion of TGD participants with systolic (9% vs. 3%, $p < 0.001$) and diastolic (3% vs. 0.5%, $p = 0.001$) blood pressure in the hypertensive range. There was no difference in the proportion of participants with blood pressure in the hypertensive range between designated males and designated females.

Laboratory Measurements—Participants with prior GnRHa exposure and one participant with a known diagnosis of type 1 diabetes mellitus were excluded from analysis of laboratory values. There have been reports of increased prevalence of hyperandrogenemia and polycystic ovarian syndrome (PCOS) in TGD youth designated female at birth. [9–11] For that reason we examined baseline levels of free testosterone as well as hirsutism as assessed by Ferriman-Gallwey scores in transmasculine youth. Although the majority of the participants designated female at birth had free testosterone levels in the normal range, there were seven participants (4%) who had free testosterone levels higher than the upper limit of normal for an adult female. There were six (4%) participants who had Ferriman-Gallwey scores indicating moderate to severe hirsutism (> 15) (Supplemental Figure 2). There was no significant relationship between free testosterone level and Ferriman-Gallwey score ($p = 0.4$). Testosterone, estradiol, and prolactin measurements were in the normal range for sex designated at birth and Tanner Stage.

Given reports of poor cardiovascular outcomes in transgender adults, we examined baseline markers of cardiovascular risk such as lipid measurements. TGD participants had levels of total and LDL-C that were similar to NHANES values (Figure 2). The proportion of participants with total cholesterol or LDL-C in the ‘poor’ range (> 200 mg/dL or >130 mg/dL, respectively) were similar across birth sex and when compared to the NHANES cohort.

In contrast, TGD participants did have significantly lower HDL-C compared to NHANES participants when controlled for BMI, race, sex designated at birth, and estimated household income (50.6 ± 12.3 mg/dL vs. 53.3 ± 13.3 mg/dL, $p = 0.001$) (Table 3 and Figure 2). Similarly, there was a significantly higher proportion of participants with HDL cholesterol less than 40 mg/dL (19%), a level deemed ‘poor’ by the National Heart, Lung, and Blood Institute[23], as compared to age matched NHANES participants (13%, $p = 0.03$). However, when comparing subgroups based on sex designated at birth, only those designated female at

birth had a higher a proportion of low HDL-C than their NHANES counterparts (designated male 28% vs. 19%, p = 0.1; designated female 15% vs. 7%, p = 0.005). There was no significant difference between the lipid measurements of participants who indicated that they currently used tobacco products and those who did not indicate current tobacco use.

The majority of participants had hemoglobin A1c (HgbA1c) in the normal range, although there were 8 participants (6%) with HgbA1c in the pre-diabetes range (5.7–6.4%) and two participants (1%) with HgbA1c in the diabetic range (> 6.4%); this was not statistically different than the NHANES comparison group (p = 0.05)

DISCUSSION

The TYC study is the largest prospective study of gender-affirming medical treatments in the United States. Here we present a baseline description of laboratory and physiologic findings for two cohorts of transgender youth recruited for this longitudinal observational study; one prior to initiating GnRHa for pubertal blockade and a second prior to initiating gender-affirming sex-steroid treatment.

There have been several recent reports of increased cardiovascular risk in transgender adults and negative changes in LDL-C and HDL-C with testosterone therapy in transgender adults.[8,24–26] We found that, even prior to starting hormonal treatments, HDL-C was lower in our cohort of TGD participants compared to NHANES comparison group; this difference was not attributable to differences in BMI, race, or socioeconomic status as estimated by household income by ZIP code. HDL-C is an important marker of cardiovascular risk, and increasing HDL-C is considered an important step in reducing the risk of poor metabolic and cardiovascular outcomes later in life.[28,29] In a meta-analysis of studies of adult cisgender individuals, a 1 mg/dL increase in HDL-C was associated with a 2–3% decreased in cardiovascular risk.[30] Thus, the difference between TGD and NHANES individuals of 2.7 mg/dL represents a 5–8% increase in cardiovascular risk in the TGD population. Low HDL-C levels are associated with tobacco use, obesity, and low rates of exercise.[27] The rate of tobacco use in our cohort was similar to rates in U.S. adolescents and there was no difference in lipid measurements between those who indicated they had used tobacco and those who did not.

Increasing physical activity has been shown to improve HDL-C [31], and transgender adolescents have lower self-reported physical activity as compared to their cis-gender peers, likely secondary to a more negative perception of their body and lack of supportive environments and opportunities (i.e., gyms, teams, etc.).[32,33] Further research is required to investigate if lower levels of physical activity lead to lower HDL-C in this group; however, those adolescents presenting for gender affirming care with unfavorable HDL-C at baseline should be counseled to increase physical activity in an effort to mitigate the risk presented by low HDL-C.

There have been anecdotal reports of increased BMI amongst transmasculine individuals in an effort to conceal female-associated fat distribution.[34] However, our data suggest that this is not a widespread phenomenon, as we found no difference in BMI Z-score or the

proportion of overweight and obese individuals for transmasculine TYC participants when compared to the NHANES comparison group for either the GnRHa or GAH cohort. Likewise, there have been concerns that transfeminine individuals may strive for a lower BMI in pursuit of a more stereotypically feminine physique.[34–36] However, we did not find any difference between BMI Z-score or percentage of transfeminine participants classified as underweight in the blocker cohort compared to the NHANES controls, and in fact, the transfeminine participants in the GAH cohort had slightly higher, not lower, BMI Z-scores than the NHANES controls.

The negative correlation observed between height Z-score and age for birth-designated male participants in the GnRHa cohort is an expected consequence of recruiting individuals by pubertal stage. Participants who remain in early puberty (Tanner II or III) at older ages will be relatively shorter than their peers who have already experienced a pubertal growth spurt.

Both systolic and diastolic blood pressure measurements were higher than NHANES measurements in both cohorts and both sex designated at birth groups. We suspect that this systematic difference may not represent a true difference between TGD youth and the general population, but rather is secondary to different methodologies and environments between clinic measurements captured by the TYC study and those utilized by the NHANES study.[37] For example, the typical “white-coat hypertension” of a clinic visit may be further enhanced by the stress of anticipating a sensitive discussion of gender identity.

There has been suggestion of a link between masculine gender identity and exposure to androgens, supported by reports of an increased prevalence of PCOS and elevated androgen levels amongst transgender men.[9–11] A more recent report using contemporary criteria for PCOS did not find an increased prevalence of PCOS in transgender men, but there was an increased incidence of biochemical hyperandrogenism.[38] In our cohort of transmasculine participants studied prior to GAH, 4% had an elevated free testosterone level greater than the upper limit of normal for a female. Although not sufficient for a diagnosis of PCOS, this result is similar to prevalence data for PCOS amongst women of reproductive age in the United States in general.[38] Thus, our data do not suggest an increased prevalence of PCOS in transmasculine youth.

The data here represent a baseline description of a diverse sample of TGD youth recruited from four geographically diverse sites in the United States. The sites are all large, urban, university-based referral centers, and thus our study fails to capture TGD individuals who access medical care at rural or community sites or those who are unable to access gender-affirming care. The bias introduced by recruitment from urban centers and by participation in a research study in general resulted in a higher average socioeconomic status and greater predominance of white participants than the general US population. Although this was controlled for in the analysis presented here, it may affect the generalizability of results.

CONCLUSION

TGD children and adolescents recruited for the TYC study had lower HDL-C than the general United States population but otherwise are similar in terms of their anthropometric,

metabolic, and physiologic parameters. More research is needed to identify additional factors that may explain lower HDL-C in TGD youth. Counseling regarding optimizing modifiable risk factors to improve cardiovascular outcomes such as smoking cessation and improvement in physical activity levels should be offered to youth who enter medical gender transition with an unfavorable HDL-C. Forthcoming data on this cohort as they embark on gender-affirming treatment will be valuable in guiding practitioners caring for this population with much-needed information on the outcome of currently used medical treatments on anthropometric measurements and metabolic outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

This work was supported by National Institutes of Health grants R01 HD082554, T32 DK007699, and T32 DK007161 as well as grant 2019119 from the Doris Duke Charitable Foundation.

Abbreviations:

TGD	Transgender/gender-diverse
GnRHa	Gonadotropin-releasing hormone analog
DSM-V	Diagnostic and Statistical Manual of Mental Disorders 5th edition
GAH	Gender-affirming hormones
NHANES	National Health and Nutritional Examination Survey
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol

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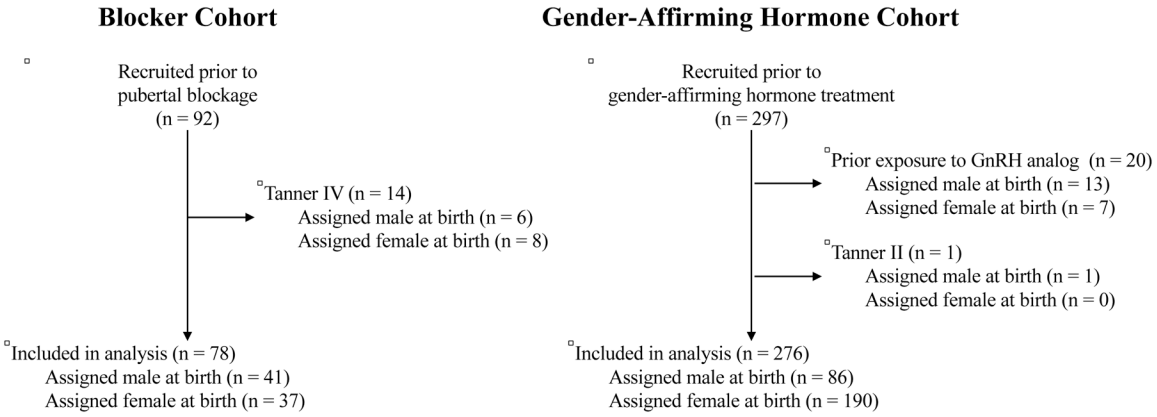

Figure 1.
Flowsheet of subject selection.

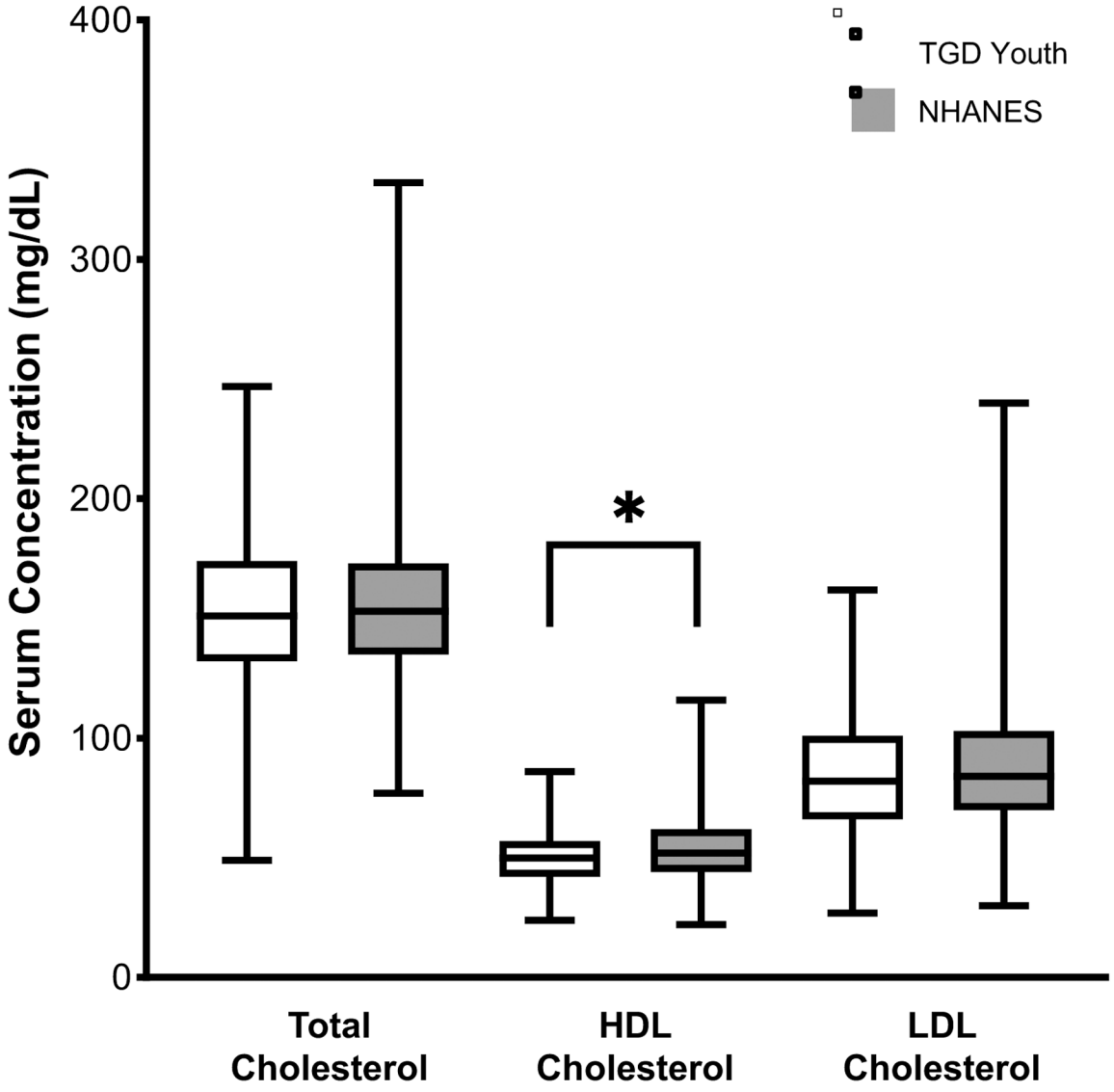

Figure 2. Cholesterol measurements of participants in the gender-affirming hormone cohort.
Box represents interquartile range. Central line is the median of the sample. Minimum and maximum values are represented by the black lines. The asterisk indicates a significant difference (p = 0.001) in HDL cholesterol between study participants and NHANES participants.

Table 1.

Baseline characteristics of participants

	Puberty Blocker Cohort			Gender-Affirming Hormone Cohort		
	Total (n = 78)	**Assigned male at birth (n = 41)**	**Assigned female at birth (n = 37)**	**Total (n = 296)**	**Assigned male at birth (n = 99)**	**Assigned female at birth (n = 197)**
Age, median (range), y	11 (8 – 14)	11 (9 – 14)	10 (8 – 13)	16 (12 – 20)	16 (12 – 20)	16 (12 – 20)
Affirmed Gender, n (%)						
Female	17 (22%)	18 (43%)	0 (0)	44 (15%)	44 (44%)	0 (0)
Male	21 (27%)	0 (0)	20 (54%)	82 (28%)	0 (0)	82 (42%)
Transgender Female (male-to-female)	20 (26%)	20 (49%)	0 (0)	50 (17%)	50 (50%)	0 (0)
Transgender Male (female-to-male)	15 (19%)	0 (0)	15 (41%)	103 (35%)	0 (0)	103 (53%)
Gender Fluid	2 (3%)	2 (5%)	0 (0)	2 (1%)	0 (0)	2 (1%)
Gender Queer	0 (0)	0 (0)	0 (0)	2 (1%)	1 (1%)	1 (0.5%)
Non-binary	3 (4%)	1 (2%)	2 (5%)	12 (4%)	3 (3%)	9 (5%)
Other	0 (0)	0 (0)	0 (0)	1 (0.3%)	1 (1%)	0 (0)
Race/Ethnicity, n (%)						
White	44 (57%)	17 (43%)	27 (73%)	187 (63%)	64 (65%)	123 (63%)
Black or African-American	3 (4%)	2 (5%)	1 (3%)	13 (4%)	4 (4%)	9 (5%)
Asian	1 (1%)	1 (3%)	0 (0)	13 (4%)	4 (5%)	9 (5%)
American Indian/Alaska Native	1 (1%)	1 (3%)	1 (3%)	3 (1%)	0 (0)	3 (1.5%)
Native Hawaiian/Pacific Islander	0 (0)	0 (0)	0 (0)	1 (0.3%)	0 (0)	1 (0.5%)
Multi-Race	9 (12%)	5 (13%)	4 (11%)	9 (3%)	5 (5%)	4 (2%)
Other	1 (1%)	1 (3%)	0 (0)	3 (1%)	2 (2%)	1 (0.5%)
Hispanic or Latino	14 (18%)	10 (25%)	4 (11%)	63 (21%)	16 (16%)	47 (24%)
Unknown	5 (6%)	4 (10%)	1 (3%)	4 (1%)	4 (4%)	0 (0)
Tanner Stage, n (%)						
II	50 (64%)	32 (78%)	18 (49%)	9 (3%)	9 (10%)	0 (0)
III	28 (36%)	9 (22%)	19 (51%)	9 (3%)	6 (7%)	3 (2%)
IV	-	-	-	27 (9%)	9 (10%)	18 (10%)
V	-	-	-	228 (84%)	66 (73%)	162 (89%)
Unknown	0 (0)	0 (0)	0 (0)	23 (8%)	9 (9%)	14 (7%)
Current tobacco use, n (%) *	-	-	-	26 (9%)	12 (14%)	14 (7%)

J Adolesc Health. Author manuscript; available in PMC 2021 September 01.

	Puberty Blocker Cohort			Gender-Affirming Hormone Cohort		
	Total (n = 78)	**Assigned male at birth (n = 41)**	**Assigned female at birth (n = 37)**	**Total (n = 296)**	**Assigned male at birth (n = 99)**	**Assigned female at birth (n = 197)**
Median Household Income of reported ZIP Code, n (%)						
< $54,999	13 (17%)	10 (24%)	3 (8%)	59 (21%)	24 (26%)	35 (19%)
$55,000 – $74,999	19 (25%)	7 (17%)	12 (33%)	65 (24%)	21 (23%)	44 (24%)
$75,000 – $99,999	19 (25%)	12 (29%)	7 (19%)	86 (31%)	25 (27%)	61 (33%)
>$100,000	26 (34%)	12 (29%)	14 (39%)	68 (24%)	23 (25%)	45 (24%)
Unknown	1 (1%)	0 (0)	1 (3%)	18 (6%)	6 (6%)	12 (6%)
Caregiver employment status, n (%) **						
Unemployed	-	-	-	11 (4%)	8 (8%)	3 (2%)
Employed part time	-	-	-	10 (3%)	2 (2%)	8 (4%)
Employed full time	-	-	-	265 (90%)	88 (89%)	177 (90%)
Retired	-	-	-	5 (2%)	0 (0)	5 (3%)
Unknown				5 (2%)	1 (1%)	4 (2%)
Caregiver education status, n (%) **						
Less than high school	-	-	-	10 (3%)	5 (5%)	5 (3%)
High school graduate	-	-	-	98 (33%)	31 (31%)	67(34%)
Bachelor’s degree	-	-	-	63 (21%)	23 (23%)	40 (20%)
Master’s degree	-	-	-	58 (20%)	15 (15%)	43 (22%)
Professional or doctorate degree	-	-	-	28 (9%)	11 (11%)	17 (9%)
Unknown				39 (13%)	11 (11%)	25 (13%)

* Current use was defined as daily, weekly, or monthly use in the past three months.

** Caregiver employment and education status were not collected for participants in the puberty blocker cohort.

Table 2

Anthropometric measurements of participants compared to matched NHANES comparison group

	Puberty Blocker Cohort						Gender-Affirming Hormone Cohort *					
	TGD Youth			Matched NHANES Comparison Group			TGD Youth			Matched NHANES Comparison Group		
	Total (n = 78)	Assigned male at birth (n = 41)	Assigned female at birth (n = 37)	Total (n = 1125)	Assigned male at birth (n = 578)	Assigned female at birth (n = 547)	Total (n = 276)	Assigned male at birth (n = 86)	Assigned female at birth (n = 190)	Total (n = 1095)	Assigned male at birth (n = 547)	Assigned female at birth (n = 548)
Height, mean (SD), cm		151.5 (8.1)	145.4 (9.7)	-	147.5 (15.1)	144.8 (12.8)	-	173.6 (7.6)‡	163.3 (6.6)≠	-	169.6 (10.4)	159.5 (8.1)
Height Z-score, mean (SD)	0.29 (1.10)	0.37 (1.06)	0.19 (1.15)	0.17 (1.03)	0.25 (1.02)	0.1 (1.03)	0.09 (1.00)†	−0.25 (0.93)	0.15 (1.03)≠	−0.12 (1.06)	−0.08 (1.03)	−0.17 (1.08)
Weight, mean (SD), kg	43.3 (11.6)	45.5 (11.5)	40.8 (11.3)	45.4 (17.8)	46.1 (19)	44.6 (18.4)	68.8 (18.7)	72.3 (19.0)	67.3 (18.4)≠	67.6 (21.2)	71.4 (22.6)	63.9 (18.9)
Weight Z-score, mean (SD)	0.36 (1.10)	0.44 (1.08)	0.27 (1.12)	0.61 (1.18)	0.66 (1.21)	0.55 (1.15)	0.67 (1.12)†	0.42 (1.25)	0.78 (1.05)	0.59 (1.23)	0.58 (1.27)	0.6 (1.19)
BMI, mean (SD), kg/m^2	19.4 (3.7)	19.6 (3.5)	19.1 (3.9)	20.5 (5.1)	20.5 (5.2)	20.6 (5.0)	24.8 (6.3)	23.7 (5.7)	25.2 (6.5)	24.7 (6.6)	24.6 (6.7)	24.9 (6.5)
BMI Z-score, mean (SD)	0.36 (1.06)	0.39 (1.10)	0.32 (1.02)	0.64 (1.11)	0.66 (1.15)	0.63 (1.08)	0.62 (1.15)	0.34 (1.26)‡	0.74 (1.07)	0.30 (0.98)	−0.23 (0.44)	0.71 (1.08)
BMI categories, n (%)												
Underweight	1 (1%)	1 (2%)	0 (0)	7 (0.6%)	4 (0.7%)	3 (0.6%)	4 (2%)	1 (1%)	3 (2%)	16 (2%)	7 (1%)	9 (2%)
Normal weight	53 (68%)	28 (68%)	25 (68%)	650 (58%)	342 (59%)	308 (56%)	152 (56%)	51 (62%)	101 (53%)	557 (53%)	294 (55%)	263 (50%)
Overweight	19 (24%)	10 (24%)	9 (24%)	277 (25%)	132 (23%)	145 (26%)	66 (24%)	21 (25%)	45 (24%)	250 (24%)	113 (21%)	137 (26%)
Obese	5 (6%)	2 (5%)	3 (8%)	191 (17%)	100 (17%)	91 (16%)	50 (18%)	10 (12%)	40 (21%)	238 (22%)	120 (23%)	118 (22%)
Systolic blood pressure, mean (SD), mmHg	111 (11)†	112 (11)≠	110 (11)≠	104 (9)	105 (10)	103 (9)	116 (11)†	120 (12)≠	114 (10)≠	111 (10)	114 (10)	108 (9)
Diastolic blood pressure, mean (SD), mmHg	63 (8)†	63 (9)≠	62 (8)≠	54 (9)	53 (13)	54 (13)	65 (9)†	67 (10)≠	64 (9)≠	61 (11)	60 (12)	61 (10)
Systolic blood pressure > 95th percentile, n (%)	9 (12%)†	5 (12%)≠	4 (11%)	36 (3%)	17 (3%)	19 (4%)	24 (9%)†	9 (11%)≠	15 (8%)≠	28 (3%)	16 (3%)	12 (2%)

	Puberty Blocker Cohort						Gender-Affirming Hormone Cohort *					
	TGD Youth			Matched NHANES Comparison Group			TGD Youth			Matched NHANES Comparison Group		
	Total (n = 78)	Assigned male at birth (n = 41)	Assigned female at birth (n = 37)	Total (n = 1125)	Assigned male at birth (n = 578)	Assigned female at birth (n = 547)	Total (n = 276)	Assigned male at birth (n = 86)	Assigned female at birth (n = 190)	Total (n = 1095)	Assigned male at birth (n = 547)	Assigned female at birth (n = 548)
Diastolic blood pressure > 95th percentile, n (%)	4 (5%)†	2 (5%)‡	2 (5%)‡	4 (0.4%)	1 (0.2%)	3 (0.6%)	9 (3%)†	5 (6%)‡	4 (2%)‡	5 (0.5%)	3 (0.6%)	2 (0.4%)

* Participants with prior GnRH analog use and known diagnosis of type 1 diabetes mellitus were excluded from the analysis.

† $p < 0.05$ when compared to NHANES comparison group matched by age and sex assigned at birth and adjusted for race and estimated household income.

‡ $p < 0.05$ when compared to NHANES age-matched comparison group by sex assigned at birth.

Table 3

Laboratory measurements of participants in the gender-affirming hormone cohort compared to age-matched comparison group from NHANES

	Gender-Affirming Hormone Cohort*			Matched NHANES Comparison Group		
	Total (n = 276)	**Assigned male at birth (n = 86)**	**Assigned female at birth (n = 190)**	**Total (n = 1095)**	**Assigned male at birth (n = 547)**	**Assigned female at birth (n = 548)**
Estradiol, median (interquartile range), pg/mL						
Tanner IV	-	20 (13 – 21)	53 (24 – 139)	-	-	-
Tanner V	-	22 (17 – 25)	44 (21 – 90)	-	-	-
Total Testosterone, median (interquartile range), ng/dL						
Tanner IV	-	277 (144 – 424)	25 (16 – 30)	-	-	-
Tanner V	-	426 (295 – 573)	26 (18 – 36)	-	-	-
Free Testosterone, median (interquartile range), pg/mL						
Tanner IV	-	4 (3 – 52)	2.5 (1.5 – 3.0)	-	-	-
Tanner V	-	71 (14 – 91)	2.4 (1.3 – 3.5)	-	-	-
Prolactin, mean (SD), ng/mL	-	8.8 (4.1)	-	-	-	-
Total Cholesterol, mean (SD) mg/dL	155 (33)	149 (34)	157 (32)	157 (30)	154 (30)	159 (30)
Total Cholesterol > 200 mg/dL, n (%)	19 (8%)	7 (7%)	14(8%)	73 (8%)	34 (7%)	39 (9%)
HDL Cholesterol, mean (SD) mg/dL	50.6 (12.3) †	45.6 (10.7) ‡	52.6 (12.4) ‡	53.3 (13.3)	51.1 (12.8)	55.6 (13.4)
HDL Cholesterol < 40 mg/dL, n (%)	45 (19%) †	19 (28%)	26 (15%) ‡	125 (13%)	91 (19%)	34 (7%)
LDL Cholesterol, mean (SD) mg/dL	84.8 (26.2)	81.5 (29.8)	86.2 (24.4)	88.7 (26.7)	88.6 (27.7)	88.8 (25.7)
LDL Cholesterol > 130 mg/dL, n (%)	12 (6%)	5 (8%)	7 (5%)	24 (6%)	14 (7%)	10 (5%)
HgbA1c, mean (SD), %	5.2 (0.5)	5.3 (0.3)	5.2 (0.5)	5.3 (0.4)	5.2 (0.3)	5.2 (0.4)
HgbA1c 5.7% – 6.4%, n (%)	8 (6%)	2 (6%)	6 (6%)	35 (4%)	15 (3%)	20 (5%)
HgbA1c > 6.4%, n (%)	2 (1%)	0 (0)	2 (2%)	2 (0.2%)	0 (0)	2 (0.5%)

*Participants with prior GnRH analog use were excluded

†$p < 0.05$ when compared to NHANES age-matched comparison group.

‡$p < 0.05$ when compared to NHANES age-matched comparison group by sex assigned at birth