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Apolipoprotein Changes Following Gender-Affirming Hormone Therapy: A Prospective Cohort Study

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ABSTRACT

Purpose: Increased cardiovascular disease (CVD) risk in transgender individuals may be associated with gender-affirming hormone therapy (GAHT). Apolipoproteins are sensitive markers of lipid-related CVD risk and this study evaluated prospective changes in apolipoproteins following GAHT.

Methods: This study included 87 transgender individuals (transmasculine (TransM) *n*=59; transfeminine (TransF) *n*=28). Outcomes were analysed at baseline and following 1 year of GAHT in 55 individuals without prior GAHT use (GAHT-naïve, TransM *n*=34; TransF *n*=21) and cross-sectional data were analysed in 32 individuals already using GAHT at baseline (GAHT-ongoing, TransM *n*=25; TransF *n*=7). The primary outcome was 16 apolipoproteins measured by targeted proteomics. Standard lipids, body composition assessed by dual-energy X-ray absorptiometry, BMI, and waist-to-hip ratio were assessed.

Results: In TransM GAHT-naïve, mean (SD) age was 27 (±10) years and BMI was 26.0 (±4.2) kg/m^2. Masculinising GAHT was followed by decreased ApoA-I, ApoE, HDL, and Lp(a)KIV-2. In TransF GAHT-naïve, mean age at baseline was 27 (±7) years and mean BMI was 22.6 (±4.2) kg/m^2. Feminising GAHT was followed by increased ApoA-I, ApoJ, ApoL-I, and Lp(a) components, while ApoC-I decreased, and standard lipids were unchanged. In cross-sectional comparisons, TransF GAHT-ongoing (median GAHT duration 56 months) had higher ApoJ compared with TransF GAHT-naïve at 1 year, whereas apolipoproteins were comparable in TransM GAHT-ongoing vs. TransM GAHT-naïve at 1 year.

Conclusion: Apolipoproteins changed significantly following GAHT, and alterations in apolipoproteins were only partly reflected by standard lipid changes. Measurement of apolipoproteins could provide additional insight into CVD risk during GAHT and warrants further investigation.

Trial registration: ClinicalTrials.gov (Identifier: NCT04254354 (03/03/20), NCT05169762 (01/02/22))

INTRODUCTION

Transgender individuals experience incongruence between their sex assigned at birth and their gender identity [1, 2]. Transmasculine individuals (TransM) are assigned female at birth but identify as male, while transfeminine individuals (TransF) are assigned male at birth but identify as female. Gender-affirming hormone therapy (GAHT) is considered a central part of transgender care [1, 2]. GAHT aims to alleviate gender dysphoria by aligning secondary sex characteristics with gender identity [1, 2]. Masculinising GAHT consists of testosterone [1-3], while feminising GAHT consists of estradiol, often combined with an anti-androgen [1, 2]. GAHT is typically continued lifelong, highlighting the importance of understanding the potential long-term effects of GAHT on somatic health [2, 4].

Transgender individuals have a higher risk of cardiovascular disease (CVD) than cisgender individuals of the same birth sex, which may partly be ascribed to the use of GAHT [5]. A meta-analysis reported 40% higher risk of CVD, with increased risk of stroke and myocardial infarction in TransM compared to cisgender controls and increased risk of stroke and venous thromboembolism in TransF [6]. In a recent large cohort study, TransM on GAHT had a 4-fold higher risk of myocardial infarction and a 1.5-fold higher risk of stroke compared with cisgender women from the background population [7]. TransF on GAHT had a 1.8-fold increased risk of venous thromboembolism compared with cisgender men, whereas the risk of arterial cardiovascular events was not increased after adjustment for socioeconomic status [7].

Dyslipidemia is recognised as a prominent risk factor for CVD, and current treatment guidelines recommend routine lipid monitoring during GAHT [8, 9]. Masculinising GAHT is associated with an atherogenic lipid profile characterised by decreased high-density lipoprotein (HDL) and increased low-density lipoprotein (LDL), total cholesterol, and triglycerides [2, 3, 10], whereas feminising GAHT is associated with less consistent lipid changes [2, 10, 11]. Apolipoproteins reflect the balance of atherogenic and atheroprotective lipoproteins and provide information about lipid-related CVD risk beyond standard lipid measures [8, 12, 13]. Evidence on apolipoprotein changes following GAHT in transgender individuals is limited to one prospective study measuring ApoA-I and ApoB [3]. Masculinising GAHT was associated with higher ApoB and unchanged ApoA-I, while feminising GAHT was associated with unchanged ApoB and ApoA-I [3]. ApoB reflects the number of circulating atherogenic lipoprotein particles and outperforms standard lipids in predicting CVD risk in cisgender populations [8, 12, 14], and ApoA-I is the main structural protein of HDL, where higher ApoA-I levels reflect atheroprotective lipoprotein capacity, and lower CVD risk [8, 14].

Lipoprotein(a) (Lp(a)) is independently associated with ischaemic CVD in cisgender populations, even when

standard lipid levels are normal [15, 16]. In addition, a range of other apolipoproteins may be applied in CVD risk assessment (**Supplemental Table 1**). Prospective changes in a detailed apolipoprotein profile following GAHT remain to be investigated.

The aim of the present study was to evaluate changes in a panel of 16 apolipoproteins following 1 year of masculinising or feminising GAHT in transgender individuals.

MATERIALS AND METHODS

Study design and setting

This prospective, single-centre cohort study was conducted at the Centre of Gender Identity (CKI) at Odense University Hospital, Denmark. A detailed study protocol for the study cohort was previously published [17]. The study design was identical for individuals receiving masculinising and feminising GAHT. Study outcomes were assessed at baseline and 1 year. Two papers have been published in the study cohort regarding cardiac function [18] and muscle strength [19].

Participants and GAHT

From February 2020 to January 2025, 161 transgender individuals were assessed for eligibility after completing their baseline visit at the CKI. A total of 54 participants were lost to follow-up. An additional 20 participants were not included due to comorbidity or use of lipid-lowering medications. Apolipoprotein analyses were performed in participants who completed both baseline and 1-year follow-up visits. The present study included 87 participants (TransM *n*=59; TransF *n*=28), who were divided into two groups depending on GAHT use before enrolment (**Fig. 1**). GAHT was prescribed according to the national and international guidelines [9, 20].

GAHT-naïve participants were defined as individuals who had not received GAHT before baseline (TransM GAHT-naïve *n*=34; TransF GAHT-naïve *n*=21). In the GAHT-naïve group, masculinising GAHT consisted of transdermal testosterone gel (46-69 mg daily; *n*=14) or intramuscular testosterone undecanoate (1000 mg every 10-14 weeks; *n*=20). Feminising GAHT was estradiol tablets (2-6 mg daily; *n*=17), transdermal estradiol patches (100 μg/24 h, twice weekly; *n*=2) or transdermal estradiol spray (1.5-3 mg daily; *n*=2) and the anti-androgen cyproterone acetate (CPA) (*n*=21). In the TransF GAHT-naïve group, one participant initiated statin therapy within the follow-up period.

GAHT-ongoing participants were individuals who had initiated GAHT before enrolment. The GAHT-ongoing cohort was assessed at baseline for cross-sectional comparison (TransM GAHT-ongoing *n*=25; TransF GAHT-ongoing *n*=7). In the GAHT-ongoing group, masculinising GAHT consisted of transdermal testosterone gel (46-69 mg daily; *n*=2) or intramuscular testosterone undecanoate (1000 mg every 10-14 weeks; *n*=23). Feminising GAHT consisted of estradiol tablets (2-6 mg daily; *n*=4), transdermal estradiol patches (100 µg/24 h, twice weekly; *n*=1), transdermal estradiol spray (1.5-3 mg daily; *n*=1) or transdermal estradiol gel (1.5-3 mg daily; *n=1*) and CPA (*n*=7).

Study outcomes

Fasting blood samples were collected by a bio-analyst between 8:00 and 9:00 following an overnight fast.

Apolipoprotein profiling by targeted proteomics: Measurements were conducted using a multiple-reaction-monitoring mass spectrometry (MRM-MS) panel previously applied in the Odense Gestational Diabetes Mellitus Follow-Up Study (OGFUS) [21]. The predefined panel consisted of 16 apolipoproteins: Apo(a) [Lp(a)KIV-2, Lp(a)PeptidaseS1], A-I, A-II, A-IV, B-100, C-I, C-II, C-III, D, E, F, H, J, L-I, and M. Sample preparation for MRM-MS was conducted uniformly across groups according to Hallig et al. [21]. For each sample, 5 µL of tryptic serum digest was combined with 10 µL buffer A (0.1% formic acid) and 5 µL of a balanced mixture of 64 heavy peptides prepared in 0.1% formic acid and 15% acetonitrile. A volume corresponding to 0.5 µg protein was loaded onto an Evotip in accordance with the manufacturer's recommendations. Samples were analysed using an integrated microflow Evosep One HPLC system coupled to a TSQ Altis triple quadrupole mass spectrometer equipped with an EASY-Spray ion source (Evosep Biosystems and Thermo Fisher Scientific). The Evosep One was configured with an 8 cm analytical column, and data acquisition was performed in scheduled selected reaction monitoring (SRM) mode using a 60-samples-per-day liquid chromatography method. Solvent buffer A and solvent buffer B (100% acetonitrile, 0.1% formic acid) were used for chromatographic separation. To monitor analytical performance, serum pool quality control samples were prepared in four replicates and distributed evenly across each 96-well plate. The mean inter-assay coefficient of variation was 17.4% (4.7-25.3%). A complete list of measured apolipoproteins, abbreviations, and associated lipoproteins is provided in **Supplemental Table 1**.

Lipid and hormone measures by immunoassay and mass spectrometry: Total cholesterol and HDL were measured using enzymatic colorimetric methods. LDL was calculated [22]. Serum total testosterone was

measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) after ether extraction. The intra-assay coefficient of variation (CV) for total testosterone was <10% for concentrations >0.2 nmol/L and <30% for concentrations between 0.1-0.2 nmol/L. Estradiol was analysed with a standardised electrochemiluminescence immunoassay (Roche Cobas Elecsys Estradiol III), and its results were determined through a calibration curve. CV was 3.5% for concentrations ~ 1.53 nmol/L and 5.7% for ~ 0.36 nmol/L.

Body composition: Body mass index (BMI) was calculated from height and weight. Total fat mass (kg and %), fat mass in the upper/lower body, and total lean mass were measured using dual-energy X-ray absorptiometry (DXA; Horizon A Discovery) following standardised protocols. Waist and hip circumference were measured manually using a measuring tape, from which a waist-to-hip ratio (WHR) was calculated.

Statistics

The present study reports a predefined 16-apolipoprotein targeted proteomics panel as the study outcome. A formal power calculation specific to the apolipoprotein outcomes was not possible due to limited prior data on expected effect sizes. Sample size was instead guided by the power calculation for the secondary endpoint of upper body muscle strength and power in the registered protocol [17], which indicated that 39 participants were sufficient to detect a 10% within-participant difference with 80% power at a 5% significance level.

Data are presented as mean ± standard deviation (SD). Within-individual changes from baseline to 1 year are expressed as delta (Δ)-values. Data distribution of Δ-values was assessed using Q-Q plots and the Shapiro-Wilk test. Statistical significance of Δ-values was assessed using paired *t*-tests for normally distributed variables and Wilcoxon signed-rank tests for non-normally distributed variables. Raw light/heavy (L/H) peptide ratios were normalised to the mean L/H ratio of three albumin peptides. Normalised L/H ratios from multiple peptides belonging to the same protein were averaged to generate a single protein value. Fold change was calculated by dividing the protein level in the case group by the protein level in the reference group. The resulting values were converted into z-scores. There were no missing values for any apolipoprotein or clinical variable, and no outliers were excluded from the analyses.

In the TransF GAHT-naïve group, one participant initiated statin therapy within the follow-up period. Sensitivity analyses excluding this patient did not change the direction or statistical significance of the results.

In a cross-sectional comparison, mean z-scores of apolipoproteins were compared between GAHT-naïve participants at 1 year and GAHT-ongoing participants at baseline using unpaired t-tests for normally distributed variables and Wilcoxon rank-sum tests (Mann-Whitney U) for non-normally distributed variables.

The comparison included only apolipoproteins that changed significantly over 1 year in GAHT-naïve participants. Correlations between Δ-values of each apolipoprotein and Δ-values of lipids, body composition, and anthropometric measures (BMI and WHR) were assessed using Pearson's correlation coefficient for normally distributed variables and Spearman's rank correlation for non-normally distributed variables. P-values <0.05 were considered statistically significant. MRM-MS raw files were processed using Skyline and further analysed in RStudio (RStudio Team [2020]). All analyses were conducted using STATA BE, version 18.

RESULTS

Characteristics

The study included 87 participants (TransM *n*=59; TransF *n*=28) (**Fig. 1**). The GAHT-naïve group consisted of 55 participants (TransM *n*=34; TransF *n*=21). Baseline and 1-year clinical characteristics for GAHT-naïve participants are presented in **Table 1**.

In TransM GAHT-naïve, 59% (20/34) received injectable testosterone undecanoate and 41% (14/34) received transdermal testosterone gel. In TransM GAHT-naïve, fat mass measures decreased from baseline to 1 year, with fat mass decreasing by 13% and lean mass increasing by 8% during follow-up (both $p<0.001$). In TransF GAHT-naïve, 81% (17/21) received oral estradiol and 19% (4/21) received transdermal estradiol (patch or spray). In TransF GAHT-naïve, fat mass measures increased during follow-up, with fat mass increasing by 35% ($p<0.001$) and lean mass decreasing by 3% ($p=0.02$) (**Table 1**).

The GAHT-ongoing group included 32 participants (TransM *n*=25; TransF *n*=7). Baseline clinical characteristics for GAHT-ongoing participants are presented in **Supplemental Table 2**. The median duration of GAHT was 46 months (*range:* 10-99) in TransM GAHT-ongoing and 56 months (*range:* 20-119) in TransF GAHT-ongoing. Mean age was 30 (±10) years in TransM GAHT-ongoing and 39 (±15) years in TransF GAHT-ongoing, and mean BMI was 25.6 (±5.0) kg/m² and 31.6 (±7.4) kg/m², respectively. In TransM GAHT-ongoing, 92% (23/25) received injectable testosterone undecanoate and 8% (2/25) received transdermal testosterone gel. In TransF GAHT-ongoing, 57% (4/7) received oral estradiol and 43% (3/7) received transdermal estradiol (patch, spray, or gel).

Prospective apolipoprotein changes in TransM GAHT-naïve: In TransM GAHT-naïve participants, z-scores decreased for ApoA-I and ApoE ($p<0.001$ and $p=0.01$, respectively) (**Table 2, Fig. 2**). HDL decreased during

follow-up (p<0.001), whereas the remaining lipids were unchanged. Lp(a)KIV-2 also decreased relative to baseline (p=0.03).

Prospective changes in apolipoproteins in TransF GAHT-naïve: In GAHT-naïve participants receiving feminising GAHT, z-scores changed in 6 of the 16 apolipoproteins, with increased levels of Lp(a)KIV-2 (p=0.02), Lp(a)PeptidaseS1 (p=0.048), and a borderline increase in ApoB-100 (p=0.053). ApoA-I, ApoJ, and ApoL-I increased (p=0.01, p=0.02, and p<0.001, respectively). ApoC-I decreased (p=0.04) (**Table 2**, **Fig. 2**). No standard lipid measures changed significantly.

Apolipoproteins in GAHT-naïve at 1 year vs. GAHT-ongoing at baseline: In TransM, cross-sectional comparisons of apolipoproteins between the GAHT-naïve group at 1 year and the GAHT-ongoing group at baseline were non-significant. In TransF, ApoJ was higher in the GAHT-ongoing group at baseline compared with GAHT-naïve at 1 year (p=0.03) (**Supplemental Table 2**).

Bivariate associations between changes in apolipoproteins, lipids, and body composition

In TransM GAHT-naïve, changes in apolipoproteins were intercorrelated (r=0.4-0.8, p<0.05). Changes in ApoA-I were positively correlated with changes in HDL (r=0.8, p<0.05) and negatively correlated with changes in triglycerides (r=−0.5, p<0.05) and fat percentage (r=−0.5, p<0.05). Changes in Lp(a)KIV-2, Lp(a)PeptidaseS1, ApoC-I, ApoJ, and ApoL-I showed no consistent associations with changes in standard lipids or body composition (**Fig. 3b and Supplemental Fig. 1b**). In TransF GAHT-naïve, changes in apolipoproteins were moderately to strongly correlated with each other (r=0.5-0.8, p<0.05). Changes in ApoA-I showed a positive correlation with changes in HDL (r=0.4, p<0.05). Changes in ApoE were positively correlated with changes in Lp(a)KIV-2 (r=0.8, p<0.05). Changes in ApoA-I, ApoE, and Lp(a)KIV-2, and changes in body composition were not statistically significant (**Fig. 3a and Supplemental Fig. 1a**).

DISCUSSION

This prospective study is the first to evaluate changes in a full panel of 16 apolipoproteins following 1 year of GAHT. Alterations in apolipoproteins differed between masculinising and feminising GAHT, as masculinising GAHT shifted the apolipoprotein profile toward a more atherogenic profile and feminising GAHT was linked to concurrent atherogenic and atheroprotective apolipoprotein changes.

Following masculinising GAHT, we reported decreased levels of ApoA-I, HDL, and Lp(a)KIV-2, supporting a more atherogenic apolipoprotein profile. Low levels of ApoA-I and HDL are associated with lower cholesterol

efflux capacity and reduced atheroprotective function in cisgender populations and predict higher CVD risk [8, 23, 24]. Decreased levels of HDL following masculinising GAHT are supported by previous studies [2, 10]. Our finding of decreased Lp(a)KIV-2 on masculinising GAHT is novel and has not previously been reported, while decreased Lp(a)KIV-2 has been observed in healthy cisgender men following testosterone exposure [25, 26]. Lp(a)KIV-2 is a repeated protein domain in apolipoprotein(a) and determines circulating Lp(a) levels [15]. Lower circulating Lp(a) levels predict reduced risk of atherosclerotic CVD in prospective cohort studies [27, 28]. The findings from the present study expand previous results in transgender men, where Lei et al. reported increased ApoB but unchanged ApoA-I following masculinising GAHT [3], which could support an increased burden of atherogenic lipoprotein particles. In the study by Lei et al. [3], a small cohort of adult transgender men (n=16) underwent gonadotropin-releasing hormone (GnRH)-induced suppression followed by 11 months of testosterone undecanoate 1000 mg, and ApoA-I and ApoB were assessed by nuclear magnetic resonance-based particle profiling at baseline and following masculinising GAHT [3]. The study design by Lei et al. [3] included a phase of GnRH-a induced hypogonadism, which could have an adverse effect on lipid metabolism [29], and testosterone undecanoate was given in the full study period in contrast to the present study where testosterone dosage was gradually increased, and 14/34 patients were treated with transdermal testosterone at 12 months. The discrepant data regarding ApoB between the present study and the study by Lei et al. could therefore be explained by different study designs and different magnitude of testosterone exposure. In accordance, ApoB and ApoA levels were unchanged following testosterone supplementation in hypogonadal cisgender men [30], whereas androgen abuse is associated with increased ApoB levels [31]. Our observations of unchanged ApoB-100 during masculinising GAHT could suggest an altered balance between atherogenic and atheroprotective pathways rather than an isolated increase in the number of atherogenic particles. Our findings of concurrent decreases in ApoA-I, HDL, and Lp(a)KIV-2 suggest that initiation of masculinising GAHT is associated with coordinated alterations across HDL- and LDL-related apolipoprotein pathways that are not fully captured by standard lipid measures [8, 13]. The reduction in Lp(a)KIV-2 could to some extent outbalance the concurrent decrease in ApoA-I and HDL, but prospective studies including hard CVD endpoints are needed to determine the best predictor of adverse CVD outcomes in transgender cohorts.

ApoE levels decreased following 1 year of masculinising GAHT in the present study. ApoE plays a key role in lipoprotein clearance and lipid transport [8], and specific ApoE genotypes have been linked to CVD risk in cisgender populations [32]. However, circulating ApoE is not an established independent predictor of cardiovascular outcomes, making the clinical implications for CVD risk uncertain.

In cross-sectional analyses, we found that apolipoprotein z-scores at 1 year in TransM GAHT-naïve were comparable to apolipoprotein levels in the GAHT-ongoing group (median GAHT duration 46 months) at baseline. This comparison was cross-sectional and unadjusted, and therefore the results should be interpreted as a descriptive observation that should be confirmed in a larger prospective study.

Initiation of feminising GAHT in the present study was associated with increased levels of the Lp(a)-related markers Lp(a)KIV-2 and Lp(a)PeptidaseS1. Peptidase S1 is a domain of Lp(a) that contributes to its pro-thrombotic properties [15, 16], and increased Lp(a)PeptidaseS1 reflects an atherogenic shift in lipid profile. The borderline increase in ApoB-100 (p=0.053) further indicated a potential increase in atherogenic lipoprotein particle burden during feminising GAHT [12, 14]. This finding contrasted with the evidence that circulating Lp(a) levels decrease following 17β-estradiol and norethisterone acetate therapy in postmenopausal women [33], and postmenopausal estradiol hormone replacement therapy is considered to have a positive impact on cardiovascular risk [34]. However, in the present study, CPA was part of the GAHT regimen in all TransF participants, and oral estradiol was used by 17 out of 21 participants, which could have impacted the study results. In transgender women, use of CPA has been associated with reduced HDL [35], whereas HDL tended to increase following GAHT regimens including spironolactone [10]. In contrast, GAHT regimens with GnRH analogues have been associated with more neutral lipid effects compared with CPA-based regimens [3, 36]. In support of this hypothesis, Lei et al. reported no significant changes in ApoA-I or ApoB following feminising GAHT consisting of a GnRH agonist combined with either oral or transdermal estradiol [3]. Furthermore, in cisgender men, androgen deprivation in prostate cancer was associated with increased LDL and triglycerides [37, 38]. These findings suggest that the modality of androgen suppression is an important mediator of lipoprotein changes following feminising GAHT.

ApoC-I decreased following initiation of feminising GAHT in the present study, which could be associated with improved clearance of triglyceride-rich lipoproteins [39] and more favourable triglyceride metabolism [39]. A concurrent increase in ApoA-I may reflect a higher atheroprotective lipoprotein capacity.

ApoJ and ApoL-I increased following feminising GAHT in the present study. ApoJ and ApoL-I are involved in lipid transport and inflammatory pathways [8, 16], but ApoJ and ApoL-I are not established as independent predictors of CVD risk [8].

In cross-sectional analyses, ApoJ was higher in the TransF GAHT-ongoing group (median GAHT duration 56 months) at baseline compared with GAHT-naïve after 1 year of GAHT, which could support ongoing lipid

changes beyond the first year of GAHT. However, this cross-sectional comparison could be susceptible to confounding by the older age, higher BMI, and heterogeneous treatment duration of the GAHT-ongoing group.

In the present study, associations between changes in apolipoproteins and changes in body composition were weak or absent. This finding is in accordance with previous prospective studies of standard lipids in transgender cohorts [2, 10] and supports that lipid changes during GAHT primarily reflect direct hormonal modulation rather than GAHT-derived changes in body composition. Importantly, apolipoprotein changes observed in the present study occurred despite limited changes in standard lipid measures. This supports that measurement of apolipoproteins provides additional information apart from routine CVD risk markers and measurement of selected apolipoproteins could be a future tool to improve risk stratification and monitoring strategies regarding CVD risk following GAHT in transgender individuals [2, 3, 8]. However, the clinical utility of apolipoprotein profiling for CVD risk assessment remains unproven, and prospective studies with hard CVD outcomes in transgender cohorts are needed before it can be recommended as a routine clinical tool.

A key strength of this study was the prospective study design with within-individual follow-up allowing for assessment of GAHT-related effects on study outcomes. All blood samples were collected under standardised fasting conditions and analysed using a targeted proteomics with a standardised protocol and consistent laboratory conditions, ensuring analytical consistency across time points. The applied apolipoprotein panel has previously been validated, supporting its suitability for profiling apolipoprotein changes [21]. Body composition was assessed using DXA, providing measures of body composition, rather than using anthropometric measures alone. Study limitations included small sample size, which limited statistical power. Assessing multiple apolipoproteins increases the risk of chance findings, but changes in apolipoproteins were generally consistent in direction across related markers. The study cohort was required to complete both baseline and 1-year visits, which may have introduced selection bias. While the 1-year follow-up allowed detection of apolipoprotein changes, longer-term effects of GAHT were not assessed. This study did not include transmasculine participants using short-acting testosterone esters, and masculinising GAHT was limited to transdermal gel and long-acting testosterone undecanoate. Similarly, only 19% (4/21) of transfeminine GAHT-naïve participants used transdermal estradiol, with the majority receiving oral estradiol. These findings may therefore not generalise to individuals using other GAHT formulations, which have been

associated with differing lipid effects. The study lacked cisgender control groups, limiting generalisability and direct comparison with cisgender reference patterns.

Conclusion

Initiation of masculinising and feminising GAHT induced opposing changes in apolipoprotein profiles, which were only partly reflected by changes in standard lipids. Future studies should evaluate whether changes in apolipoprotein levels during GAHT translate into long-term cardiovascular outcomes.

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STATEMENTS AND DECLARATIONS

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Disclosures and competing interests

The authors declare no conflict of interest. The authors have no relevant financial or non-financial interests to disclose. Generative AI was used as a supportive tool to formulate STATA command syntax, rephrase sentences for clarity, and correct grammatical errors. All statistical analyses, methodological decisions, interpretations of results, and the wording of the study were conducted by the author. Generative AI was not used to generate academic content, results, or interpretations.

Author contributions

Conceptualisation and investigation: Sara Ravn Bach, Dorte Glintborg, and Louise Lehmann Christensen. Funding: Dorte Glintborg, Louise Lehmann Christensen, Jan Frystyk, and Marianne Skovsager Andersen. Data curation: Sara Ravn Bach, Mathilde Kamp Nørlund, Louise Lehmann Christensen, and Dorte Glintborg. Statistical analyses: Sara Ravn Bach, Emilie Bukh Madsen, and Martin Overgaard. Writing: Sara Ravn Bach, Dorte Glintborg, Louise Lehmann Christensen, and Martin Overgaard. All the authors reviewed and approved the manuscript.

Ethics

The Danish Data Protection Agency (19/27572, 21/36299) and the Regional Committee on Health Research Ethics for Southern Denmark (S-20190108, S-20210089) approved the present study. ClinicalTrials.gov identifiers: NCT04254354, NCT05169762. All participants received oral and written study information and provided written informed consent. Data were collected and managed using Research Electronic Data Capture (REDCap) hosted at Open Patient data Explorative Network (OPEN) [40, 41].

Data availability statement

The study data are available from the corresponding author upon reasonable request. The data are not publicly available due to ethical and data protection restrictions.

TABLE 1 Clinical characteristics at baseline and 1 year in GAHT-naïve TransM and TransF

	Baseline	1 year	Δ-change	*p-value*	Baseline	1 year	Δ-change	*p-value*
	TransM (n=34)				**TransF (n=21)**			
Age (years)	27 (10)	-	-	-	27 (7)	-	-	-
Weight (kg)	73.9 (11.7)	73.2 (11.1)	-0.7 (4.7)	0.42	73.3 (14.4)	77.2 (15.8)	3.8 (4.1)	**<0.001*** [a]
BMI (kg/m^2)	26.0 (4.2)	25.7 (4.2)	-0.4 (1.7)	0.20 [a]	22.6 (4.2)	23.8 (4.5)	1.2 (1.3)	**<0.001*** [a]
WHR	0.8 (0.1)	0.8 (0.1)	0.0 (0.1)	0.45	0.8 (0.1)	0.8 (0.1)	0.0 (0.1)	0.12
Fat mass, upper body (kg)	13.7 (5.2)	12.2 (4.8)	-1.4 (1.9)	**<0.001***	9.6 (4.7)	11.3 (5.0)	1.7 (1.2)	**<0.001*** [a]
Fat mass, lower body (kg)	12.4 (4.0)	10.4 (3.0)	-2.0 (2.2)	**<0.001***	8.1 (2.7)	11.3 (2.9)	3.3 (1.2)	**<0.001***
Fat ratio (upper/lower)	1.2 (0.5)	1.2 (0.3)	0.0 (0.5)	**<0.001*** [a]	1.2 (0.2)	1.0 (0.2)	-0.2 (0.1)	**<0.001*** [a]
Fat mass (kg)	29.8 (9.7)	25.9 (8.3)	-3.9 (4.1)	**<0.001***	20.2 (8.3)	27.3 (9.9)	7.1 (6.1)	**<0.001*** [a]
Fat mass (%)	42.0 (7.1)	36.5 (6.8)	-5.5 (3.4)	**<0.001***	28.8 (6.5)	34.9 (5.5)	6.1 (2.5)	**<0.001***
Lean mass (kg)	38.4 (4.0)	41.6 (3.4)	3.2 (2.0)	**<0.001***	46.3 (7.3)	45.0 (7.8)	-1.3 (2.2)	**0.02*** [a]
Fat-to-lean ratio	0.8 (0.2)	0.6 (0.2)	-0.2 (0.1)	**<0.001***	0.4 (0.1)	0.6 (0.2)	0.2 (0.1)	**<0.001***
Testosterone (nmol/L)	0.9 (0.4)	21.7 (14.2)	20.7 (14.1)	**<0.001*** [a]	18.1 (5.9)	0.5 (0.2)	-17.6 (5.9)	**<0.001***
Estradiol (nmol/L)	0.34 (0.38)	0.21 (0.17)	-0.13 (0.39)	0.20 [a]	0.10 (0.04)	1.00 (1.90)	0.90 (1.89)	**<0.001***

All data are presented as mean (SD)
P-values represent within-individual changes in study outcomes from baseline to 1 year
*P-values <0.05 are considered statistically significant and presented in **bold**
Δ-change is calculated as "1 year - baseline"
[a]Δ-change was tested with Wilcoxon signed-rank test when non-normally distributed

Abbreviations: GAHT, gender-affirming hormone therapy; TransM, transmasculine individuals; TransF, transfeminine individuals; BMI, body mass index; WHR, waist-to-hip ratio; SD, standard deviation; p-value, probability value; Δ, delta

TABLE 2 Apolipoproteins and lipids at baseline and 1 year in GAHT-naïve TransM and TransF

	Baseline	1 year	Δ-change	*p-value*	Baseline	1 year	Δ-change	*p-value*
Apolipoprotein/lipid	**TransM (n=34)**				**TransF (n=21)**			
Lp(a)KIV-2 (z-score)	0.30 (1.49)	-0.08 (1.41)	-0.38 (0.99)	**0.03***	-0.61 (1.16)	0.00 (1.24)	0.61 (1.08)	**0.02***
Lp(a)Peptidase S1 (z-score)	0.24 (1.48)	-0.04 (1.49)	-0.28 (0.93)	0.09	-0.56 (1.22)	-0.03 (1.10)	0.53 (1.16)	**0.048***
ApoA-I (z-score)	0.36 (1.10)	-0.25 (0.90)	-0.61 (0.75)	**<0.001***	-0.41 (0.62)	-0.06 (0.59)	0.35 (0.59)	**0.01***
ApoA-II (z-score)	0.03 (1.11)	-0.30 (1.01)	-0.33 (1.00)	0.06	-0.23 (0.66)	-0.12 (0.73)	0.11 (0.53)	0.35
ApoA-IV (z-score)	-0.07 (1.10)	-0.02 (1.10)	0.05 (0.88)	0.74	-0.28 (1.07)	-0.20 (0.84)	0.08 (1.15)	0.76
ApoB-100 (z-score)	0.07 (1.43)	-0.02 (1.08)	-0.09 (1.20)	0.72[a]	-0.36 (0.80)	0.02 (0.76)	0.37 (0.83)	0.053
ApoC-I (z-score)	0.16 (1.14)	-0.09 (1.20)	-0.25 (0.83)	0.08	0.10 (0.74)	-0.24 (0.56)	-0.34 (0.69)	**0.04***
ApoC-II (z-score)	-0.10 (1.04)	-0.07 (1.13)	0.03 (0.81)	0.80	-0.11 (0.86)	-0.24 (0.83)	-0.13 (0.72)	0.41
ApoC-III (z-score)	-0.02 (1.22)	-0.06 (1.11)	-0.05 (0.89)	0.76	-0.41 (1.14)	-0.09 (1.05)	0.33 (0.86)	0.10
ApoD (z-score)	-0.02 (1.08)	-0.13 (1.03)	-0.11 (0.76)	0.41	0.11 (0.91)	0.04 (0.64)	-0.07 (0.70)	0.67
ApoE (z-score)	0.41 (1.37)	0.00 (1.36)	-0.41 (0.79)	**0.01***	-0.29 (0.89)	0.00 (1.02)	0.28 (0.79)	0.12
ApoF (z-score)	0.09 (1.20)	-0.17 (1.10)	-0.26 (1.16)	0.20	-0.22 (1.04)	-0.15 (1.17)	0.08 (1.05)	0.74
ApoH (z-score)	0.24 (0.98)	0.12 (1.15)	-0.12 (0.79)	0.37	-0.37 (0.65)	-0.27 (0.77)	0.09 (0.69)	0.55
ApoJ (z-score)	0.33 (1.04)	0.01 (0.77)	-0.32 (0.86)	0.08[a]	-0.41 (0.65)	-0.07 (0.57)	0.34 (0.59)	**0.02***
ApoL-I (z-score)	-0.10 (1.17)	-0.06 (0.93)	0.05 (1.28)	0.27[a]	-0.43 (0.84)	0.05 (0.74)	0.48 (0.62)	**<0.001***
ApoM (z-score)	-0.03 (0.97)	-0.19 (1.02)	-0.16 (0.84)	0.27	-0.13 (0.72)	-0.23 (0.67)	-0.10 (0.47)	0.32
Total cholesterol (mmol/L)	4.3 (1.0)	4.2 (0.9)	-0.1 (1.0)	0.94[a]	4.1 (0.6)	3.9 (0.6)	-0.1 (0.6)	0.37
HDL (mmol/L)	1.4 (0.4)	1.2 (0.3)	-0.2 (0.2)	**<0.001***	1.4 (0.3)	1.4 (0.3)	0.0 (0.3)	0.62
LDL (mmol/L)	2.5 (0.9)	2.5 (0.8)	0.0 (0.9)	0.33[a]	2.3 (0.6)	2.2 (0.5)	0.0 (0.4)	0.80[a]
Triglycerides (mmol/L)	0.9 (0.6)	1.1 (0.6)	0.1 (0.5)	0.06[a]	0.9 (0.4)	0.9 (0.3)	-0.1 (0.4)	0.49

All data are presented as mean (SD)

P-values represent within-individual changes in study outcomes from baseline to 1 year

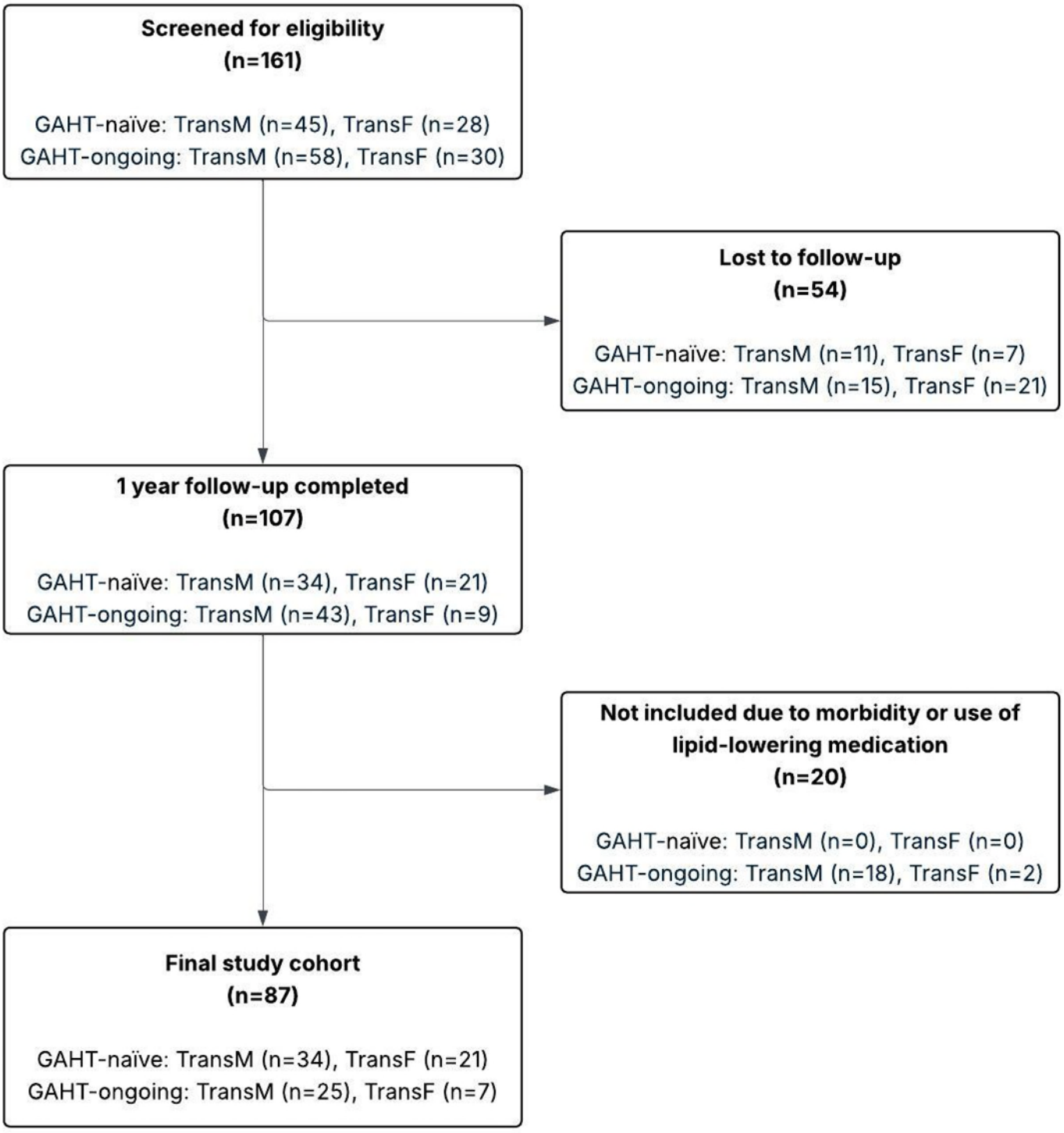
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Δ-change is calculated as “1 year - baseline”

[a]Δ-change was tested with Wilcoxon signed-rank test when non-normally distributed

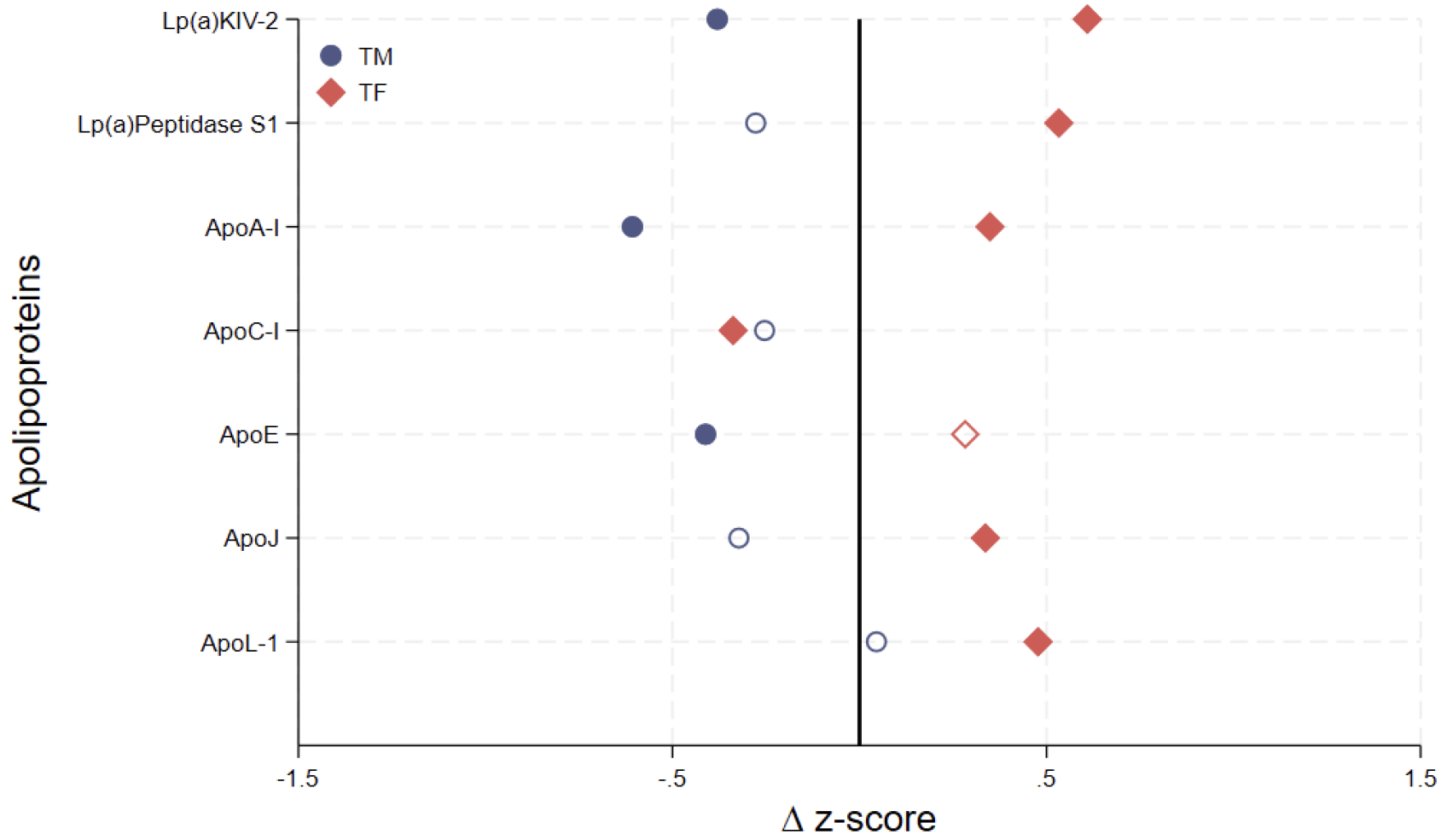
Abbreviations: GAHT, gender-affirming hormone therapy; TransM, transmasculine individuals; TransF, transfeminine individuals; Lp, lipoprotein; Apo, apolipoprotein; KIV, kringle IV type 2; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation; p-value, probability value; Δ, delta

FIGURE 1 Flowchart of included TransM and TransF study participants



Abbreviations: TransM, transmasculine; TransF, transfeminine; GAHT, gender-affirming hormone therapy

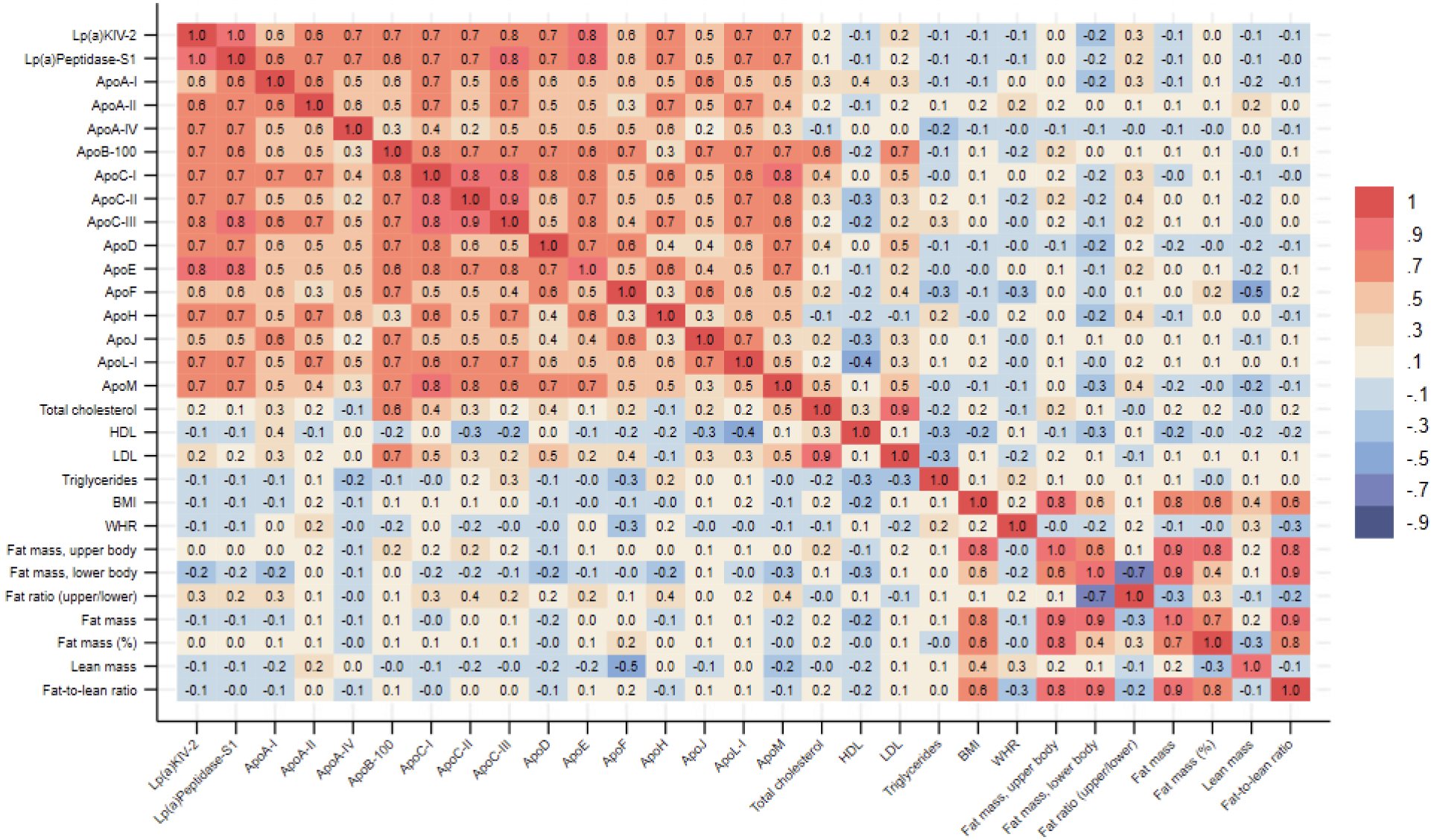
FIGURE 2 Changes in apolipoproteins from baseline to 1 year of GAHT in TransM and TransF individuals. Only apolipoproteins showing significant within-group change after 1 year of GAHT in GAHT-naïve are presented.



Marks show mean-values of within-group Δ z-scores (1-year − baseline) in apolipoprotein z-scores.
Blue marks represent TransM individuals (TM)
Red marks represent TransF individuals (TF)
Unfilled marks indicate non-significant changes (TransM: Lp(a)Peptidase S1, ApoC-I, ApoJ, ApoL-I; TransF: ApoE)
The vertical line denotes no change (Δ = 0)

Abbreviations: TransM, transmasculine; TransF, transfeminine; GAHT, gender-affirming hormone therapy; Lp, lipoprotein; KIV, kringle IV type 2; Apo, apolipoprotein; Δ, delta

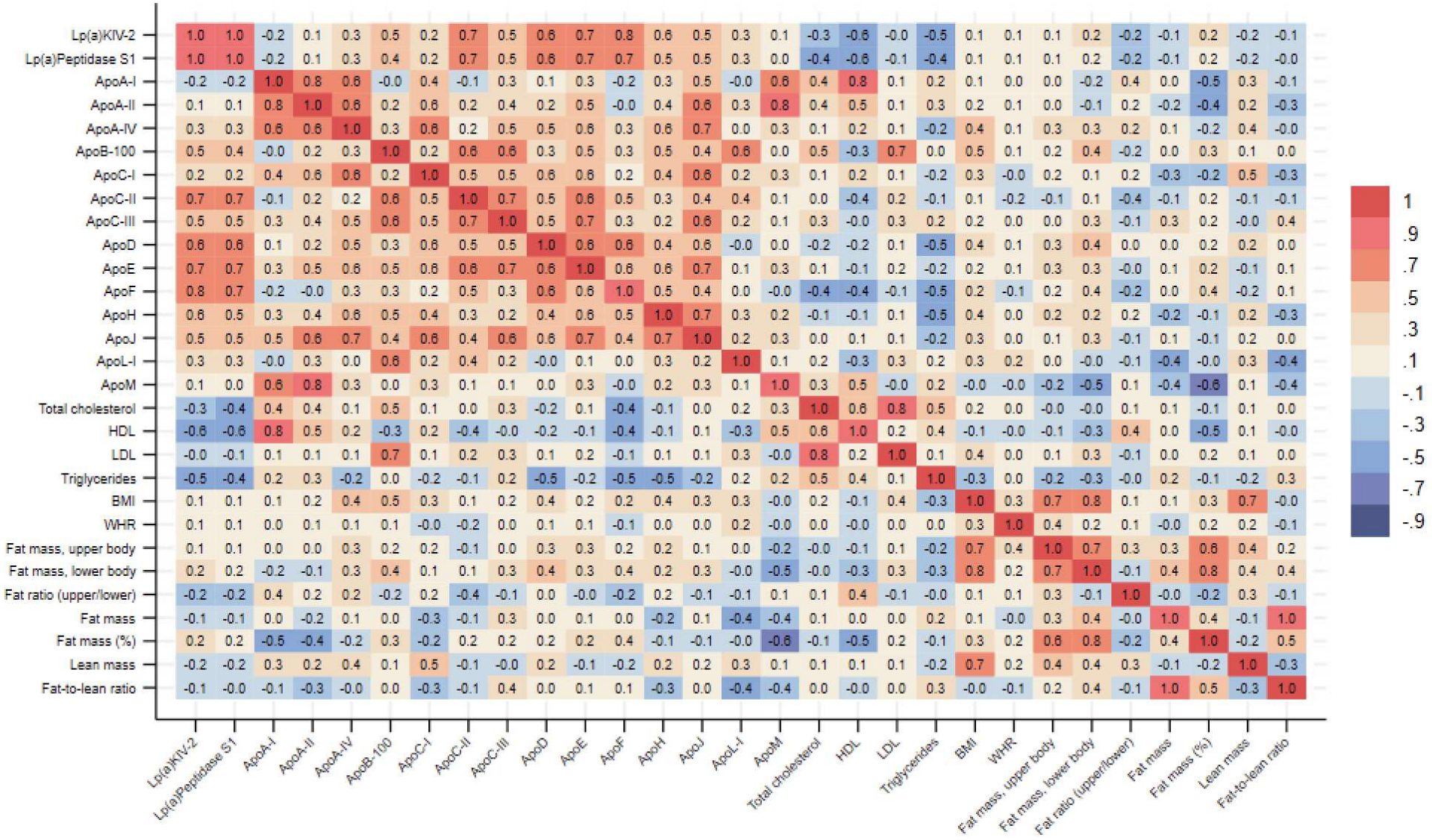
FIGURE 3a Correlation heatmaps of changes in apolipoproteins, lipids, and body composition from baseline to 1 year in TransM individuals.



Data are presented as Pearson correlation coefficient (r)
Statistical significance and values recalculated using Spearman's rank correlation for non-normally distributed variables are presented in the supplemental material

Abbreviations: TransM, transmasculine; Lp, lipoprotein; KIV, kringle IV type 2; Apo, apolipoprotein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index; WHR, waist-to-hip ratio

FIGURE 3b Correlation heatmaps of changes in apolipoproteins, lipids, and body composition from baseline to 1 year in TransF individuals.



Data are presented as Pearson correlation coefficient (r)
Statistical significance and values recalculated using Spearman's rank correlation for non-normally distributed variables are presented in the supplemental material

Abbreviations: TransF, transfeminine; Lp, lipoprotein; KIV, kringle IV type 2; Apo, apolipoprotein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index; WHR, waist-to-hip ratio

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