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ORIGINAL RESEARCH

Impact of Gender-Affirming Hormonal Therapy on Cardiovascular Risk Factors in Transgender Health

An Updated Meta-Analysis

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ABSTRACT

BACKGROUND Gender-affirming hormone therapy (GAHT) is common among transgender individuals, but its impact on lipid profile and cardiovascular health is not well studied.

OBJECTIVES The authors performed a systematic review and meta-analysis of existing literature to assess the impact of GAHT on lipid profiles and metabolic cardiovascular risk factors in transgender individuals.

METHODS Online databases including MEDLINE/PubMed, Embase, and Cochrane Central registry were searched to find studies on lipid profile changes in women who are transgender, also referred to as transfeminine (TF), and men who are transgender, also referred to as transmasculine (TM) before and after GAHT. Baseline comorbidities were analyzed using descriptive statistics, and R-statistical software was used to analyze the mean difference in lipid profile change between the two cohorts (pre- and post-GAHT therapy) including transgender patients.

RESULTS Overall, 1,241 TM and 992 TF patients were included from 12 observational studies and 12 randomized controlled trials. The mean age among TM and TF was 28 years and 30 years, respectively. The mean follow-up duration (including pre- and post-GAHT therapy) was 28 months in TM patients and 39 months in TF patients. When compared to baseline measures, TM patients had a significant increase in low-density lipoprotein, triglyceride levels, and total cholesterol while high-density lipoprotein levels decreased. In TF patients, there was a significant increase in triglyceride levels.

CONCLUSIONS GAHT affects lipid profiles in transgender patients; however, additional studies are needed to determine how these changes impact clinical outcomes. (JACC Adv. 2024;3:101265) Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CVD = cardiovascular disease

DBP = diastolic blood pressure

GAHT = gender-affirming hormone therapy

HDL = high-density lipoprotein

IM = intramuscular

LDL = low-density lipoprotein

ROB = Risk of Bias

SBP = systolic blood pressure

SMD = standard mean difference

SQ = subcutaneous

TC = total cholesterol

TF = transfeminine

TG = triglyceride

TM = transmasculine

VTE = venous thromboembolism

Transgender is a broad term encompassing individuals whose gender identity differs from the one assigned to them at birth.[1] Transgender individuals often go through gender-affirming hormone therapy (GAHT) or surgeries to achieve their desired sex appearance. Transgender men, also referred to as transmasculine (TM) use testosterone to obtain masculine features, while transgender women, also referred to as transfeminine (TF) utilize estrogen and antiandrogen hormones like spironolactone for feminization.[2]

The use and effects of GAHT have significantly been studied in premenopausal and postmenopausal women and males with hypogonadism. Supplementing androgen to hypogonadal males has been suggested to increase body muscle mass with positive effects on lipid and glycemic profiles or negative outcomes as reported by the World Health Organization controlled trial on the use of combined contraceptive pills that increase the risk of the cardiovascular and thrombotic incident.[3-5] However, there are limited data regarding long-term clinical safety and outcome of hormonal therapy in transgender individuals.

Several studies on GAHT in healthy individuals suggest that estrogen and testosterone may elevate the risk of metabolic syndrome by inducing insulin resistance, dyslipidemia, and increased abdominal fat deposition, which leads to an increased risk of cardiovascular diseases (CVDs).[6-8] However, conflicting conclusions arise from other studies indicating the short-term safety of GAHT for transgender individuals.[9] The long-term cardiovascular safety of GAHT remains uncertain, primarily due to the current evidence relying heavily on expert opinion and retrospective case series, utilizing varied GAHT regimens, including older protocols, and occasionally lacking guidelines-based proactive risk management.

Therefore, we conducted a systematic review and meta-analysis of currently available literature to evaluate the influence of GAHT on the lipid profile and metabolic CVD risk factors that can impact cardiovascular outcomes in transgender individuals.

METHODS

This systematic review was conducted by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The study eligibility criteria included populations that are either: 1) TF or TM individuals; 2) transgender individuals on GAHT; 3) age >12 years; 4) baseline reporting on metabolic and lipid profiles; and 5) outcomes reporting on changes in metabolic and lipid profiles before and after GAHT use. The exclusion criteria were age <12 years, no reporting of lipid profile or desired outcome, and patient pool not including TF or TM individuals.

A literature search was conducted on Medline/PubMed, Embase, and Cochrane for trials or observational studies with the abovementioned inclusion criteria using a systematic search strategy by PRISMA from inception until January 2023. Search terms employed using Boolean Operators "OR" and "AND" among and between 2 subsets of keywords as "Transgender persons," "transsexual persons" AND "sex hormones" OR "hyperlipidemias" OR "metabolome."

STUDY SELECTION. All available clinical trials or observational studies were evaluated. Two authors (S.R. and M.H.) independently reviewed the search results for studies that met the eligibility criteria. Any uncertainty regarding study selection was resolved with consensus with a third author (Y.S.).

In the first phase, titles and abstracts were screened and studies fulfilling the inclusion were selected for the second phase. In the second phase, we went through the full texts of the selected studies and further narrowed down our selection based on whether the studies reported items for data extraction.

PRIMARY AND SECONDARY OUTCOMES. The primary outcome of the study was the lipid profile of the TF and TM patients including triglyceride (TG) levels, total cholesterol (TC) levels, low-density lipoprotein

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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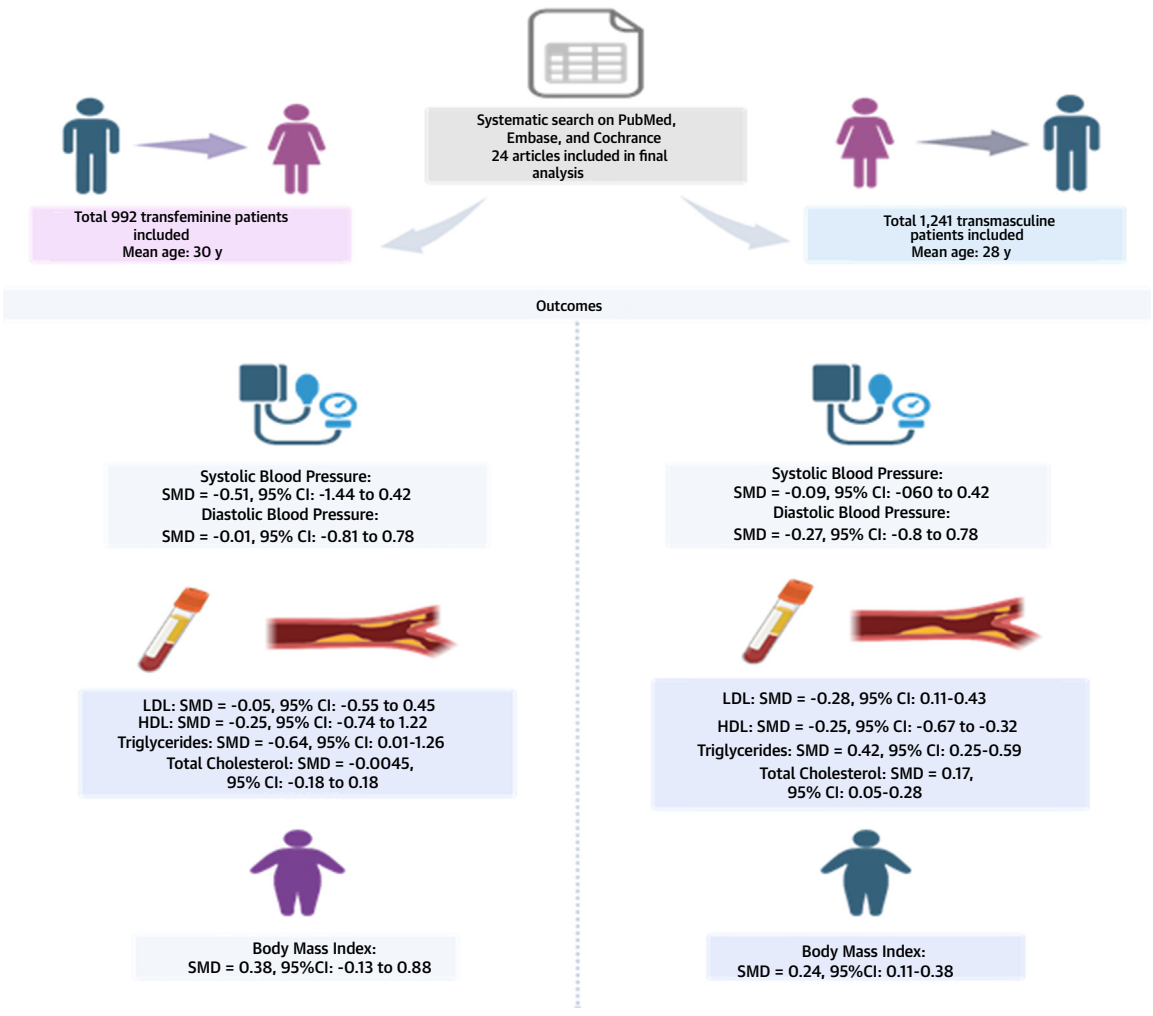
CENTRAL ILLUSTRATION **Impact of Gender-Affirming Hormonal Therapy on Cardiovascular Risk Factors in Transgender Health: An Updated Meta-Analysis**



Rahman SU, et al. JACC Adv. 2024;3(10):101265.

The outcomes of lipid profile comparison of pre- and post-GAHT use among transmasculine (TM) and transfeminine (TF) populations. Abbreviations as in Figure 2.

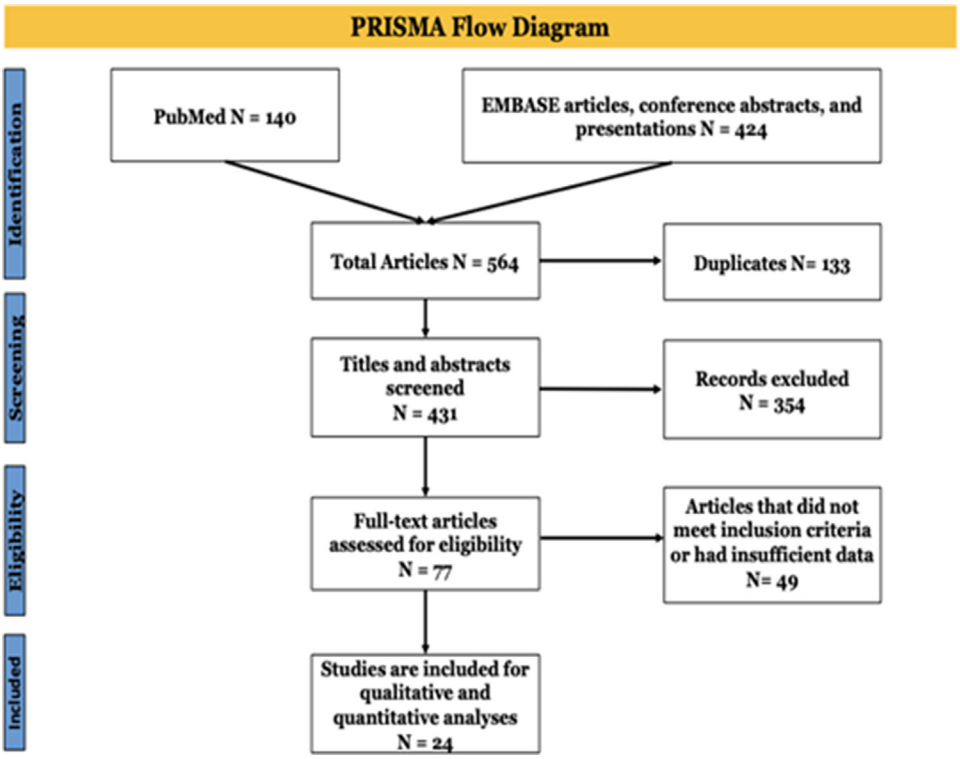
(LDL), and high-density lipoprotein (HDL). Secondary outcomes included other factors that could have impacted CV outcomes including body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP).

COMPARISON OF OUTCOMES. We compared the change in the variables mentioned above from their baseline levels before the initiation of GAHT to their levels after the application of GAHT.

DATA COLLECTION AND STATISTICAL ANALYSIS. Statistical analysis was performed using the CRAN-R software. Data from each study included after the secondary screening were extracted in a Microsoft Excel sheet. Data elements collected were the number of TF and TM individuals, androgen or estrogen use, and mean age. Other characteristics collected were TG, TC levels, LDL, HDL, BMI, SBP, and DBP before and after GAHT.

A *meta-cont* module was used along with the inverse variance random effects model to calculate the pooled standard mean difference (SMD) with a probability value of $P < 0.05$ considered to be statistically significant. The "test for overall effect" was reported

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow of the Search Strategy for Systematic Review and Meta-Analysis



as a z-value corroborating the 95% CI's inference. Higgins I-squared (I^2) was determined as a measure of statistical heterogeneity where values of ≤50% corresponded to low to moderate heterogeneity while values ≥75% indicated high heterogeneity.[10] For heterogeneity of more than 50%, we conducted a leave-one-out analysis to assess for studies contributing the most to heterogeneity using the meta-inf module in CRAN-R software. We also conducted a subgroup analysis based on follow-up duration. Four subgroups were identified: 1) up to 1 year; 2) 1 to 3 years; 3) 3 to 5 years; and 4) 5 to 10 years. The publication bias was depicted graphically and numerically as a forest plot and Begg's test.[11] The quality assessment of the included articles was performed using the Cochrane Risk of Bias (ROB) and Newcastle Ottawa Scale.[12-14]

RESULTS

Our search identified 564 articles and following the removal of duplicates (n = 89), 475 records were screened in the first phase. Among them, 431 articles were removed. In the second phase, after removing duplicates and irrelevant studies, a total of 44 articles were selected for a full-length analysis. Of these, 24 studies were included in the final analysis which reported on our desired outcome. A total of 1241 TM and 992 TF individuals were included in our review (**Central Illustration**, **Figure 1**, Supplemental S1).

We included all GAHT therapies used for gender affirmation that were administered in various formulations such as oral, intramuscular (IM) injections, subcutaneous (SQ) injections, and gel. The GAHT utilized included combination of 17-β-estradiol and cyproterone acetate (oral), ethinyl estradiol (oral), goserelin acetate (SQ), and estradiol valerate (oral) for TF; and testosterone undecanoate (IM), lynestrenol (oral), testosterone cypionate (IM), testosterone enanthate (IM), testoviron depot (IM), anastrozole (oral), and testosterone gel for TM.

The mean follow-up duration for which studies were conducted (including pre- and post-GAHT therapy) was 27.69 months in TM patients and 39.23 months in TF patients. The mean SBP was 120.40 ± 11.31 mm Hg in TM patients and 119.60 ± 14.90 mm Hg in TF patients. The mean diastolic pressure was 73.96 ± 9.07 mm Hg in TM

TABLE 1 Baseline Demographics, Treatment Regimens, and Follow-Up Duration of Individual Transmasculine (TM) Studies Included

Patient #	First Author, Year	Follow-Up Duration (months)[a]	Number of FTM Transgender Individuals	GAHT Regimen Used (Formulation)	Mean Age (y)
1	Abdala et al, 2018[15]	12	30	Testosterone undecanoate (IM) or enanthate (IM)	27 ± 8
2	Asscheman et al, 1994[16]	6	10	Testosterone undecanoate (IM)	30 ± 5.76
3	Auer et al, 2016[17]	12	20	Testosterone undecanoate (IM)	–
4	Bunck et al, 2006[18]	3	30	Anastrozole (oral)	37.1 ± 7
5	Chandra et al, 2010[19]	12	12	Testosterone, crypionate (IM)/enanthate (IM)	29 ± 9
6	Cocchetti et al, 2021[20]	24	165	Testosterone undecanoate (IM), enanthate (IM), and transdermal gel	26.78 ± 7.48
7	Deutsch et al, 2015[21]	6	31	Testosterone cypionate (IM)	27 ± 6.9
8	Elbers et al, 2003[22]	12	20	Testosterone esters (IM)	26 ± 6
9	Giltay et al, 2004[23]	4	81	Testosterone esters (IM)/Testosterone undecanoate (IM)	36.7
10	Jacobeit et al, 2007[24]	12	12	Testosterone undecanoate (IM)	33 ± 6
11	Jacobeit et al, 2009[25]	36	17	Testosterone undecanoate (IM)	34 ± 7
12	Klaver et al, 2020[26]	84	121	Mixed testosterone esters "Sustanon"; testosterone propionate, phenylpropionate, isocaproate, and decanoate (IM)	15.2 ± 2
13	Korpaisarn et al, 2021[27]	24	39	Testosterone enanthate (IM)	27.8 ± 6
14	Leemaqz et al, 2023[28]	57	196	Testosterone ethanate (IM)/cypionate (IM)	16.4 ± 7.2
15	Liu et al, 2021[29]	27	45	Testosterone cypionate (IM)	26 ± 1.1
16	Milionis et al, 2023[30]	18	33	Testosterone undecanoate (IM)	23.45 ± 5.9
17	Mueller et al, 2010[31]	24	45	Testosterone undecanoate (IM)	30.4 ± 9.1
18	Ott et al, 2011[32]	60	89	Testosterone undecanoate (IM)/lynestrenol (oral)	35.7 ± 11.4
19[b]	Pelusi et al, 2014[33]	12	15	Testoviron depot (IM)	30.9 ± 5.41
19[b]	Pelusi et al, 2014[33]	12	15	Testosterone gel	29.4 ± 5.05
19[b]	Pelusi et al, 2014[33]	12	15	Testosterone undecanoate (IM)	28.2 ± 4.69
20	Quiros et al, 2015[34]	48	97	Testosterone (IM and transdermal)	28.6 ± 8.6
21	Tangpricha et al, 2010[35]	12	12	Testosterone esters (IM), cypionate (IM), and enanthate (IM)	29 ± 9
22	Wierckx et al, 2012[36]	120	50	Testosterone esters (IM)	37 ± 8.2
23	Wierckx et al, 2014[37]	12	53	Testosterone undecanoate (IM)	24.5 ± 7.5

Values are mean ± SD unless otherwise indicated. [a]Duration refers to follow-up duration which is after initiation of GAHT. [b]Pelusi et al, 2014 is a single unique study that has included 3 different testosterone formulations (testosterone depot IM injections, testosterone gel, and testosterone undecanoate). All 3 were separately included to analyze individual effects of the treatment regimen.

BMI = body mass index; FTM = female to male; GAHT = gender-affirming hormone therapy; HDL = high-density lipoprotein; IM = intramuscular; LDL = low-density lipoprotein; TC = total cholesterol; TG = triglyceride.

Continued on the next page

patients and 71.73 ± 10.40 mm Hg in TF patients. The mean age of the TM and TF cohorts was 28 years and 30 years, respectively. Baseline characteristics for TF and TM individuals are shown in **Tables 1 and 2**, respectively.

TM INDIVIDUALS' PRIMARY AND SECONDARY OUTCOMES. TM individuals showed a statistically significant elevation in the primary outcomes when compared to the baseline, including LDL (SMD: 0.28 mg/dl [95% CI: 0.11-0.44] $P = <0.01$, $I^2 = 61.1\%$), TG levels (SMD: 0.42 mg/dL [95% CI: 0.25-0.59] $P = <0.01$, $I^2 = 62.8\%$), TC (SMD: 0.17 mg/dL [95% CI: 0.05-0.29] $P = <0.01$, $I^2 = 30.5\%$) while HDL levels were significantly decreased from baseline (SMD: −0.50 mg/dl [95% CI: −0.67 to −0.32] $P = <0.01$, $I^2 = 65.0\%$) (**Figure 2**, **Table 3**).

Regarding secondary outcomes, BMI was significantly elevated when compared to the baseline (SMD: 0.24 kg/m^2 [95% CI: 0.11-0.38] $P = <0.01$, $I^2 = 0.0\%$). However, no significant relationship between SBP (SMD: −0.09 mm Hg [95% CI: −0.61 to 0.42] $P = 0.72$, $I^2 = 89.4\%$) and DBP (SMD: −0.27 mm Hg [95% CI: −0.76 to 0.21] $P = 0.27$, $I^2 = 88.9\%$) was studied (Supplemental S2, **Table 3**).

SUBGROUP ANALYSIS. We further performed subgroup analysis to account for follow-up duration as it varied in various studies. Based on subgroup analysis for TM individuals, HDL levels showed significant reduction at up to 1 year, 1 to 3 years, and 3 to 5 years follow-up. However, a nonsignificant reduction was found in 5 to 10 years follow-up. In the case of LDL, significant elevation was seen in up to 1 year and 3 to 5 years follow-up but nonsignificant elevation in 1 to 3 years and 5 to 10 years follow-up. In the case of TG, significant elevation was seen in up to 1 year, 1 to 3 years, and 5 to 10 years follow-up but nonsignificant

TABLE 1 Continued

Mean BMI (kg/m^2)	Mean Systolic Blood Pressure (mm Hg)	Mean Diastolic Blood Pressure (mm Hg)	Mean TG Levels (mg/dL)	Mean LDL Levels (mg/dL)	Mean TC Levels (mg/dL)	Mean HDL Levels (mg/dL)
25	–	–	88.3 ± 32.8	101.2 ± 25.1	175 ± 42.37	50.1 ± 10.9
–	–	–	93 ± 31	109.82 ± 28.23	184.45 ± 186	54.52 ± 10.44
23.49 ± 4.55	–	–	77.95 ± 41.49	106.52 ± 30.39	77.95 ± 41.49	53.1 ± 13.9
25.6 ± 2.9	–	–	149.73 ± 147.96	116.1 ± 48.37	186.76 ± 42.57	42.57 ± 12.77
27.5 ± 5.2	–	–	92 ± 72	113 ± 22	184 ± 26	52 ± 11
25.06 ± 5.73	116.05 ± 13.62	73.33 ± 10.25	59.16 ± 43.05	102.32 ± 27.42	171.73 ± 30.4	57.57 ± 14.29
29.2 ± 2.8	120 ± 5.75	72 ± 4	75 ± 14	93 ± 8.25	177 ± 9.5	58 ± 5.5
20.8 ± 2.6	126.9 ± 10.2	70.1 ± 8.5	77.5 ± 12.27	113.3 ± 34.03	170.15 ± 38.67	40.99 ± 8.507
22.8 ± 4.53	126.62 ± 13.14	79.80 ± 8.00	61.95 ± 9.56	105.2 ± 33.3	176.72 ± 33.64	54.5 ± 16.6
–	–	–	–	140.5 ± 47	215.8 ± 58.5	51.7 ± 10.8
28.3 ± 2.8	–	–	88 ± 14	139 ± 48	218 ± 47	50 ± 11
21.6	120	67	70.87	81.2	150.81	58
23.6 ± 4.5	–	–	86.4 ± 44.4	131.7 ± 36.8	207.4 ± 40.8	57.2 ± 13.1
–	–	–	85.7 ± 49.1	95.2 ± 27.4	170.8 ± 32.4	58.7 ± 14.2
20.6 ± 0.4	122.5 ± 2.7	74.1 ± 1.7	85.4 ± 7.7	104.2 ± 3.2	165.1 ± 4.8	63.9 ± 2.6
24.47 ± 4.19	–	–	64.93 ± 21.4	88.67 ± 25.69	156.69 ± 23.55	55.5 ± 11.05
24.1 ± 4.5	129.3	81	120.5 ± 64	131.2 ± 32.4	185.8 ± 33.4	61.8 ± 16.3
22.6 ± 4.4	–	–	108.6 ± 69.8	111.7 ± 34.2	187.9 ± 45.6	53.2 ± 14.4
22.3 ± 4.33	–	–	57.4 ± 34.85	92.6 ± 27.44	174.4 ± 28.35	70.2 ± 13.72
23.9 ± 4.87	–	–	60.8 ± 36.81	82 ± 27.44	161.3 ± 28.35	67.8 ± 13.72
22.1 ± 4.69	–	–	72.5 ± 33.4	83.3 ± 28.89	161.5 ± 28.35	62.9 ± 18.05
25 ± 4.7	118.2 ± 9.1	75.2 ± 8.9	70.6 ± 30.7	103.8 ± 38.7	166 ± 35.1	52.2 ± 12.2
27.5 ± 5.2	–	–	92 ± 72	113 ± 22	184 ± 26	52 ± 11
24.8 ± 3.8	124.7 ± 14.4	81.3 ± 10.7	124.1 ± 27.8	–	200.8 ± 10.1	–
–	111.5 ± 12.6	70.2 ± 10.5	69.8 ± 10	98.4 ± 26.3	171.9 ± 28.1	56.3 ± 12.7

elevation in 3 to 5 years follow-up. Regarding TC, significant elevation was seen in up to 1 year follow-up but nonsignificant elevation was observed in 1 to 3 years, 3 to 5 years, and 5 to 10 years follow-up. For BMI, up to 1-year follow-up showed significant elevation, however, 1 to 3 years and 3 to 5 years follow-up durations showed nonsignificant elevation. Regarding SBP and DBP, none of the subgroups showed any significant changes. These results are shown in Supplemental S4A.

TF INDIVIDUALS' PRIMARY AND SECONDARY OUTCOMES. TF individuals showed a statistically significant increase in TG levels only when compared to the baseline levels (SMD: 0.64 mg/dL [95% CI: 0.01-1.26] $P = 0.05$, $I^2 = 91.6\%$). There was no statistically significant change in the rest of the primary outcomes including LDL (SMD: −0.05 mg/dL [95% CI: −0.56 to 0.46] $P = 0.85$, $I^2 = 91.6\%$), HDL (SMD: 0.25 mg/dL [95% CI: −0.74 to 1.23] $P = 0.62$, $I^2 = 97.6\%$), and TC (SMD: 0.005 mg/dL [95% CI: −0.18 to 0.18] $P = 0.96$, $I^2 = 67.2\%$) (**Figure 3**, **Table 4**).

Regarding secondary outcomes, there was no statistically significant change observed in SBP when compared to the baseline (SMD: −0.51 mm Hg [95% CI: −1.44 to 0.43] $P = 0.29$, $I^2 = 96.6\%$), DBP (SMD: −0.01 mm Hg [95% CI: −0.81 to 0.78] $P = 0.97$, $I^2 = 88.1\%$), and BMI (SMD: 0.38 kg/m^2 [95% CI: −0.13 to 0.88] $P = 0.14$, $I^2 = 91.9\%$) (Supplemental S3, **Table 4**).

SUBGROUP ANALYSIS. For TF individuals, the impact of follow-up duration on HDL levels did not show any significant change. LDL showed no significant changes in up to 1 year, 1 to 3 years, and 3 to 5 years follow-up, and only showed mild statistically significant reduction in 5 to 10 years follow-up. For TG, similarly up to 1 year, 1 to 3 years, and 3 to 5 years follow-up did not show any significant change, and only mild significant change was observed in 5 to 10 years follow-up. Regarding SBP, no subgroup showed any significant results. For DBP, only 1 to 3 years follow-up showed mild significant elevation. Up to 1 year follow-up showed nonsignificant elevation but 3 to 5 years and 5 to 10 year follow-up subgroups showed nonsignificant reduction. Thus, overall, the result is nonsignificant. Regarding BMI, all the subgroups showed nonsignificant elevation. The results of the subgroup analysis are shown in Supplemental S4B.

TABLE 2 Baseline Demographics, Treatment Regimens, and Follow-Up of Individual Transfeminine (TF) Studies Included

Patient #	First Author, Year	Follow-Up Duration (months)[a]	Number of MTF Transgender Individuals	GAHT Regimen Used (Formulation)	Mean Age (y)	Mean BMI (kg/m^2)
1	Auer et al, 2016[17]	12	20	Estradiol valerate (oral), cyproterone acetate (oral)	–	23.9 ± 4.34
2	Cocchetti et al, 2021[20]	24	144	Estradiol valerate (oral)	31.84 ± 11.46	23.46 ± 4.48
3	Deutsch et al, 2015[21]	6	16	17-beta estradiol (oral)/estradiol valerate (oral)/spironolactone (oral)	29 ± 9.4	14.55 ± 1.075
4	Dittrich et al, 2005[38]	24	60	Ethinyl estradiol (oral)/17-β-estradiol (oral)	38.37 ± 11.36	24.19 ± 4.34
5	Elbers et al, 2003[22]	12	17	Ethinyl estradiol (oral)	23 ± 5	21.7 ± 3.5
6	Klaver et al, 2020[26]	84	71	17-β estradiol (oral)	14.6 ± 1.8	20.2
7	Leemaqz et al, 2023[28]	57	170	Estrogen plus spironolactone (oral)	29.9 ± 9.5	–
8	Liu et al, 2021[29]	27	65	Conjugated estrogen and cyproterone acetate (oral)	27.9 ± 0.7	22.6 ± 0.3
9	Mueller et al, 2010[31]	24	84	Goserelin acetate (SQ)	36.3 ± 11.3	22.3 ± 0.42
10	Ott et al, 2011[32]	60	80	17-β-estradiol/cyproterone acetate (oral)	26 ± 6.3	23.7 ± 6
11	Quiros et al, 2015[34]	48	150	Estrogen therapy with antiandrogen activity (oral)	32.4 ± 10.1	24.2 ± 4.3
12	Wierckx et al, 2012[36]	120	50	Cyproterone acetate, exogenous estrogen (oral)	43 ± 10.4	25.3 ± 5.4
13	Wierckx et al, 2014[37]	12	53	Cyproterone acetate, estradiol valerate (oral)	30.3 ± 14.4	–

Values are mean ± SD unless otherwise indicated. [a]Duration refers to follow-up duration after initiation of GAHT.
MTF = male to female; SQ = subcutaneous; other abbreviations as in Table 1.

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PUBLICATION BIAS. To ascertain the bias, we plotted funnel plots and then used Begg's test to assess for funnel plot asymmetry.[11] The plot's vertical axis uses standard error to estimate the sample size of the study, thereby, plotting larger studies at the top and smaller studies at the bottom. The horizontal spread depicts the power and effect sizes of the included studies. We did a numerical assessment of the funnel plot scatter using Begg's test that did not show any publication bias or small study effects (Supplemental S5).

QUALITY ASSESSMENT. Bias assessment of randomized controlled trials was done using the Cochrane ROB tool.[12] In all of the intervention studies, there was no blinding because of the interventional nature of GAHT and parallel single-arm designs with no intergroup comparison. This raises a concern for selection bias. In most of the studies, data regarding matching are also not available. There is minimal risk of detection bias as all the outcomes were laboratory measures and robust data regarding laboratory methods are available. The risk of reporting bias was minimal due to adequate reporting of outcomes. The overall risk of bias was high. The detailed ROB tool assessment of the intervention studies is given in Supplemental S6.

Quality assessment of non-randomized studies was assessed by the Newcastle-Ottawa Scale.[14] In all non-interventional studies, the quality of study population selection, comparability of the selected sample with the general population, and methods of measuring the outcome were assessed as depicted in Supplemental S7. The overall risk of bias for the observational studies included in the study was low.

HETEROGENEITY. In general, the high heterogeneity observed in the outcomes studied in our analysis is likely due to several factors. Firstly, it encompasses studies utilizing diverse GAHT approaches. Secondly, most of the studies in our analysis exhibited notable selection bias, both in non-randomized observational studies and even in randomized controlled trials, contributing to a high risk of overall bias. Thirdly, such pronounced heterogeneity may be explained by sampling bias.

To further assess heterogeneity, we conducted a leave-one-out analysis. In TM individuals, the outcomes with >50% heterogeneity were HDL, LDL, TG, SBP, and DBP. For HDL, almost all studies contributed equally to heterogeneity except Liu et al.[29] Omitting this study resulted in an overall pooled HDL of −0.55 mg/dL (95% CI: −0.7 to −0.40; $P < 0.01$) compared to the baseline and a decrease in I^2 value to 50%. For LDL, the study contributing the most to heterogeneity was again Liu et al.[29] Omitting this study led to a pooled LDL increase of 0.35 mg/dL (95% CI: 0.24 to 0.49; $P < 0.01$) from baseline and a resultant heterogeneity of 31%. The rest of the studies contributed equally to heterogeneity. For TG, all the studies contributed to heterogeneity except Wierckx et al.[37] Omitting this study led to a total heterogeneity of 51% and a pooled increase in TG from a baseline of 0.389 mg/dL (95% CI: 0.24-0.53; $P < 0.01$). Regarding SBP, the study contributing to heterogeneity was again Liu et al[29] while all other studies contributed

TABLE 2 Continued

Mean Systolic Blood Pressure (mm Hg)	Mean Diastolic Blood Pressure (mm Hg)	Mean TG Levels (mg/dL)	Mean LDL Levels (mg/dL)	Mean TC Levels (mg/dL)	Mean HDL Levels (mg/dL)
–	–	92.32 ± 52.66	112.99 ± 34.16	92.32 ± 52.66	53.95 ± 11.66
124.92 ± 14.91	76.24 ± 11.06	97.11 ± 89.56	102.83 ± 31.7	176.75 ± 39.08	54.59 ± 13.58
71 ± 2.875	49.5 ± 5.25	54.24 ± 9.375	69.5 ± 10.5	110.5 ± 12.5	37.25 ± 4
–	–	110 ± 75.49	–	188 ± 45.81	–
121.4 ± 9.9	67.1 ± 7.5	61.56 ± 9.72	99.38 ± 33.64	162.4 ± 34.8	47.18 ± 12.374
120	65	70.8	73.47	143.07	54.13
–	–	111.8 ± 60.2	100.5 ± 33.8	173 ± 37	49.9 ± 13.1
119.9 ± 1.9	70.2 ± 1.1	76.7 ± 4.7	124.3 ± 3.7	183.4 ± 3.8	57.9 ± 2.1
–	–	112.9 ± 8.69	115.8 ± 5.96	185.32 ± 6.82	56.75 ± 4.58
–	–	85.5 ± 50.6	107.9 ± 30.1	176.7 ± 38.3	56.6 ± 12.4
115.5 ± 11.9	72.9 ± 10.1	90 ± 56.6	104.3 ± 23	164.3 ± 29.1	45.4 ± 12.7
124.8 ± 16.6	77.1 ± 10.1	89.5 ± 18.3	–	197.8 ± 17.1	–
125.1 ± 13.8	70.2 ± 10.5	80.4 ± 15.3	99.4 ± 29	171.5 ± 32.7	52.9 ± 13.5

equally to heterogeneity. Omitting Liu et al[29] decreased heterogeneity to 68% and a change in SBP of 0.12 mm Hg (95% CI: −0.15 to 0.37; $P = 0.38$) from baseline. Regarding DBP, all studies contributed equally to heterogeneity except Liu et al.[29] Omitting this study led to a decrease in heterogeneity to 50% and a final pooled change in DBP of −0.02 mm Hg (95% CI: −0.23 to 0.19; $P = 0.85$) from baseline. Supplemental S8A.

In TF individuals, regarding HDL, all studies contributed equally to heterogeneity. Regarding LDL, Liu et al[29] contributed most to heterogeneity. Omitting it led to a decrease in heterogeneity to 72% and a pooled LDL difference of −0.18 mg/dL (95% CI: −0.43 to 0.06; $P = 0.15$) from baseline. Regarding TC, Cocchetti et al[20] and Wierckx et al[37] contributed the most to heterogeneity. Removing Cocchetti et al decreased heterogeneity to 51% with pooled TC of 0.06 mg/dL (95% CI: -0.11 to 0.23; $P = 0.48$) as compared to baseline; while removing Wierckx et al decreased heterogeneity to 54% with pooled TC of 0.07 mg/dL (95% CI: -0.09 to 0.22; $P = 0.40$) from baseline. Regarding TG, all studies contributed almost equally to heterogeneity. Regarding SBP, Liu et al[29] contributed the most to heterogeneity. Its omission led to a decreased heterogeneity to 90% with a pooled SBP difference of −0.08 mm Hg (95% CI: -0.60 to 0.44; $P = 0.77$) compared to baseline. For DBP, Deutsch et al[21] contributed the most to heterogeneity. Its omission led to a decrease in I^2 levels to 68% and pooled DBP changed to about 0.33 mm Hg (95% CI: 0.08-0.05; $P = 0.01$). Here omission of the most heterogeneous study changed the results to a statistically significant increase in DBP as compared to baseline. Deutsch et al had a short follow-up duration, which likely skewed the overall effect and contributed to the normalization of DBP. Also, medication adherence was not consistently tracked among most patients, a limitation acknowledged within the study. Regarding BMI, Mueller et al[31] was the most heterogeneous study and its omission led to a decrease in I^2 value to 57% and pooled BMI differed by 0.20 kg/m^2 (95% CI: −0.04 to 0.43; $P = 0.10$) from baseline Supplemental S8B.

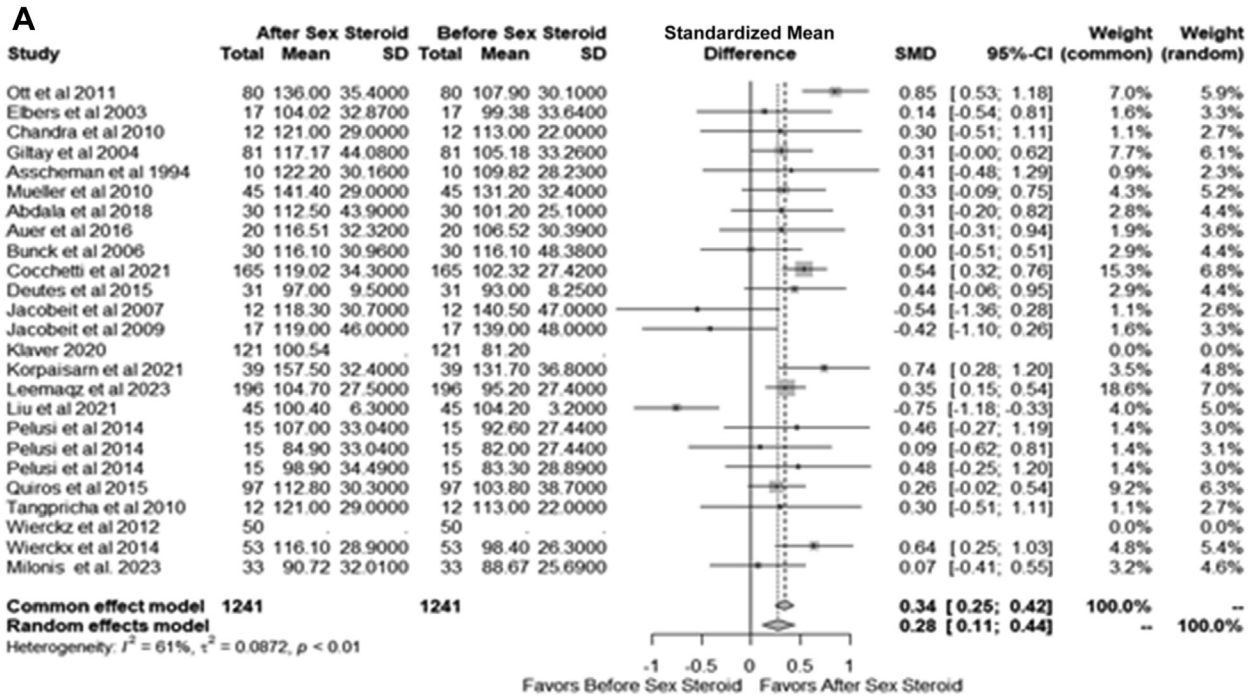
Compared to other studies, Liu et al[29] differed significantly in methodology, potentially contributing to high heterogeneity. While other studies included some patients with baseline dyslipidemia, Liu et al[29] opted to exclude individuals with dyslipidemia. Follow-up duration was variable in Liu et al[29] with some participants monitored at 3 months, others at 6 months, and some for even longer periods. Moreover, loss to follow-up was high as compared to the other studies, also contributing to high heterogeneity.

DISCUSSION

We performed a systematic review and meta-analysis to outline the effect of GAHT on lipid profile in transgender patients. Our results show a statistically significant increase in TG levels in transgender women with no significant changes in TC, LDL, HDL levels, or changes in SBP and DBP when compared to the baseline levels. On the other hand, transgender men had a statistically significant increase in TG, LDL, and TC levels and a decrease in HDL levels with no significant changes in SBP or DBP as compared to the baseline levels.

The primary class of estrogen (17-β estradiol) and ethinyl estradiol were the most commonly used regimens given to transgender women in our selected

FIGURE 2 Forest Plots for Primary Outcomes Comparing Lipid Profile Pre- and Post-GAHT Use Among Transmasculine (TM) Individuals

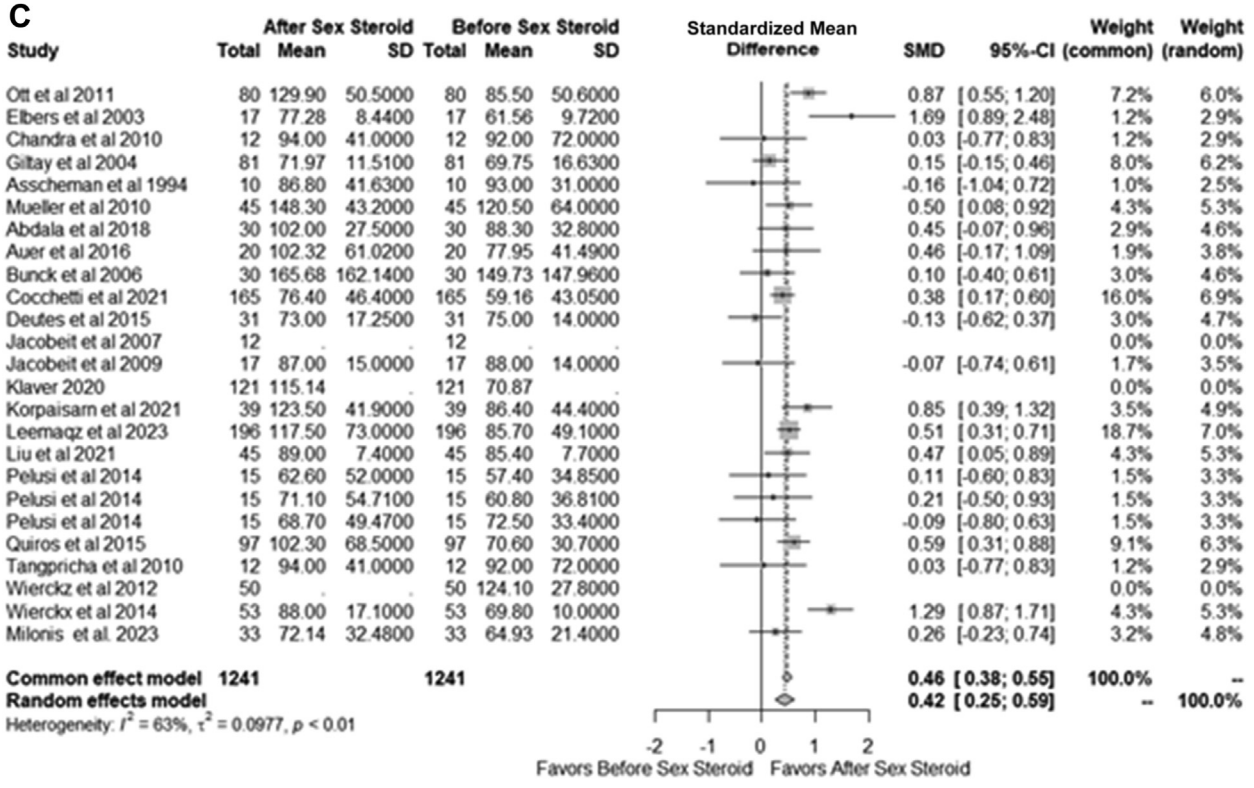


(A) Change in LDL levels pre-GAHT (baseline) and post-GAHT use. (B) Change in HDL levels pre-GAHT (baseline) and post-GAHT use. (C) Change in TG levels pre-GAHT (baseline) and post-GAHT use. (D) Change in TC levels pre-GAHT (baseline) and post-GAHT use. GAHT = gender-affirming hormone therapy; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SMD = standard mean difference; TC = total cholesterol; TG = triglyceride.

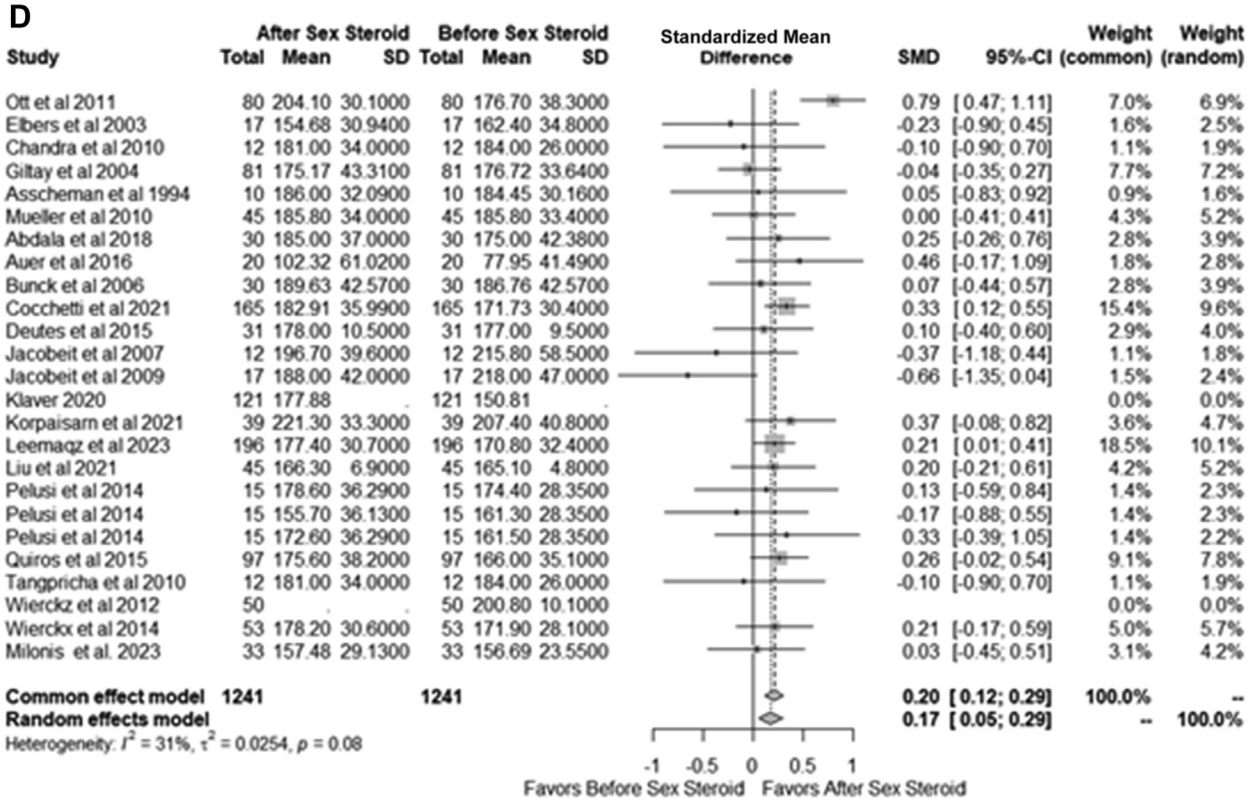
Continued on the next page

FIGURE 2 Continued

C



D



studies. The amount of estrogen used in transgender individuals is much higher than in women on hormone replacement therapy or oral contraceptive pills (5 mg estradiol/24 h compared to 100 μg estradiol/24 h) which could explain the variability of the results on lipid profiles.[39] For instance, in a study by Walsh et al postmenopausal women on low-dose estrogen (1.25 mg/day) have favorable outcomes in lipid profile as there was a 19% increase in HDL and an 18% reduction in LDL level, which could protect women against atherosclerosis.[40] In addition to that, the mode of delivery may be another contributing factor, as transdermal 17-estradiol is the safest method of administration in terms of thromboembolic events, which might have mitigated effects on lipid profiles in comparison to the oral form.[7,41] On the other hand, studies by New et al[42] found an increased level of HDL and TC and lower LDL in transgender women compared to men who are not on treatment which correlates with our study findings.

Testosterone therapy in eugonadal cisgender men might increase TG levels and reduce TC, LDL, and HDL levels in cisgender eugonadal men. On the other hand, androgen deficiency is linked with an increase in TG, TC, LDL, and HDL levels.[43,44] However, the effect of testosterone on lipid profile in transgender men in our meta-analysis shows a significant increase in TG, LDL, and TC levels and a decrease in HDL levels. Our results correlate with a large retrospective study performed on 89 transgender men individuals who had GAHT and reported that TGs, TC, and LDL levels were increased, while HDL was decreased.[45]

GAHT can adversely affect lipid profiles, potentially increasing the risk of myocardial infarction and ischemic stroke. This risk is attributed to alterations in cholesterol levels resulting from hormone therapy. Moreover, GAHT has been associated with an increased risk of venous thromboembolism (VTE).[46-48] The use of oral ethinyl estradiol in transgender women carries a significant 20-fold increased risk of spontaneous VTE.[49] Notably, all VTE cases occurred in patients using oral ethinyl estradiol, except for a single case using transdermal 17-β-estradiol in the latter study.[45] Estradiol valerate is a novel estrogen with fewer side effects than ethinyl estradiol and is now the most commonly prescribed form of estrogen in transgender women.[50]

Numerous studies have explored the metabolic impacts of GAHT in transgender individuals, but findings are frequently conflicting and inconclusive. This is largely due to the observational and retrospective nature of the studies, which involve populations with varied hormone regimens, often without medical supervision.[51-54] While our analysis suggests an association of GAHT with dyslipidemia, which could potentially indicate a higher cardiovascular mortality risk, it remains uncertain whether transgender individuals have a higher cardiovascular mortality rate compared to the general population.[55]

TABLE 3 Pooled Outcomes of CV Risk Factors After GAHT Initiation in Transmasculine Individuals

	Standard Mean Difference (SMD)	95% CI	*P* Value	I^2
LDL (mg/dL)	0.28	0.11-0.43	<0.01	61.1%
HDL (mg/dL)	−0.50	−0.67 to −0.32	<0.01	65.0%
TG (mg/dL)	0.42	0.25-0.60	<0.01	62.8%
TC (mg/dL)	0.17	0.05-0.29	<0.01	30.5%
SBP (mm Hg)	−0.09	−0.61 to 0.42	0.72	89.4%
DBP (mm Hg)	−0.27	−0.76 to −0.21	0.27	88.9%
BMI (kg/m^2)	0.24	0.11-0.38	<0.01	0.0%

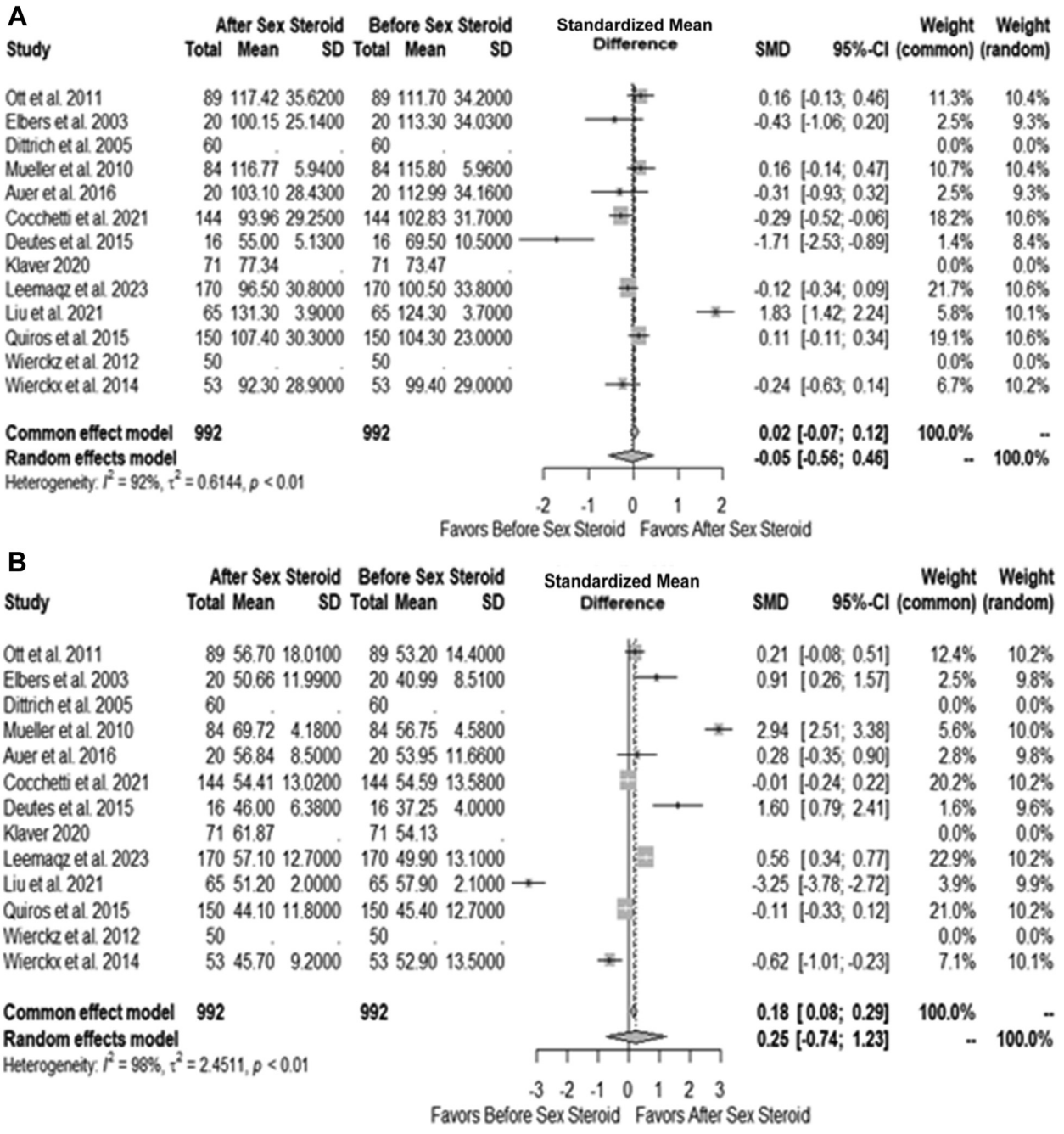
CV = cardiovascular; DBP = diastolic blood pressure; SBP = systolic blood pressure; other abbreviations as in Table 1.

A previous meta-analysis conducted by Elamin et al in 2010 concluded that current level of evidence is of low quality, characterized by significant imprecision and heterogeneity.[56] Similarly, previous systematic reviews suggest that the current data on GAHT in transgender patients are limited and of low quality.[22,52,57,58]

In summary, our meta-analysis reveals statistically significant changes in lipid profiles among transgender individuals undergoing GAHT. However, the clinical implications of GAHT on lipid profiles remain unclear. Current evidence is insufficient to draw definitive conclusions about its impact. Additional research is essential to determine if these changes affect cardiovascular morbidity and mortality. Long-term studies with extended follow-up are crucial to gain a comprehensive understanding of these potential impacts.

STUDY LIMITATIONS. We did not have a long-term follow-up of data and CVD data available including myocardial infarction and major adverse cardiovascular events due to dyslipidemia in the transgender population. Individual genetic, dietary, and lifestyle factors can act as confounders and effect modifiers that can alter the results. The study includes data sets from older studies that used ethinyl estradiol as part of GAHT. Ethinyl estradiol is known to be pro-thrombotic, which is why it is no longer used in GAHT. Limited evidence from small studies with

FIGURE 3 Forest Plots for Primary Outcomes Comparing Lipid Profile Pre- and Post-GAHT Use Among Transfeminine (TF) Individuals



(A) Change in LDL levels pre-GAHT (baseline) and post-GAHT use. (B) Change in HDL levels pre-GAHT (baseline) and post-GAHT use. (C) Change in TG levels pre-GAHT (baseline) and post-GAHT use. (D) Change in TC levels pre-GAHT (baseline) and post-GAHT use. Abbreviations as in Figure 2.

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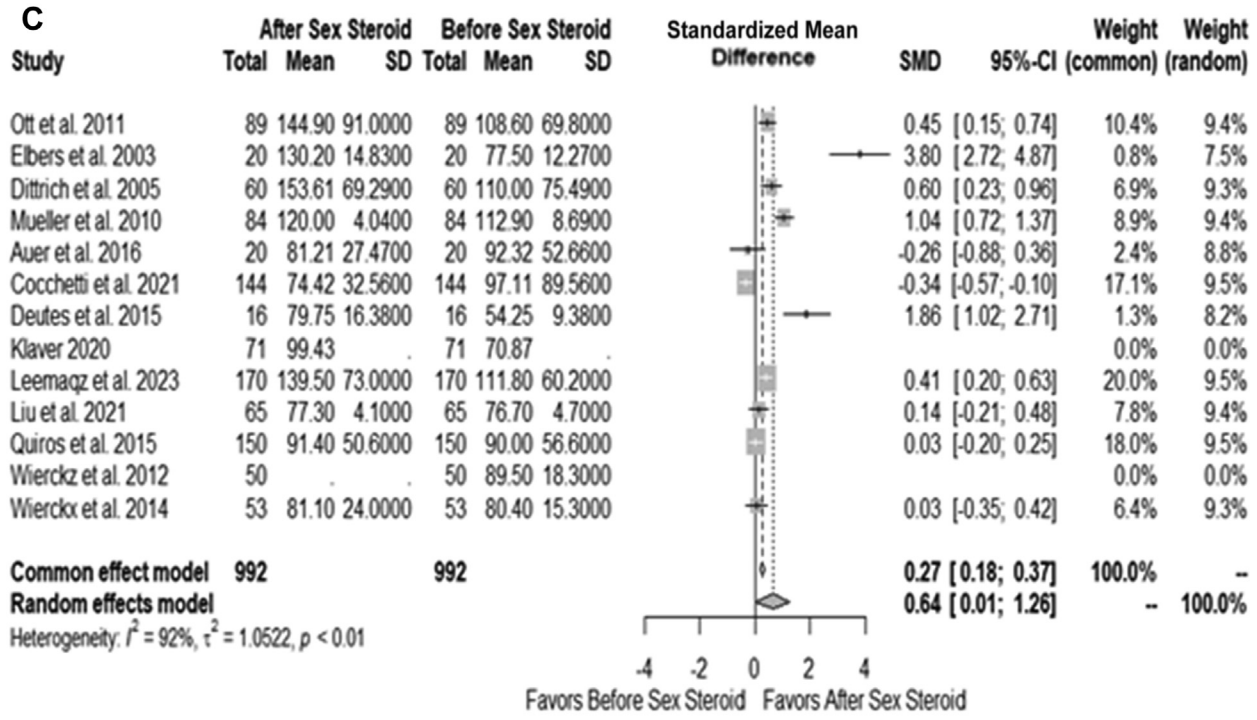
FIGURE 3 Continued



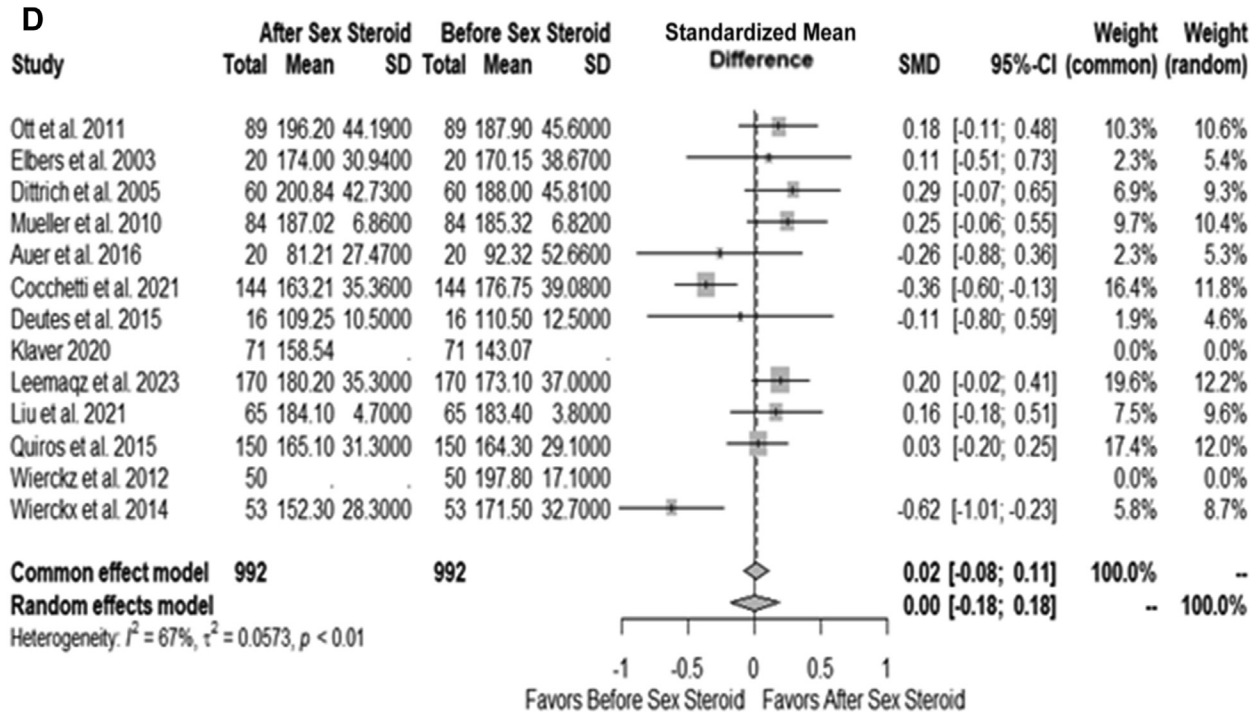


TABLE 4 Pooled Outcomes of CV Risk Factors After GAHT Initiation in Transfeminine Individuals

	Standard Mean Difference (SMD)	95% CI	*P* Value	I^2
LDL (mg/dL)	−0.05	−0.56 to 0.46	0.85	91.6%
HDL (mg/dL)	0.25	−0.74 to 1.23	0.62	97.6%
TG (mg/dL)	0.64	0.01-1.27	0.05	91.6%
TC (mg/dL)	0.004	−0.18 to 0.18	0.96	67.2%
SBP (mm Hg)	−0.51	−1.44 to 0.43	0.29	96.6%
DBP (mm Hg)	−0.01	−0.81 to 0.79	0.97	88.1%
BMI (kg/m^2)	0.38	−0.13 to 0.88	0.14	91.9%

Abbreviations as in Tables 1 and 3.

diverse hormone treatments and follow-up durations makes drawing definitive conclusions challenging.

Because of high heterogeneity, even statistically significant results do not translate into clinical significance. A similar observation was made by a meta-analysis done 14 years ago.[56] The available evidence regarding the effects of GAHT in TM and TF individuals remains low in quality with a lot of imprecisions precluding its clinical use.

CONCLUSIONS

Our meta-analysis found that the initiative of GAHT in TM individuals was associated with increases in LDL, TGs, TC, and a decrease in HDL levels. In TF individuals, GAHT was associated with an increase in TG levels only. There was no impact on blood pressure or BMI. Whether these changes in lipids after GAHT translate into unfavorable clinical outcomes is yet to be determined.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Our analysis encompassed data from a substantial cohort of TM and TF patients, revealing notable alterations in lipid levels following GAHT.

COMPETENCY IN PATIENT CARE: It is critical to stratify cardiovascular risk based on alterations in lipid profiles and BMI, and devising appropriate management strategies tailored to individual patient needs, to optimize cardiovascular health outcomes in transgender patients undergoing GAHT.

TRANSLATIONAL OUTLOOK: Health care providers should consider comprehensive lipid profile assessments and cardiovascular risk stratification in the management of transgender patients. Additionally, further research endeavors are imperative to elucidate the long-term clinical implications of these lipid profile changes and optimize therapeutic strategies to mitigate cardiovascular risk in this population.

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KEY WORDS dyslipidemia, hyperlipidemia, gender-affirming hormonal therapy GAHT, lipid profile, trans feminine TF, trans masculine TM

APPENDIX For the research question, PICO, and search strategy as well as supplemental tables and figures, please see the online version of this paper.