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Effects of gender affirming hormone therapy on body mass index in transgender individuals: A longitudinal cohort study

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ABSTRACT

Introduction: Many transgender people take hormone therapy to affirm their gender identity. One potential long-term consequence of gender affirming hormone therapy is increased body mass index (BMI), which may be associated with metabolic syndrome, cardiovascular disease and higher mortality. Only a few published studies explored changes in BMI in transgender people taking gender affirming hormone therapy (GAHT).
Objective: To examine the changes in BMI longitudinally in response to GAHT in transgender women and men.
Methods: We conducted a retrospective cohort study of transgender individuals who received GAHT from the endocrinology clinic between January 1, 2000 and September 6, 2018. Subjects who sought GAHT were included if they had two separate measurements of BMI and were excluded if they had a BMI greater than 35 kg/m^2 or were missing demographic data at entry. We used a linear mixed model to analyze the longitudinal change in BMI.
Results: There were a total of 227 subjects included in this cohort. Among subjects already on GAHT, transgender women were receiving GAHT longer than transgender men (6.59 ± 9.35 vs 3.67 ± 3.43 years, p-value = 0.04). Over the period of 7 years, there was a significant increase in BMI in transwomen who newly initiated GAHT (p-value 0.004). There were no changes in BMI in transgender men and women already on GAHT or in transgender men who newly initiated GAHT in the study.
Conclusion: We conclude that BMI significantly increases in transwomen but not in transmen after initiation of GAHT in a single center based in the United States. In transwomen and transmen, BMI appears to be stable following 3 to 6 years of GAHT. Future investigations should examine the causes for increased BMI in transgender women including type of GAHT, diet and lifestyle, and association with risk of metabolic syndrome and cardiovascular disease.

Introduction

Transgender persons receive gender affirming hormone therapy (GAHT) to align their physical characteristics with their affirmed gender identity and to improve quality of life [1]. The long-term risks of GAHT are low, but may include higher incidence of venous thromboembolism, cerebrovascular accidents (CVA) and cardiovascular disease (CVD) in transgender women and polycythemia, acne, and androgenic alopecia in transgender men [2,3]. Guidelines from the Endocrine Society and World Professional Association for Transgender Health exist to help mitigate the risk that potentially could occur from GAHT [4,5]. These guidelines recommend maintaining hormone values in the range expected for the affirmed gender and avoiding supraphysiologic doses of GAHT.

One area of concern for transgender people is increased body weight following hormone therapy [6,7]. Some studies demonstrate an increase in weight among both transgender women and transgender men [8]. Transfeminine hormone increases body fat and decreases lean body

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mass, whereas transmasculine hormone decreases body fat and increases lean body mass [9–11]. The increases in body weight, particularly fat mass, in transgender women may explain why GAHT is associated with increased CVA and CVD in transgender women but not in transgender men [12]. Increases in fat mass in transgender women as compared to transgender men may also predispose transgender women to increased risk of metabolic syndrome [13,14].

Body mass index (BMI) is highly correlated with adiposity, and is a commonly used clinical tool to assess risk for obesity and related metabolic diseases [15–19]. Several studies have documented that a high BMI is significantly associated, in both men and women, with metabolic syndrome [20,21], CVDVD [22–25] and mortality [26–29]. To date, only a few published studies have explored changes in BMI in transgender people taking GAHT. In transgender women, a significant increase in BMI was reported following GAHT for 12 months [30,31]. Conversely, transgender men were found to have a significantly higher BMI after 6 months [32,33] and after 54 months [31,34] following GAHT [35,36]. More longitudinal data on changes in BMI in response to GAHT, especially in the United States, are needed.

The purpose of this study is to examine the changes in BMI longitudinally, over seven years, in response to GAHT in both transgender women and men. We conducted a retrospective single center cohort study with a focus on changes in BMI. We hypothesized that GAHT would lead to changes in BMI in both transgender men and women. We further classified individuals in the cohort by whether they entered the cohort before or after the initiation of GAHT. We adjusted our primary outcome of interest by age and duration of GAHT.

Methods

Cohort ascertainment and data collection

This waswa a retrospective study of transgender patients seen at the Emory Clinic between January 1, 2000 and September 6, 2018. The study was approved by the Emory Institutional Review Board.

The study participants were transgender patients who sought GAHT at our clinic, and received care from a single provider. The treatment protocol for gender affirming hormones followed the Endocrine Society clinical practice guidelines for treatment of gender-dysphoric/gender-incongruent persons [4,37]. Typically, transgender women received oral, transdermal or intramuscular estradiol along with spironolactone. Transgender men received intramuscular or transdermal testosterone. Subjects who were already taking GAHT and subjects who were evaluated before being prescribed GAHT were included in the study. Subjects were excluded if they were missing demographic data including BMI, had a single visit, or had a BMI higher than 35 kg/m^2 upon entry into the cohort. Subjects with BMI greater than 35 kg/m^2 were excluded because they were statistical outliers by the Z-scores statistical test. Subjects who had BMI values greater than 2 standard deviations from the mean at entry into the cohort were excluded from the study.

Data on each subject'ssubj age, height and weight, and GAHT were extracted from the electronic medical records. BMI was the primary outcome of interest. BMI was calculated by dividing weight in pounds (lbs) by height in inches (in) squared and multiplying by a conversion factor of 703 to obtain the corresponding value in kg/m^2.

Statistical analysis

Statistical analyses of the association between duration of GAHT and changes in BMI were performed using linear mixed-effects models separately for four groups: 1) transgender women who initiated GAHT after enrollment in the study; 2) transgender women who enrolled in the study while already on GAHT; 3) transgender men who initiated GAHT after enrollment in the study; and 4) transgender men who enrolled in the study while already on GAHT. The exposure of interest was duration of GAHT measured in quarters (3-month intervals), and the primary outcome was BMI change over time. The random effects models were constructed to take into account that the temporal change in BMI may differ across subjects; however age at baseline was included in the model as a fixed effect to avoid possible co-linearity with time.

All four models had the following form:

$BMI_{ij} = \beta_0 + \beta_1 Age_{ij} + \beta_2 Time_{ij} + v_{i0} + v_{i1} Time_{ij} + e_{ij}$ for $i \in \{1, \ldots, n\}$, and $j \in \{1, \ldots, m\}$ where

- BMI_{ij} is the response for j^{th} measurement of i^{th} patient.
- β_0 is the fixed intercept for the regression model.
- β_1 is the fixed slope for Age.
- $v_{i0} \overset{iid}{\sim} N(0, \sigma_0^2)$is the random intercept for i^{th} subject.
- $v_{i1} \overset{iid}{\sim} N(0, \sigma_1^2)$ is the random slope for i^{th} subject.
- $e_{ij} \overset{iid}{\sim} N(0, \sigma_e^2)$is a Gaussian error term.

The results of the models were expressed as linear regression coefficients (β) and the corresponding 95% confidence intervals (CI). The main measure of association was β estimate for GAHT, which represents average change in BMI with each additional quarter (3-month interval) of treatment duration. In addition, statistical results of the fixed effects were fitted by restricted maximum likelihood (REML) and presented with Satterthwaite's approximation method in the lmerTest R package.

To facilitate visualization of changes of BMI over time, we constructed boxplots of BMI distributions. This approach presents boxes showing median values, ranges and quartiles of BMI for each quarter. If the sample size for a given quarter was too small ($n \leq 2$), the boxplot for that quarter was omitted from the plot.

Results

Cohort description

We identified 227 transgender individuals who were potentially eligible for inclusion in the study. Thirteen individuals were not included because of a missing BMI value at the first recorded visit. We also excluded 33 subjects who had initial BMI greater than 35 kg/m^2 and 36 subjects who had only a single visit during the period of study. The final analytic cohort consisted of 145 transgender individuals further classified into 4 groups: 59 transgender women and 46 transgender men who were not yet initiated but subsequently started on GAHT and 25 transgender women and 15 transgender men who were already receiving GAHT (Fig. 1)

The baseline demographic characteristics of the study cohort are presented in Table 1. Subjects who were already taking GAHT prior to entry in the cohort were significantly older than the subjects not already taking GAHT in both transgender women (43.91 ± 15.58 years old vs 32.75 ± 11.67 years old) and transgender men (40.40 ± 13.11 years old vs 27.36 ± 8.84 years old). Most of subjects in each group were Caucasian. For subjects who entered the cohort already on GAHT, the mean BMI in transgender women and men were similar upon entry in the cohort (Table 1). The mean height and weight of transgender women were significantly higher than that of transgender men, p-value < 0.001 and p-value $= 0.02$, respectively. For subjects who entered cohort before the initiation of GAHT, transgender men and women had similar baseline BMI values. Transgender women already on GAHT were receiving GAHT longer than transgender men already on GAHT (6.6 years vs 3.7 years, p-value $= 0.04$). In subjects who entered cohort already on hormone therapy, the mean BMI in transgender women and men were similar upon entry in the cohort compared to those who were naïve to GAHT.

Longitudinal BMI changes among transgender women

In transgender women who entered the cohort already on GAHT, there were no significant changes in BMI over the study period

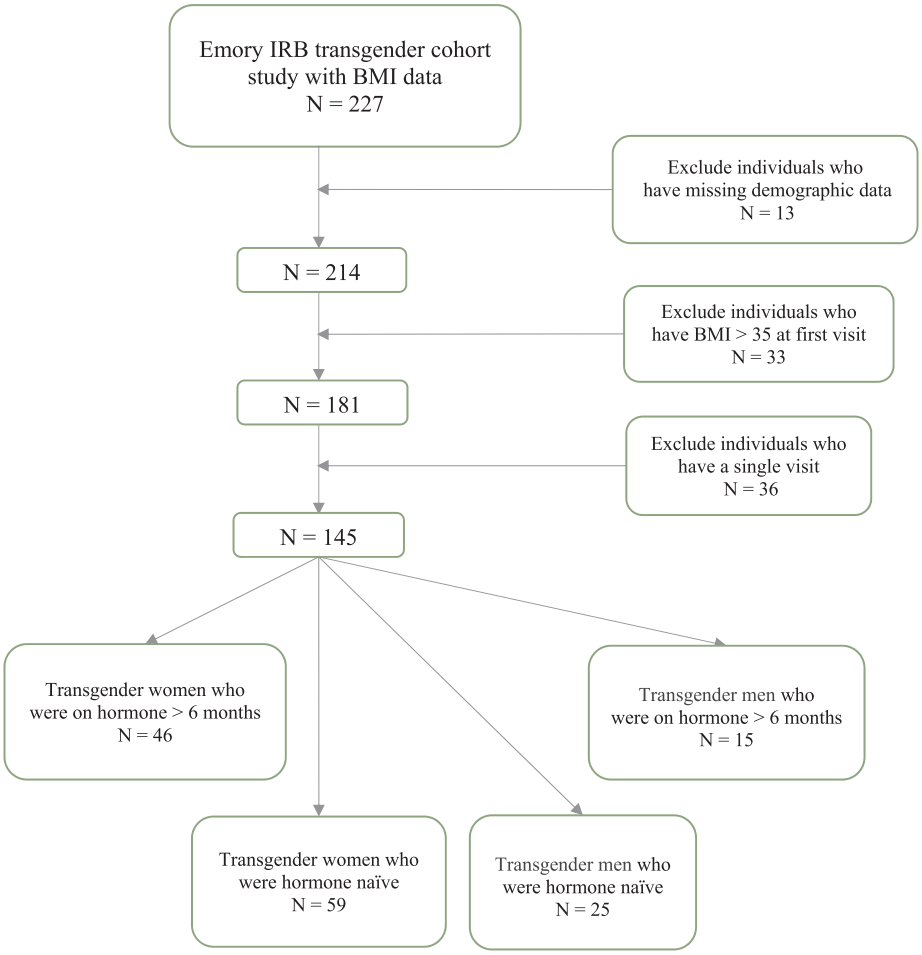

Fig. 1. Flow diagram of study participants.

(Fig. 2A). Transgender women who entered the cohort before the initiation of GAHT and then subsequently began GAHT experienced increases in BMI over the study period of 7 years. The changes in BMI appeared to be especially more prominent in the lower quartiles of BMI (Fig. 2B). Among transgender women who enrolled in the study prior to starting GAHT, BMI increased on average 0.125 kg/m^2 (95% CI 0.04–0.21, p-value = 0.004) per each additional quarter of therapy duration. In the corresponding analyses for transgender women who joined the cohort already on GAHT, the BMI changes were in the same direction but less pronounced and not statistically significant (β = 0.08, 95% CI −0.004–0.16, p-value = 0.064) (Fig. 2). In transgender women initiating on GAHT, the linear mixed model showed a significant relationship between age and duration of GAHT (Table 2, Model 2).

Table 1
Baseline characteristics of transgender women and transgender men who underwent gender affirming hormone therapy (GAHT).

	Transgender women		Transgender men	
	Already on GAHT (n = 46)	Hormone naïve (n = 59)	Already on GAHT (n = 15)	Hormone naïve (n = 25)
Age	43.9 ± 15.6	32.8 ± 11.7*	40.4 ± 13.1	27.4 ± 8.8†*
Race (%)				
Caucasian	52.1%	71.2%	66.7%	68.0%
African American	23.9%	8.5%	6.7%	12.0%
Asian	4.4%	1.7%	6.7%	0%
Multiple	0%	1.7%	6.7%	4.0%
Unknown	19.6%	16.9%	13.2%	16.0%
BMI (kg/m^2)	26.3 ± 4.7	24.7 ± 4.7	26.6 ± 4.2	24.4 ± 5.4
Height (Inches)	69.7 ± 3.6	69.5 ± 2.4	64.6 ± 3.1†	65.4 ± 3.1†
Weight (Pounds)	182.6 ± 41.8	169.1 ± 34.6	158.6 ± 30.5†	147.7 ± 34.5†
Years on Hormone	6.6 ± 9.35	0	3.7 ± 3.43†	0

Values are given as mean ± SD of the 46 transgender women who entered the cohort already on GAHT compared with 59 transgender women who entered the cohort before the initiation of GAHT and the 15 transgender men who entered the cohort already on GAHT and 25 transgender men who entered the cohort before the initiation of GAHT are in both comparisons. BMI, body mass index *$P < 0.05$ (p-values represent significance from log-transformed variables when relevant). We also compare transgender women to transgender men who already on hormone and transgender women to transgender men who hormone naïve. †$P < 0.05$ (p-values represent significance from log-transformed variables when relevant).

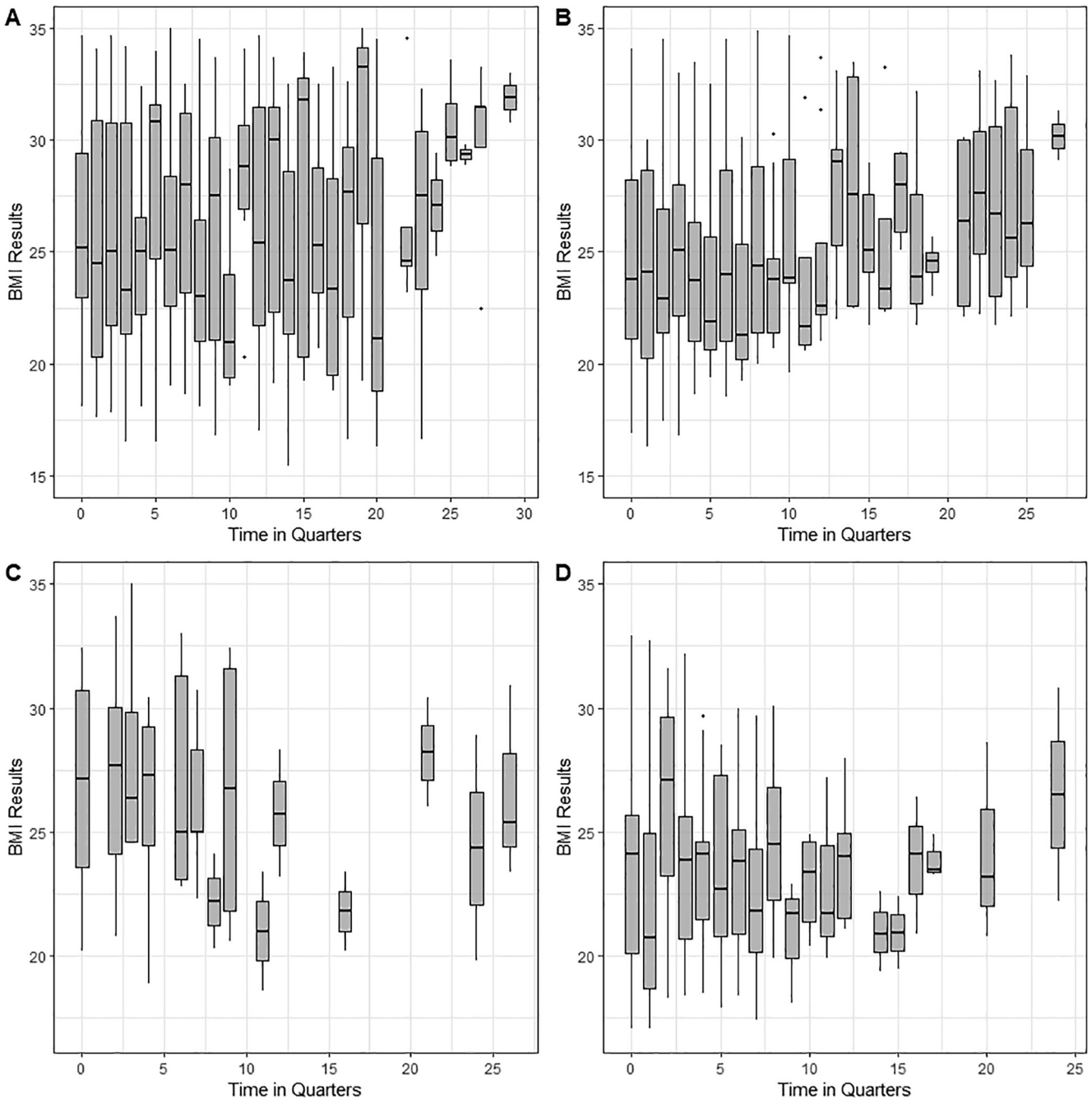

Fig. 2. Boxplots for course of BMI levels in four cohorts of transgender men and women receiving gender affirming hormone therapy over the period of 7 years. A: transgender women who entered the cohort after on GAHT for more than 6 months (P-value = 0.064). B: transgender women who entered the cohort prior to starting GAHT (P-value = 0.004). C: transgender men who entered the cohort after on GAHT for more than 6 months (P-value = 0.739). D: transgender men who entered the cohort prior to starting GAHT (P-value = 0.790).

Longitudinal changes in BMI among transgender men

Transgender men who entered the cohort on GAHT did not experience a change in BMI during the study period (Fig. 2C). Likewise, transgender men who entered the cohort prior to starting GAHT and subsequently began GAHT did not see changes in BMI over 7 years following the initiation of GAHT (Fig. 2D). In the linear mixed-model, neither BMI and age were correlated in both groups. Also, there was no correlation between BMI and duration of hormone therapy in both groups (Table 2, Model 3 & 4).

Discussion

This retrospective cohort of transgender individuals undergoing GAHT over a period of 7 years demonstrated a significant increase of BMI in transgender women who entered the cohort before the initiation of GAHT and no changes in BMI among transgender women already on GAHT for an average of 6.6 years. There were no significant changes in BMI in transgender men regardless of the timing of enrolment relative to GAHT initiation. The increase in BMI among transgender women appeared to occur primarily in the first 24 months of therapy followed by a plateau around the third year of GAHT. This may explain why transgender women already on GAHT prior to entry in the cohort did

Table 2
Association of BMI in four cohorts of transgender men and women receiving gender affirming hormone therapy with age and duration of taking gender affirming hormone therapy (GAHT) using linear mixed model.

Model 1: Transgender women who entered the cohort after on GAHT for more than 6 months (N = 46)

Fixed Effects	Estimate	95%CI	P-value
Intercept	18.66	[14.91, 22.41]	< 0.001
Age (years)	0.17	[0.08, 0.25]	< 0.001
GAHT duration (quarters)	0.08	[−0.004, 0.16]	0.064

Model 2: Transgender women who entered the cohort prior to starting GAHT (N = 59)

Fixed Effects	Estimate	95%CI	P-value
Intercept	19.62	[16.24, 23.0]	< 0.001
Age (years)	0.15	[0.05, 0.25]	0.004
GAHT duration (quarters)	0.13	[0.04, 0.21]	0.004

Model 3: Transgender men who entered the cohort after on GAHT for more than 6 months (N = 15)

Fixed Effects	Estimate	95%CI	P-value
Intercept	20.85	[13.5, 28.21]	< 0.001
Age (years)	0.14	[−0.03, 0.31]	0.101
GAHT duration (quarters)	−0.020	[−1.28, 1.24]	0.739

Model 4: Transgender men who entered the cohort prior to starting GAHT (N = 25)

Fixed Effects	Estimate	95%CI	P-value
Intercept	19.62	[14.2, 25.05]	< 0.001
Age (years)	0.16	[−0.03, 0.34]	0.093
GAHT duration (quarters)	−0.02	[-0.14,0.11]	0.790

P-value represent significance from log-transformed variables when relevant.

not demonstrate changes in this BMI during our study.

Reports on BMI among the transgender population have been mixed. Two prospective observational studies conducted in Europe reported that BMI increased in transgender women after 12 months of GAHT [30,38,39]. Another longitudinal cohort study in transgender girls in Europe also reported a significant increase in BMI from the start of GAHT from a mean age of 15 years up to the age of 22 years [40]. However, other studies have not reported increases in BMI over a similar period of time [8,10,41], although they have reported an increase in total body fat along with a significant decrease in lean body mass. The European Network for the Investigation of Gender Incongruence (ENIGI) study reported that the BMI at the initiation of GAHT appears to be a determinant of changes in body composition. A higher baseline BMI in transgender women was related to a smaller increase in body fat and larger decrease in lean body mass [42]. Four observational studies of transgender women in the US observed no change in BMI [10,43–45]. In transgender men, three studies show no change in BMI [44–46]; three studies showed an increase in BMI [10,43,47] and one study observed a decrease in BMI [48]. Results from these US-based studies are not directly comparable to ours because these studies were relatively small with cohort size of between 16 and 38 and short term had follow-up periods in the range of 6–35 months [10,43–48]. Our findings also differ from those published in Europe likely due to the differences in GAHT regimens. Our regimen for transwomen includes spironolactone whereas the main testosterone-lowering medication used in Europe is cyproterone. Cyproterone seems to have a stronger anti-androgenic effect than spironolactone which may lead to differences in body composition and adiposity.

In transgender men, there have been a few studies examining the long-term changes following GAHT on BMI. One previous observational study in Europe suggested a significant increase in BMI following 36 months of GAHT [49]. Additionally, one clinical trial of transgender men assigned participants to 3 different testosterone formulations and reported a significant increase in BMI after 54 months of treatment in all three study arms [34]. In contrast to these results, we found no changes in BMI after 7 years in both subjects who entered the cohort before initiation of GAHT and subjects who were already on GAHT. We hypothesize that testosterone may decrease body fat and increase lean body mass leading to an unchanged BMI. Other cohort studies examining transgender men on GAHT reported similar findings on BMI over the periods of 12 months and 24 months [35,50]. Therefore, it is possible that changes in body composition occurred in the transgender men in our cohort without detectable changes in BMI.

Higher BMI typically reflects increases in adiposity in most adults [51]. Elevated BMI is strongly associated with visceral adiposity, cardiometabolic disease and mortality in the general population [23,51–53]. For transgender women taking GAHT, a gain in fat, a decline in lean body mass, and an increase in insulin resistance have been reported, while the opposite effects are seen in transgender men [8,14,54]. These changes would predict that transgender women should be at higher risk for cardiovascular events compared to transgender men, which is in agreement with previous reports [9,55–59]. Moreover, one randomized controlled trial suggests that dose of GAHT may impact changes in BMI [6]. In order to decrease cardiovascular morbidity, particularly among transgender women, more attention should be paid to decreasing cardiovascular risk factors such as BMI and other factors such as hypertension, hyperlipidemia, and tobacco use [60]. Furthermore, longer term studies evaluating the impact of GAHT on BMI and other risk factors need to be conducted.

Some limitations of these data warrant consideration. It is important to acknowledge that BMI is a surrogate of adiposity; it does not provide indication of body composition or body fat distribution. Our study was not able to directly link GAHT to increased BMI because there may be other confounding factors such as diet, exercise, mental health status, lifestyle or behaviors that may affect or mediate this association. Another limitation of our study is that some subjects in the cohort were already on GAHT so we do not have their starting BMI prior to GAHT. As this was a retrospective chart review, we based our height measurements on clinic collected data. One potential source of error could be the measurement of height; although height for each patient was measured consistently at each visit using a stadiometer. Finally, we may not have a sufficiently long enough follow-up period or sample size to definitively say that BMI does not change following GAHT among transgender men.

We conclude that BMI significantly increases in transgender women but not in transgender men after initiation of GAHT in a single center based in the United States. In both transgender women and transgender men, BMI appears to be stable following 3 to 6 years of GAHT. Future investigations should focus on what factors may lead to increases in BMI including type of GAHT, changes in diet and lifestyle and what is the relationship between increased BMI and risk of metabolic syndrome and cardiovascular disease.

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CRediT authorship contribution statement

Pichatorn Suppakitjanusant: Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Yuhan Ji:** Formal analysis, Writing - original draft. **Mary O. Stevenson:** Data curation, Writing - original draft, Writing - review & editing. **Panicha**

Chantrapanichkul: . R. Craig Sineath: Data curation, Writing - original draft, Writing - review & editing. **Michael Goodman:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Resources, Supervision. **Jessica A. Alvarez:** Writing - original draft, Writing - review & editing. **Vin Tangpricha:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Resources, Supervision.

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