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MESTRADO INTEGRADO EM MEDICINA

Impacto da terapêutica hormonal de afirmação de género nos fatores de risco cardiovascular em indivíduos transgénero

Francisca Mangas Neto da Palma

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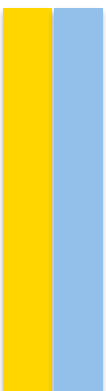

Impact of gender-affirming hormone therapy on cardiovascular risk factors in transgender individuals

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

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Resumo

Introdução: As pessoas transgénero têm um risco cardiovascular (RCV) mais elevado em comparação com a população geral. A terapêutica hormonal de afirmação de género (THAG), usada para alinhar as características físicas com a identidade de género, tem um impacto incerto nos fatores de RCV. Alguns estudos sugerem que a THAG pode exacerbar o RCV através de alterações na pressão arterial (PA), insulinorresistência, perfil lipídico e composição corporal.

Objetivo: Avaliar o impacto da THAG no perfil lipídico, PA e índice de massa corporal (IMC) em pessoas transgénero.

Métodos: Foi realizado um estudo retrospetivo e longitudinal na Consulta Multidisciplinar de Medicina Transgénero, Unidade Local de Saúde de Santo António, de outubro de 2021 a janeiro de 2024. O estudo recolheu e analisou dados sociodemográficos, história médica pessoal e familiar e dados clínicos e laboratoriais de todos os indivíduos observados durante o referido período. De forma a avaliar alterações no perfil lipídico, na PA e no IMC desde o período pré-tratamento até um ano após o início da GAHT, reunimos um subconjunto de participantes (Coorte A) que tinham dados de duas ou mais avaliações diferentes no tempo. A análise estatística foi realizada usando o IBM SPSS Statistics 28.0.1.0 e foi utilizado um nível de significância de 0,05.

Resultados: O estudo abrangeu 232 indivíduos transgénero (152 trans masculinos e 80 trans femininos; idade mediana, 23 anos) os quais revelaram taxas elevadas de uso de tabaco (37,3%) e uso de substâncias ilícitas (11,5%). Entre os indivíduos trans femininos, verificam-se reduções consistentes, mas não significativas, na PA sistólica e triglicerídeos (TG) aos 3, 6 e 9 meses. Indivíduos trans masculinos exibiram uma tendência para o aumento da PA sistólica, embora nenhuma alteração tenha atingido significância estatística. Os indivíduos trans masculinos tiveram um aumento significativo do IMC aos 3, 6 e 9 meses (Δmáx. = 1.01 kg/m^2; $p < 0.01$) e uma diminuição significativa do colesterol HDL em todos os momentos (Δmáx. = -10.47 mg/dL; $p < 0.001$).

Conclusão: Os dados observados sugerem que a THAG pode modificar o perfil lipídico de pessoas trans, contudo a curto prazo o seu impacto não é clinicamente relevante, o que suporta a segurança da THAG. Por outro lado, a prevalência de outros fatores de RCV nesta população ressalta a necessidade de uma vigilância e intervenção adequadas para minimizar o RCV. Estudos complementares são essenciais para elucidar a relação entre a THAG e os seus efeitos cardiovasculares a longo prazo.

Palavras-chave: Pessoas Transgénero; Doença Cardiovascular, Fatores de Risco de Doença Cardiovascular, Terapêutica Hormonal de Afirmação de Género

Abstract

Introduction: Transgender individuals exhibit a higher cardiovascular risk compared to the general population. Gender-affirming hormone therapy (GAHT), used to align physical characteristics with gender identity, has an unclear impact on cardiovascular risk factors. Some evidence suggests that GAHT may exacerbate cardiovascular risk, through changes in blood pressure, insulin resistance, lipid profile and body composition.

Objective: This study aims to evaluate the impact of GAHT on lipid profile, blood pressure, and body mass index (BMI) in transgender individuals.

Methods: A retrospective longitudinal study was conducted at the Multidisciplinary Clinic of Transgender Medicine, *Unidade Local de Saúde de Santo António*, from October 2021 to January 2024. The study collected and analysed sociodemographic data, lifestyle behaviours, personal and family medical histories as well as clinical and laboratory data of all individuals observed within this timeframe. To evaluate changes in lipid profiles, blood pressure, and BMI from baseline up to one year after starting GAHT, we focused on a subset of participants (Cohort A) who had data from two or more different points in time. Statistical analysis was performed using IBM SPSS Statistics 28.0.1.0 and a significance level of 0.05 was used.

Results: The study included 232 transgender individuals (152 trans men and 80 trans women; median age 23) who showed high rates of tobacco use (37.3%) and illicit substance use (11.5%). Among trans feminine individuals, there were consistent but non-significant decreases in systolic blood pressure (SBP) and triglycerides (TG) at 3, 6, and 9 months. Trans masculine individuals exhibited a trend of increasing SBP, though no changes reached statistical significance. Trans masculine individuals experienced a significant increase in BMI at 3, 6, and 9 months (Δmax of 1.01 kg/m^2; $p<0.01$) and a significant decrease in HDL cholesterol at all time points (Δmax of -10.47 mg/dL; $p<0.001$).

Conclusion: The observed trends suggest that GAHT may impact lipid profiles. Although these changes are statistically significant, they are clinically irrelevant. Our data indicate that GAHT appears to be safe in the short term. However, the prevalence of other cardiovascular risk factors highlights the need for routine monitoring in this population. Further research is essential to address significant knowledge gaps regarding the long-term cardiovascular effects of GAHT.

Keywords: Transgender Persons; Cardiovascular Disease, Heart Disease Risk Factors, gender-affirming hormone therapy

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List of Abbreviations and Acronyms

ACE	Angiotensin-Converting Enzyme
BMI	Body Mass Index
CAC	Coronary Artery Calcium
CIMT	Carotid Intima-Media Thickness
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
GAHT	Gender-Affirming Hormone Therapy
HDL-C	High-Density Lipoprotein Cholesterol
ICD	International Classification of Diseases
IQR	Interquartile Range
LDL-C	Low-Density Lipoprotein Cholesterol
OSA	Obstructive Sleep Apnoea
PCOS	Polycystic Ovary Syndrome
SBP	Systolic Blood Pressure
SD	Standard Deviation
TC	Total Cholesterol
TG	Triglycerides
Trans	Transgender

Tables and Figures List

Introduction

The term transgender (trans) refers to individuals whose identity and/or gender expression differs from what is expected of the sex assigned at birth (considering current socio-cultural standards) or does not fit into conventional binary categories (non-binary). [1,2,3]

The trans population has increased considerably over the last few decades and has comprised progressively younger individuals. It is estimated that around 100 to 2000 / 100,000 individuals in the United States self-identify as transgender. [4] In specialized centres for individuals who seek or receive transgender care, this figure falls to 1-30 / 100,000 individuals. [4] In Portugal, there is no estimate of how many trans people there are, however, 2653 trans people have had their gender change officialised in the civil registry from 2011 to 2023. [5] These figures also point to a growing trend, with 2023 being the year with the most requests so far. [5]

The 11th revision of the International Classification of Diseases (ICD) defines gender incongruence within the section "Conditions related to sexual health" as a marked and persistent incongruence between an individual's experienced gender and the assigned sex, which often leads to a desire to "transition", to live and be accepted as a person of the experienced gender. [6,7] It can be manifested by a feeling of disagreement or dislike with one's primary and/or secondary sexual characteristics and a desire to align the individual's body according to the experienced gender.[6,7] Therefore, medical care for the trans population is mostly aimed at gender affirmation through social, psychological interventions, hormonal and surgical treatment, depending on individual needs, with proven beneficial effects in mental health and quality of life. [8]

In general, gender affirming hormone therapy (GAHT) is considered a safe therapy and is often one of the first interventions to be initiated. [9,10] Trans women (sex assigned at birth male, gender identity female) are generally treated with oral antiandrogens to suppress endogenous testosterone and oral or transdermal oestrogens to induce feminisation. [9,11] Trans men (sex assigned at birth female, gender identity male) are generally treated with intramuscular or transdermal testosterone to induce masculinisation. [9,11]

There is a studied relationship between sex at birth and the prevalence of cardiovascular disease (CVD): before the age of 55, females have a lower prevalence of CVD compared to males, while after the age of 55, the risk of CVD in females is twice that of males at the same age. [12,13] However, the role played by sex hormones in this difference remains uncertain. [14,15] The declining oestrogen levels during perimenopause coinciding with the aforementioned increased CVD risk led to the hypothesis that oestrogen was protective to the heart and vasculature. [16,17] However, studies like

the Women's Health Initiative Trials challenged this due to heightened cardiovascular events in postmenopausal women receiving oestrogen therapy, leading to its premature termination, suggesting instead a potential increase in cardiovascular risk with oestrogen administration. [16,17] The doubt is even greater in trans people who receive treatment with hormones of the opposite sex. [14,15]

In transgender people, GAHT has been associated with the potential worsening of cardiovascular risk factors (such as increased blood pressure, insulin resistance and lipid disorders) and changes in body composition. [9,18-20] Although there is no consistent association between these changes and the increase in cardiovascular morbidity and mortality observed, previous studies have shown an increased risk of stroke, myocardial infarction and venous thromboembolism in trans women and myocardial infarction in trans men undergoing GAHT. [9]

A recent meta-analysis on the incidence of several major CVDs in the transgender population shed light on the complex interplay of hormonal, socioeconomic, and psychological factors in shaping cardiovascular health outcomes in transgender populations by revealing that both transgender women and men have a 40% higher risk of CVD compared with cisgender people of the same birth sex. This was believed to be primarily due to socioeconomic factors and minority stress, rather than hormonal factors, as the risk of arterial CVD is similar when comparing trans women and trans men.[16] The study further revealed higher venous thrombosis risk in transgender women compared to cisgender men, and lower risk in transgender men compared to cisgender women. Interestingly, no significant disparity was documented for stroke and myocardial infarction between transgender men and women. [16]

Given that CVD is one of the main causes of mortality and morbidity worldwide and that this population has a documented higher prevalence of other risk factors (smoking, alcohol and illicit drug use in addition to psychological stress associated with systemic discrimination suffered by gender minorities), it is crucial to assess the cardiovascular risk of this population and the additional impact of GAHT. [21-23]

Nevertheless, there is a scarcity of published studies on the cardiovascular profile of transgender individuals due to the lack of large longitudinal cohort studies on trans people and of appropriate control groups and the inadequate collection of information on gender identity. [9]

The primary aim of this article is to assess the effect of GAHT on lipid profile, blood pressure, and body mass index in a sample of transgender individuals undergoing hormonal treatment at a specialized centre in Portugal. A secondary goal is to characterize the population from a

sociodemographic perspective, including the hormonal regimens used, personal and family history of cardiovascular disease, and other CVD risk factors.

By exploring the role hormonal factors play in CVD risk among transgender individuals, this study aims to highlight the need for the implementation of effective preventive strategies tailored to this population. This will enable physicians to optimize GAHT strategies for each individual based on potential risks and benefits. Additionally, we hope to incite interest in further research in this understudied area and ultimately improve care for transgender individuals.

Materials and methods

We conducted a retrospective longitudinal study involving all adult transgender individuals who visited the Multidisciplinary Clinic of Transgender Medicine – Endocrinology at the *Unidade Local de Saúde de Santo António* between October 2021 and January 2024. Participants included those planning to undergo or currently undergoing GAHT. Individuals were included regardless of the starting date for hormonal treatment. Exclusion criteria included use of puberty-blockers (i.e., gonadotropin hormone-releasing hormone analogues) before GAHT, use of hormone therapy for other reasons (hypogonadism, etc.) and intersex people.

To evaluate changes in outcomes from baseline up to one year after starting GAHT, we focused on a subset of participants (Cohort A) who had data from two or more different points in time. Participants with only data beyond the 12-month mark or those with only a single observation were excluded from this cohort.

The study protocol was reviewed and approved by the local ethics committee (Ethics Committee CHUP/ICBAS – DEFI).

Procedures

Upon identification of the study population, data was retrieved from medical records. This encompassed age, sex assigned at birth, affirmed gender identity, starting date for GAHT, educational attainment, tobacco use (current, former, or never smoker), alcohol consumption (non-drinkers, habitual drinkers, and occasional drinkers), as well as current and past substance use. The latter was categorized into non-injectable and intravenous drugs to understand potential health impacts associated with each method of administration.

Data were also systematically collected on both personal and family medical histories relevant to beginning hormonal therapy, namely the presence or history of thromboembolism, hypertension, premature cardiovascular disease, premature cerebrovascular disease, hepatopathy and hormone-dependent neoplasms were noted. In trans masculine participants we also collected information on obstructive sleep apnoea (OSA), polycythaemia, and primary venous insufficiency. For trans feminine participants, the presence of polycystic ovary syndrome (PCOS) was also recorded.

Additionally, data were collected on body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) at baseline (0 months) and following the initiation of hormone therapy at 3, 6, 9, and 12 months (Cohort A).

The formulations, doses, and routes of administration of GAHT were recorded for all visits. In the context of this study, concomitant medications with known effects on the assessed variables were documented. This included the use of statins, beta blockers and angiotensin-converting enzyme (ACE) inhibitors.

Statistical Analysis

Data was analysed by International Business Machines Corporation Statistical Package for the Social Sciences (IBM SPSS) Statistics 28.0.1.0 for Windows. The normality of distribution of continuous variables was tested using the one-sample Kolmogorov-Smirnov test (for $n \geq 50$) and the Shapiro–Wilk test for smaller sample sizes ($n < 50$ samples). Continuous variables with a normal distribution were presented as mean (standard deviation [SD]); non-normal variables were reported as median (interquartile range [IQR]). Frequency and percentage were reported for categorical variables. A significance level of 0.05 was used.

Baseline characteristics and outcomes prior to hormone therapy were analysed. In Cohort A, further analysis of each outcome was performed using Generalized Additive Mixed Models (GAMMs) incorporating variables such as birth sex, time elapsed since baseline visit, and their interaction effects.

Results

The population encompassed a total of 232 individuals who met inclusion criteria, divided into trans masculine (152 participants) and trans feminine (80 participants) groups. Demographic characteristics are detailed in **Table I.**

The median **age** was 23 (IQR 8) years old, consistent across both groups. Most participants (81.9%) were aged 18 to 29 years, with 13.8% aged 30 to 39 years, and 4.3% over 40 years old. Trans masculine individuals were slightly more represented (65.5%) compared to trans feminine individuals (34.5%).

Education levels were categorized according to the Portuguese schooling system into basic education (2nd and 3rd cycles, equivalent to 6th and 9th grades), secondary education (high school, 10th to 12th grades), licentiate degrees, and master's degrees. The most common level of attainment was high school completion at 51.4%, followed by basic education at 24.9%, and higher education (licentiate and master's degrees) at 23.7%. There were no statistically significant differences in educational attainment between genders when comparing up to secondary school versus higher education.

Regarding **alcohol consumption**, 26.8% of the participants reported sporadic use (29.5% of trans masculine individuals and 21.5% of trans feminine individuals). Frequent alcohol use was notably low, observed in only 1.3% of the total participants, with similar rates between trans masculine and trans feminine groups. Tobacco use was significant, with 37.3% of participants currently using tobacco and 6.1% reporting previous tobacco use.

Substance use disorders were assessed, revealing that 11.5% of participants were current users of non-injectable drugs (9.5% of trans masculine and 15.2% of trans feminine participants). Only a single participant from the trans masculine group reported past substance abuse, accounting for 0.4% of the total participants.

Most significant **health conditions** had low incidence rates. Thromboembolism and hypertension were each present in only 2 individuals, accounting for 0.9% of the total cohort. Premature cardiovascular disease was recorded in one participant (0.4%), while no cases of premature cerebrovascular disease or hormone-dependent neoplasms were reported. Both hepatopathy and primary venous insufficiency were observed in just one individual each. No cases of OSA or polycythaemia were documented. PCOS was the most frequently observed condition, found in 9 participants within the trans masculine group.

Hypertension was the most prevalent **family history condition**, present in 19.4% of the families. Family history of thromboembolism, premature cardiovascular and cerebrovascular diseases were reported in 5.7%, 9.7% and 5.7% of the studied individuals, respectively. As to family history of hormone-dependent neoplasms, breast cancer was the most common, affecting 12.3% of the population, while ovarian, uterine and prostate cancers had prevalences of 1.8%, 4.8% and 4.0%, respectively.

Table II provides a summary of the **hormone treatment regimens** and doses administered at each visit for the study population. Most transgender women were preferentially treated with spironolactone (25 to 100 mg daily) or cyproterone acetate (10 to 100 mg daily, based on common clinical practice at the time) as an antiandrogen. These treatments were often discontinued after orchiectomy. Leuprorelin was used in a single patient at a dosage of 22.5 mg every three months. In addition to antiandrogens, oestrogen was prescribed in the form of oral oestradiol (2 to 4 mg daily) or oestradiol patches (50 to 150 mcg every three days). Oral oestradiol was the most common form of administration, with 74.1% of transgender women using it at the beginning of hormone therapy, and this percentage varied slightly over time.

Transgender men were preferentially treated with intramuscular testosterone esters (125 mg every two weeks or 125 mg to 250 mg every four weeks) or intramuscular testosterone undecanoate (1000 mg every three months). Data showed that 100% of transgender men started with testosterone esters, with usage remaining consistently high throughout the study period. Occasionally, transgender men who experienced persistent menstrual blood loss during testosterone therapy were treated with additional progestogens. Progestogen use was noted in 12.2% of transgender men at the start of hormone therapy and decreased over time.

Table III summarizes the use of additional medications, namely statins, beta blockers, and ACE inhibitors, among transgender individuals during follow-up.

Table IV contains an overview of the baseline blood pressure, BMI, and classic lipid profile.

BP values were also categorized according to the American College of Cardiology and American Heart Association's definitions of elevated BP (SBP 120–129 mm Hg), stage 1 hypertension (SBP 130–139 mm Hg or DBP 80–89 mm Hg), and stage 2 hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg) in **Table IV.**

The overall median **BMI** was 22.86 (IQR 8.57). At baseline, trans masculine participants had a significantly higher (p=0.008) median BMI of 24.24 (IQR 8.38) compared to trans feminine participants, who had a median BMI of 21.58 (IQR 9.38).

BMI values were categorized according to the major adult BMI classifications of underweight (under 18.5 Kg/m^2), normal weight (18.5 to 24.9 Kg/m^2), overweight (25 to 29.9 Kg/m^2), and obese (30 Kg/m^2 or above).

Approximately 8.4% of the overall study population was underweight, with 3.7% in the trans masculine subgroup and 18.4% in the trans feminine subgroup. Most participants (52.9%) fell within the healthy BMI range, including 51.9% of trans masculine and 55.3% of trans feminine participants. Overweight participants comprised 18.5% of the overall group, with 19.8% in the trans masculine subgroup and 15.8% in the trans feminine subgroup. The prevalence of obesity was 20.2% in the overall cohort, observed in 24.7% of the trans masculine subgroup and 10.5% of the trans feminine subgroup.

At baseline, the mean **TC** for the entire population was 167.6 mg/dL, with trans masculine individuals having a higher mean TC of 175.9 mg/dL compared to 152.4 mg/dL in trans feminine individuals ($p < 0.001$). The mean **LDL** levels were higher in trans masculine individuals (99.7 mg/dL) compared to trans feminine individuals (84.6 mg/dL), with a significant *p* value of 0.014. **HDL** levels were higher in trans masculine individuals, averaging 57.8 mg/dL, while trans feminine individuals had a mean HDL of 48.5 mg/dL ($p = 0.001$). **TG** levels did not show a significant difference between the groups, with trans masculine individuals having a mean of 98.9 mg/dL and trans feminine individuals a mean of 112.1 mg/dL.

COHORT A ANALYSIS

This cohort included 107 transgender individuals, divided into trans masculine (n=71) and trans feminine (n=36). Demographic characteristics are detailed in **Table V.**

The median age of the subpopulation cohort was 22 years (IQR 6), with both sexes exhibiting similar median ages. Most participants (89.7%) were aged between 18 and 29 years, 9.4% were aged 30 to 39 years, and the ≥40 years category was the least represented at 0.9%.

Among the 88 participants who reported their education levels, a similar trend to the full population was observed: 18.2% had completed basic education (3rd cycle), 56.8% had secondary education, and 25.0% held either licentiate or master's degrees. In this cohort, 30.8% reported sporadic alcohol use, while 2.8% reported frequent use. Tobacco use was reported by 39.3% as current users and 2.8% as former users. Substance use disorder, specifically current non-injectable drug use, was noted in 13.1% of participants. No statistically significant differences were observed between sexes regarding lifestyle behaviours.

Variation in Clinical and Biochemical data

Mean outcome readings at the various follow-up visits are listed in **Table VI**. Variation of these outcomes is analysed in **Table VII** and depicted in **Figure 1.**

For trans feminine individuals, decreases in SBP were observed at 3, 6, and 9 months, but none of these changes were statistically significant. DBP showed minor variations at all time points, all without statistical significance. Trans feminine individuals also demonstrated increases in total cholesterol at 3, 6, and 9 months, with a decrease at 12 months, but none reached statistical significance. An increase in LDL cholesterol was noted at 3, 6, and 9 months with a slight decrease at 12 months, all not statistically significant. HDL cholesterol levels increased at all measured intervals, none statistically significant. TG levels showed decreases at 6, 9 and 12 months, also not statistically significant. BMI changes from baseline included slight decreases and increases across different time points without statistical significance.

For trans masculine individuals, minimal increases in SBP were observed at 6 and 9 months, both not statistically significant. DBP showed a decrease at 3 months and smaller changes at other intervals, none statistically significant. Total cholesterol levels indicated decreases at 3, 6, 9, and 12 months, all not statistically significant. LDL cholesterol slightly decreased at 3, 6, 9, and 12 months, with no changes reaching statistical significance. HDL cholesterol levels showed statistically significant decreases at all time points: 3, 6, 9 months and 12 months (all $p < 0.001$). The maximum variance of HDL happened at 12 months with a decrease of 10.47 mg/dL. TG levels increased at all measured intervals, with the increase at 6 months being statistically significant ($p = 0.024$). BMI consistently showed increases at all time points, with increases at 3 months ($p<0.001$), 6 months ($p=0.001$), and 9 months ($p=0.01$) being statistically significant. The maximum variance of BMI happened at 6-9 months with an increase of 1.01 mg/Kg^2.

Discussion

Firstly, the characterization of our study population highlighted an important consideration when comparing CVD in transgender individuals versus the general population: the presence and potential impact of independent cardiovascular risk factors such as lifestyle behaviours. Although our study lacked a control group for statistical analysis, the prevalences found differ markedly from those in the general population.

For instance, 37.3% of our cohort reported current tobacco use, compared to 27.8% in the general Portuguese young adult population (aged 15-34).[24] Alternatively, alcohol consumption patterns showed that 26.9% of transgender individuals reported sporadic alcohol use and 1.3% reported frequent use. This contrasts with the general population (aged 15-64), where 56.4% reported current alcohol consumption within the last 30 days.[24] Additionally, 11.5% of transgender individuals reported current non-injectable drug use, indicating a notable prevalence.

Future research should include other factors such as socioeconomic status and psychological factors, including minority-associated stress, which can also influence cardiovascular risk and access to healthcare.

Secondly, in line with our objective, we analysed in Cohort A changes in BMI, lipid profile, and blood pressure with the addition of GAHT.

In our study, trans men exhibited a decreasing trend in TC and LDL-C levels, although these changes did not reach clinical significance. There was a statistically significant decrease in HDL-C levels at all time points, and an increase in TG that was significant only at 6 months. A previous systematic review showed that masculinizing hormone therapy is associated with significant increases in LDL-C, not found in our study, as well as an increase in TG and a decrease in HDL-C, which is compatible with our findings.[25]

One possible explanation for the absence of a significant increase in TG at all points in our study is that participants had regular follow-ups with endocrinology specialists. During these visits, patients were educated about the potential adverse effects of testosterone and the importance of maintaining a healthy lifestyle and diet, which may have mitigated negative changes in lipid profiles.

Our study also found an upward trend in BMI in trans men up to 9 months, as previously reported in a systematic review, albeit not consistent in all studies.[26] Given the limitations of BMI as an index and the observed stabilization at 12 months, it is plausible that the small BMI increase (Δmax of 1.01 kg/m^2; $p<0.01$) in our cohort reflects a gain in lean mass and a reduction in fat mass, as

suggested by systematic reviews. [26,27] To substantiate this hypothesis, a follow-up study with a focus on detailed body composition analysis is warranted.

The same systematic review found that feminizing hormone therapy was associated with a statistically significant increase in TG levels, but no significant differences in LDL-C and HDL-C levels. Further analysis indicated that this increase was linked to oral oestrogen therapy, whereas transdermal oestrogen led to a decrease in TG levels.[25] Given that most trans women in our study were prescribed oral oestrogens, we anticipated a similar increase. Although one was observed at 3 months and overall decrease in TG on all other time points was observed, none reaching statistical significance. This lack of statistical significance could be attributed to the limited number of trans women who met criteria for the subanalysis, thereby reducing the study's statistical power, in addition to the lower median age of Cohort A when compared to most studies included in the systematic review. We can also explain the discrepancy through regular follow up with particular importance in lifestyle aspects that can positively influence TG levels. This may also explain why we did not observe significant changes in BMI, despite other longitudinal cohort studies reporting a significant increase.[28]

Our study demonstrated an increasing trend in SBP for trans men and a decreasing trend for trans women, similar to a four-year follow-up study which found that mean SBP decreased by 4.0 mm Hg in the trans feminine group and increased by 2.6 mm Hg in the trans masculine group. [29] However, neither of these trends reached statistical significance in our study. Additionally, DBP did not follow a specific trend in either group, consistent with the findings of the same study.[29]

The changes we have observed, even if statistically significant, are small enough to not be considered clinically significant. Combined with the fact that all observed outcomes are surrogate markers for overall cardiovascular health, the effect of these findings on important patient outcomes, such as cardiovascular events during long-term therapy, remains uncertain. As such, our study can only indicate that GAHT is a safe treatment concerning cardiovascular risk in the short term, particularly when accompanied by appropriate follow-up with an Endocrinology specialist.

There are significant knowledge gaps regarding the effects of GAHT on cardiovascular outcomes that our study could not address, necessitating further research. Specifically, it is crucial to extend the follow-up period in studies to evaluate changes in cardiovascular risk factors over time as well as assess baseline and post-GAHT cardiovascular risks. A challenge in this area is that most risk assessment models (SCORE2, ASCVD, etc.) are not designed for such a young population. Similarly, given the rarity of such events at young ages, it is important to conduct studies with larger cohorts to accurately report the prevalence of events such as myocardial infarction, stroke, venous

thromboembolism, and mortality in this population. Furthermore, studies evaluating subclinical atherosclerotic disease through non-invasive methods like Carotid Intima-Media Thickness (CIMT) Test or Coronary Artery Calcium (CAC) Score could further help to understand the effects of sex hormones on cardiovascular disease.

Conclusion

Our study highlights significant findings regarding the impact of GAHT on cardiovascular risk factors in transgender individuals. We observed some statistically significant changes, particularly related to masculinizing therapy, in lipid profiles and BMI. However, these variations are likely not clinically significant, as they represent relatively small alterations in surrogate outcomes for cardiovascular health. In light of these findings, GAHT appears to be a safe treatment in the short term.

Considering the prevalence of other cardiovascular risk factors identified in our study and the numerous studies reporting other independent risk factors such as minority stress, we believe that routine monitoring of blood pressure, weight, BMI, routine blood analyses with lipid profiles, and potentially, body composition analysis in a specialized clinic is advisable. This approach would help mitigate possible hormonal effects and pre-emptively identify individuals at higher cardiovascular risk.

Our study faced limitations due to the absence of a control group and the limited sample size for certain subanalyses. We recommend that future research extend the follow-up period and include larger cohorts to better evaluate cardiovascular risks and outcomes.

Tables and Figures

Table I Baseline Characteristics of the Study Population

Characteristic	Overall (N=232)	Trans masculine (N=152)	Trans feminine (N=80)
Age — yr, median (IQR)	23 (8)	23 (8)	23 (9)
Category — no. (%)			
18-29	190 (81.9)	125 (82.2)	65 (81.3)
30-39	32 (13.8)	23 (15.1)	9 (11.3)
≥40	10 (4.3)	4 (2.6)	6 (7.5)
Education — no. (%)	(N=181)	(N=118)	(N=63)
Basic education — 2nd cycle	3 (1.7)	3 (2.5)	
Basic education — 3rd cycle	42 (23.2)	29 (24.6)	13 (20.6)
Secondary education	93 (51.4)	62 (52.5)	31 (49.2)
Licentiate Degree	37 (20.4)	23 (19.5)	14 (22.2)
Master's Degree	6 (3.3)	1 (0.8)	5 (7.9)
Lifestyle behaviours — no. (%)			
Alcohol use	(N=228)	(N=149)	(N=79)
Sporadic	61 (26.8)	44 (29.5)	17 (21.5)
Frequent	3 (1.3)	2 (1.3)	1 (1.3)
Past frequent consumption	2 (0.8)	2 (1.3)	0 -
Tobacco use	(N=228)	(N=149)	(N=79)
Current	85 (37.3)	56 (37.6)	29 (36.7)
Previous	14 (6.1)	10 (6.7)	4 (5.1)
Substance use disorder	(N=227)	(N=148)	(N=79)
Non-injectable drugs (current)	26 (11.5)	14 (9.5)	12 (15.2)
Past substance use	1 (0.4)	1 (0.7)	0 -

Trans indicates transgender; IQR, Interquartile range, Yr, year and No., number.

Table I | Baseline Characteristics of the Study Population (cont.)

Personal medical history — no. (%)	(N=227)	(N=149)	(N=78)
Thromboembolism	2 (0.9)	2 (1.3)	0
Hypertension	2 (0.9)	0	2 (2.6)
Premature cardiovascular disease	1 (0.4)	1 (0.7)	0
Premature cerebrovascular disease	0	0	0
Hepatopathy	1 (0.4)	1 (0.7)	0
Hormone-dependent neoplasms	0	0 -	0
Obstructive sleep apnoea	-	0 -	-
Polycythaemia	-	0 -	-
Polycystic ovary syndrome	-	9 (5.9)	-
Primary venous insufficiency	-	-	1 (1.3)
Family medical history — no. (%)	(N=227)	(N=149)	(N=78)
Thromboembolism	13 (5.7)	11 (7.4)	2 (2.6)
Hypertension	44 (19.4)	26 (17.4)	18 (23.1)
Premature cardiovascular disease	22 (9.7)	19 (12.8)	3 (3.8)
Premature cerebrovascular disease	13 (5.7)	10 (6.7)	3 (3.8)
Hepatopathy	11 (4.8)	8 (5.4)	3 (3.8)
Hormone-dependent neoplasms			
Breast	28 (12.3)	19 (12.8)	9 (11.5)
Ovary	4 (1.8)	2 (1.3)	2 (2.6)
Uterus	11 (4.8)	8 (5.4)	3 (3.8)
Prostate	9 (4.0)	4 (2.7)	5 (6.4)
Breast + Prostate	3 (1.3)	1 (0.7)	2 (2.6)
Breast + Uterus	1 (0.4)	1 (0.7)	- -
Obstructive sleep apnoea	- -	7 (4.7)	- -
Polycythaemia	- -	0 -	- -
Polycystic ovary syndrome	- -	2 (1.3)	- -
Primary venous insufficiency	- -	-	16 (20.5)

Trans indicates transgender; IQR, Interquartile range, Yr, year; mo, months and No., number.

Table II Hormone Treatment Regimens and Doses at Each Visit for the Study Population

	Duration on hormone therapy, mo							
	0 – 3	3 – 6	6 – 9	9 – 12	12 – 24	24 – 36	36 – 48	48 – 60
Trans feminine	(N=27)	(N=22)	(N=21)	(N=26)	(N=20)	(N=13)	(N=7)	(N=7)
Oestradiol formulation								
Oral — no. (%)	20 (74.1)	18 (81.8)	20 (95.2)	22 (84.6)	17 (85.0)	10 (76.9)	5 (71.4)	6 (85.7)
mg/day, median (IQR)	2 (0)	2 (2)	4 (2)	4 (2)	4 (0)	4 (0.5)	4 (1)	3 (4)
Transdermic — no. (%)	4 (14.8)	3 (13.6)	1 (4.8)	3 (11.5)	3 (15.0)	2 (15.4)	2 (28.6)	1 (14.3)
mg/3 days, median (IQR)	50 (0)	75 (0)	100 (0)	100 (0)	100 (0)	87.5 (17.7)	100 -	100 -
Gel — no. (%)	1 (3.7)	1 (4.5)	0 -	0 -	0 -	0 -	0 -	0 -
mg/day, median (IQR)	1 -	2 -	- -	- -	- -	- -	- -	- -
Antiandrogen								
Spironolactone — no. (%)	21 (77.8)	15 (68.2)	8 (38.1)	11 (42.3)	6 (30.0)	8 (61.5)	2 (28.6)	0 -
mg/day, median (IQR)	100 (50)	100 (50)	100 (0)	100 (0)	100 (38)	100 (50)	100 (0)	- -
Cyproterone acetate — no. (%)	4 (14.8)	4 (18.2)	13 (61.9)	12 (46.2)	13 (65.0)	5 (38.5)	3 (42.9)	6 (85.7)
mg/day, median (IQR)	17.5 (34)	31.3 (77)	25 (65)	10 (11)	50 (90)	50 (45)	10 (90)	50 (53)
Leuprorelin — no. (%)	1 (3.7)	1 (4.5)	0 -	0 -	0 -	0 -	0 -	0 -
mg/12 wk, median (IQR)	22.5 -	22.5 -	- -	- -	- -	- -	- -	- -
Trans masculine	(N=49)	(N=49)	(N=36)	(N=49)	(N=30)	(N=23)	(N=22)	(N=22)
Testosterone formulation								
IM Esters — no. (%)	49 (100)	49 (100)	36 (100)	48 (98.0)	29 (96.7)	23 (100)	22 (100)	19 (86.4)
mg/4 wk, median (IQR)	250 (0)	250 (0)	250 (0)	250 (0)	250 (0)	250 (0)	250 (0)	250 (0)
IM undecanoate — no. (%)	0 -	0 -	0 -	1 (2.0)	1 (3.3)	0 -	0 -	3 (13.6)
mg/12 wk, median (IQR)	- -	- -	- -	1000 (0)	1000 (0)	- -	- -	1000 (0)
Progestogens — no. (%)	6 (12.2)	5 (10.2)	1 (2.8)	4 (8.2)	1 (3.3)	0 -	0 -	1 (4.5)

Trans indicates transgender; IQR, Interquartile range; No., number; mo, months; wk, weeks, and IM, intramuscular.

Table III Other Treatment Regimens at Each Visit for the Study Population

Other medications — no. (%)	Duration on hormone therapy, mo							
	0 – 3	3 – 6	6 – 9	9 – 12	12 – 24	24 – 36	36 – 48	48 – 60
Trans feminine	(N=27)	(N=22)	(N=21)	(N=26)	(N=20)	(N=13)	(N=7)	(N=7)
Statin — no. (%)	0 -	0 -	0 -	0 -	0 -	0 -	1 (14.3)	0 -
Beta blocker — no. (%)	1 (3.7)	0 -	0 -	0 -	0 -	0 -	0 -	0 -
ACE inhibitor — no. (%)	1 (3.7)	0 -	0 -	0 -	0 -	0 -	0 -	0 -
Trans masculine	(N=49)	(N=49)	(N=36)	(N=49)	(N=30)	(N=23)	(N=22)	(N=22)
Statin — no. (%)	1 (2.0)	2 (4.1)	0 -	3 (6.1)	0 -	0 -	1 (4.5)	1 (4.5)
Beta blocker — no. (%)	1 (2.0)	1 (2.0)	1 (2.8)	0 -	0 -	0 -	0 -	0 -

Trans indicates transgender; ACE, Angiotensin-Converting Enzyme; No., number, and mo, months.

Table IV Baseline Blood Pressure, Body Mass Index and Lipid Profile of Study Population

Characteristic	Overall (N=114)	Trans masculine (N=78)	Trans feminine (N=36)	*p* value
Blood pressure, mmHg				
Systolic mean (SD)	121.4 (11.5)	119.9 (11.4)	124.4 (11.4)	0.052
Diastolic mean (SD)	71.1 (8.5)	71.2 (8.2)	70.9 (9.3)	0.866
Systolic Category — no. (%)				
≤ 120	49 (43.0)	39 (50.)	10 (27.8)	-
120–129	35 (30.7)	23 (29.5)	12 (33.3)	-
130–139	23 (20.2)	13 (16.7)	10 (27.8)	-
≥140	7 (6.1)	3 (3.8)	4 (11.1)	-
Diastolic Category — no. (%)				
≤ 80	97 (85.1)	68 (87.2)	29 (80.6)	-
80–89	15 (13.2)	9 (11.5)	6 (16.7)	-
≥90	2 (1.8)	1 (1.3)	1 (2.8)	-
Body mass index	(N=119)	(N=81)	(N=38)	
Median (IQR)	22.86 (8.57)	24.24 (8.38)	21.58 (9.38)	0.008
Category — no. (%)				
≤18.5	10 (8.4)	3 (3.7)	7 (18.4)	-
18.5 – 24.9	63 (52.9)	42 (51.9)	21 (55.3)	-
25.0 – 29.9	22 (18.5)	16 (19.8)	6 (15.8)	-
≥30.0	24 (20.2)	20 (24.7)	4 (10.5)	-
Lipid profile, mg/dL	(N=119)	(N=78)	(N=41)	
TC, mean (SD)	167.6 (37.0)	175.9 (35.8)	152.4 (34.7)	< 0.001
LDL, mean (SD)	94.5 (32.1)	99.7 (32.2)	84.6 (29.9)	0.014
HDL, mean (SD)	54.5 (15.4)	57.8 (15.9)	48.5 (12.6)	0.001
TG, mean (SD)	103.4 (60.8)	98.9 (44.8)	112.1 (83.2)	0.347

Trans indicates transgender; IQR, Interquartile range; SD, standard deviation; TC, total cholesterol; HDL-C, High-Density Lipoprotein Cholesterol; LDL-C, Low-Density Lipoprotein Cholesterol; TG, triglycerides.

Table V Baseline Characteristics of Cohort A

Characteristic	Overall	Trans masculine	Trans feminine
	(N=107)	(N=71)	(N=36)
Age — yr, median (IQR)	22 (6.)	22 (5.)	22.5 (8.)
Category — no. (%)			
18-29	96 (89.7)	63 (88.7)	33 (91.7)
30-39	10 (9.4)	7 (9.9)	3 (8.3)
≥40	1 (0.9)	1 (1.4)	- -
Education — no. (%)	(N=88)	(N=57)	(N=31)
Basic education - 3rd cycle	16 (18.2)	12 (21.1)	4 (12.9)
Secondary education	50 (56.8)	35 (61.4)	15 (48.4)
Licentiate Degree	20 (22.7)	10 (17.5)	10 (32.3)
Master's Degree	2 (2.3)	- -	2 (6.5)
Lifestyle behaviours — no. (%)			
Alcohol use	(N=107)	(N=71)	(N=36)
Sporadic	33 (30.8)	26 (36.6)	7 (19.4)
Frequent	3 (2.8)	2 (2.8)	1 (2.8)
Tobacco use	(N=107)	(N=71)	(N=36)
Current	42 (39.3)	28 (39.4)	14 (38.9)
Previous	3 (2.8)	3 (4.2)	- -
Substance use disorder	(N=107)	(N=71)	(N=36)
Non-injectable drugs (current)	14 (13.1)	7 (9.9)	7 (19.4)

Trans indicates transgender; IQR, Interquartile range, Yr, year, and No., number.

Table VI Mean Blood Pressure, Lipid Profile, and BMI of Cohort A

	Duration on hormone therapy, mo									
	0		3		6		9		12	
Trans feminine	(N=29)		(N=24)		(N=19)		(N=20)		(N=24)	
BMI — kg/m^2, mean (SD)	22.8	(5.8)	22.8	(5.9)	23.3	(5.7)	20.0	(5.1)	23.8	(5.6)
SBP — mmHg, mean (SD)	123.5	(11.1)	123.1	(10.8)	121.4	(9.0)	124.5	(9.3)	124.4	(9.8)
DBP — mmHg, mean (SD)	71.9	(8.5)	71.0	(10.3)	70.6	(6.9)	69.6	(7.0)	71.6	(7.1)
TC — mg/dL, mean (SD)	150.3	(36.4)	153.6	(40.7)	157.8	(35.8)	157.1	(36.0)	146.4	(28.2)
LDL — mg/dL, mean (SD)	81.6	(30.2)	85.4	(34.4)	91.0	(25.3)	85.9	(32.4)	80.1	(25.8)
HDL — mg/dL, mean (SD)	49.2	(13.7)	51.5	(12.5)	48.2	(14.4)	53.9	(14.9)	50.4	(10.3)
TG — mg/dL, median (IQR)	77	(62.)	95.5	(65.)	104.5	(73.)	79	(31.)	63.5	(53.)
Trans masculine	(N=57)		(N=45)		(N=49)		(N=32)		(N=41)	
BMI — kg/m^2, mean (SD)	23.6	(8.9)	24.2	(9.2)	25.4	(11.4)	23.7	(9.2)	24.2	(8.3)
SBP — mmHg, mean (SD)	120.0	(10.8)	120.4	(11.5)	125	(14.)	122.2	(12.3)	123.1	(12.6)
DBP — mmHg, mean (SD)	71.1	(8.5)	68.9	(9.7)	70.2	(8.7)	68.9	(9.6)	70.5	(9.9)
TC — mg/dL, mean (SD)	176.0	(37.4)	170.4	(31.5)	171.1	(36.0)	1667.3	(33.7)	167.5	(31.0)
LDL — mg/dL, mean (SD)	101.7	(33.9)	102.4	(30.0)	102.9	(32.9.)	93.9	(32.0)	100.4	(29.6)
HDL — mg/dL, mean (SD)	55.4	(12.6)	47.4	(9.7)	46.1	(10.2)	51.0	(11.2)	45.9	(10.5)
TG — mg/dL, median (IQR)	88.5	(53.)	95	(57.)	104	(87.)	93	(72.)	102.5	(56.)

Trans indicates transgender; IQR, Interquartile range; SD, standard deviation; BMI, Body Mass Index, SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; TC, total cholesterol; LDL-C, Low-Density Lipoprotein Cholesterol; HDL-C, High-Density Lipoprotein Cholesterol; TG, triglycerides.

Table VII Variation in Blood Pressure, Lipid Profile, and BMI Compared to Baseline in Cohort A

Follow-up months since baseline	Systolic Blood Pressure			Diastolic Blood Pressure		
	Mean Difference	(95% CI)	*p* value	Mean Difference	(95% CI)	*p* value
TRANS FEMININE						
Baseline - 3mo	-0.98	(-5.57 to 3.62)	1.000	-0.38	(-4.32 to 3.56)	1.000
Baseline - 6mo	-3.35	(-9.98 to 3.29)	1.000	-0.94	(-5.37 to 3.50)	1.000
Baseline - 9mo	-2.11	(-8.44 to 4.22)	1.000	-2.04	(-7.37 to 3.28)	1.000
Baseline - 12mo	-	-	-	0.80	(-3.61 to 5.21)	1.000
TRANS MASCULINE						
Baseline - 3mo	-0.23	(-3,38 to 2.92)	1.000	-2.74	(-6.76 to 1,27)	0.519
Baseline - 6mo	3.12	(-1.01 to 7.26)	0.263	-1.47	(-4.73 to 1.80)	1.000
Baseline - 9mo	1.71	(-3.15 to 6.58)	1.000	-2.42	(-7.18 to 2.33)	1.000
Baseline - 12mo	-	-	-	-0.93	(-4.23 to 2.37)	1.000
Follow-up months since baseline	**Total Cholesterol**			**Ln (TG)**		
	Mean Difference	**(95% CI)**	***p* value**	**Mean Difference**	**(95% CI)**	***p* value**
TRANS FEMININE						
Baseline - 3mo	3.49	(-8.39 to 15.38)	1.000	0.044	(-0.14 to 0.23)	1.000
Baseline - 6mo	3.58	(-10.47 to 17.62)	1.000	-0.016	(-0.24 to 0.21)	1.000
Baseline - 9mo	2.79	(-9.64 to 15.21)	1.000	-0.146	(-0.45 to 0.16)	1.000
Baseline - 12mo	-2.13	(-15.64 to 11.38)	1.000	-0.24	(-0.51 to 0.03)	0.133
TRANS MASCULINE						
Baseline - 3mo	-8.23	(-19.38 to 2.92)	0.342	0.06	(-0.10 to 0.22)	1.000
Baseline - 6mo	-10.10	(-21.80 to 1.61)	0.149	0.22	(0.018 to 0.43)	0.024
Baseline - 9mo	-7.71	(-18.49 to 3.08)	0.361	0.17	(-0.04 to 0.39)	0.213
Baseline - 12mo	-9.76	(-22.91 to 3.38)	0.342	0.11	(-0.08 to 0.30)	0.831
Follow-up months since baseline	**LDL Cholesterol**			**HDL Cholesterol**		
	Mean Difference	**(95% CI)**	***p* value**	**Mean Difference**	**(95% CI)**	***p* value**
TRANS FEMININE						
Baseline - 3mo	3.44	(-8.04 to 14.92)	1.000	3.03	(-1.64 to 7.70)	0.635
Baseline - 6mo	2.30	(-9.65 to 14.25)	1.000	1.93	(-2.85 to 6.71)	1.000
Baseline - 9mo	3.60	(-8.98 to 16.18)	1.000	3.77	(-2.73 to 10.27)	0.916
Baseline - 12mo	-1.68	(-13.36 to 10.00)	1.000	2.44	(-3.78 to 8.66)	1.000
TRANS MASCULINE						
Baseline - 3mo	-0.23	(-7.58 to 7.12)	1.000	-7.93	(-11.27 to -4.58)	<0.001
Baseline - 6mo	-2.99	(-11.39 to 5.41)	1.000	-9.72	(-13.37 to -6.06)	<0.001
Baseline - 9mo	-2.79	(-11.56 to 5.98)	1.000	-7.40	(-11.70 to -3.10)	<0.001
Baseline - 12mo	-0.19	(-8.27 to 7.88)	1.000	-10.47	(-15.06 to -5.88)	<0.001
Follow-up months since baseline	**Body Mass Index, kg/m2**					
	Mean Difference	**(95% CI)**	***p* value**			
TRANS FEMININE						
Baseline - 3mo	-0.13	(-0.78 to 0.51)	1.000			
Baseline - 6mo	0.05	(-0.68 to 0.77)	1.000			
Baseline - 9mo	-0.06	(-0.91 to 0.8)	1.000			
Baseline - 12mo	0.83	(-0.59 to 2.24)	0.783			
TRANS MASCULINE						
Baseline - 3mo	0.99	(0.37 to 1.60)	0			
Baseline - 6mo	1.01	(0.3 to 1.71)	0.001			
Baseline - 9mo	1.01	(0.16 to 1,87)	0.01			
Baseline - 12mo	0.70	(-0.33 to 1,73)	0.442			

Trans indicates transgender; CI, Confidence Interval; LDL, Low-Density Lipoprotein; HDL, High-Density Lipoprotein; Ln (TG), natural logarithm of triglycerides.

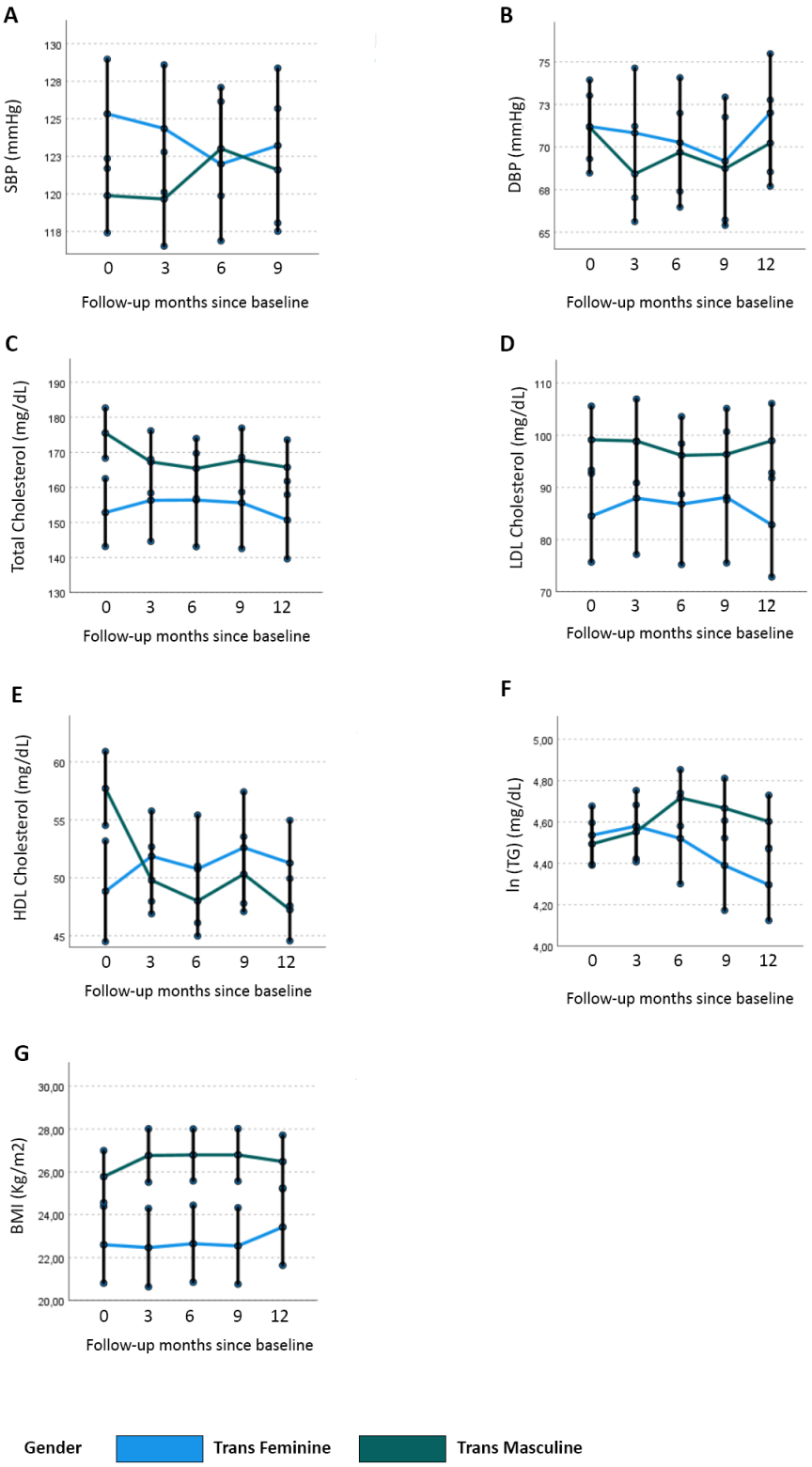

Figure 1. Blood pressure, Lipid Profile and BMI across time in Cohort A - (A) Systolic Blood Pressure (SBP) and **(B)** Diastolic Blood Pressure (DBP), **(C)** Total Cholesterol, **(D)**, Low-Density Lipoprotein (LDL) Cholesterol, **(E)**, High-Density Lipoprotein (HDL) Cholesterol, **(F)** natural logarithm of Triglycerides [ln (TG)], **(G)** Body Mass Index (BMI) across twelve months since baseline by gender

References

1. Winter S, Diamond M, Green J, et al. Transgender people: health at the margins of society. *The Lancet*. 2016/07/23/ 2016;388(10042):390-400. doi:https://doi.org/10.1016/S0140-6736(16)00683-8
2. Dubin SN, Nolan IT, Streed CG, Jr., Greene RE, Radix AE, Morrison SD. Transgender health care: improving medical students' and residents' training and awareness. *Adv Med Educ Pract*. 2018/5 2018;9:377-391. doi:10.2147/amep.s147183
3. Karalexi MA, Frisell T, Cnattingius S, et al. Cardiovascular outcomes in transgender individuals in Sweden after initiation of gender-affirming hormone therapy. *European Journal of Preventive Cardiology*. 2022;29(15):2017-2026. doi:10.1093/eurjpc/zwac133
4. Goodman M, Adams N, Corneil T, Kreukels B, Motmans J, Coleman E. Size and Distribution of Transgender and Gender Nonconforming Populations: A Narrative Review. *Endocrinology and Metabolism Clinics of North America*. 2019/06/01/ 2019;48(2):303-321. doi:https://doi.org/10.1016/j.ecl.2019.01.001
5. Carmo D. Quase 70 menores mudaram de género e de nome no registo civil neste ano. Público; 2023.
6. Reed GM, Drescher J, Krueger RB, et al. Disorders related to sexuality and gender identity in the ICD-11: revising the ICD-10 classification based on current scientific evidence, best clinical practices, and human rights considerations. *World Psychiatry*. 2016/10 2016;15(3):205-221. doi:10.1002/wps.20354
7. Organization WH. International statistical classification of diseases and related health problems. https://icd.who.int/browse11/l-m/en
8. White Hughto JM, Reisner SL. A systematic review of the effects of hormone therapy on psychological functioning and quality of life in transgender individuals. *Transgend Health*. 2016/1 2016;1(1):21-31. doi:10.1089/trgh.2015.0008
9. de Blok CJM, Wiepjes CM, van Velzen DM, et al. Mortality trends over five decades in adult transgender people receiving hormone treatment: a report from the Amsterdam cohort of gender dysphoria. *The Lancet Diabetes & Endocrinology*. 2021;9(10):663-670. doi:10.1016/S2213-8587(21)00185-6
10. Braun H, Nash R, Tangpricha V, Brockman J, Ward K, Goodman M. Cancer in Transgender People: Evidence and Methodological Considerations. *Epidemiologic Reviews*. 2017;39(1):93-107. doi:10.1093/epirev/mxw003
11. Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*. 2017;102(11):3869-3903. doi:10.1210/jc.2017-01658
12. Mikkola TS, Gissler M, Merikukka M, Tuomikoski P, Ylikorkala O. Sex Differences in Age-Related Cardiovascular Mortality. *PLOS ONE*. 2013;8(5):e63347. doi:10.1371/journal.pone.0063347
13. Martinez C, Rikhi R, Haque T, et al. Gender Identity, Hormone Therapy, and Cardiovascular Disease Risk. *Current Problems in Cardiology*. 2020/05/01/ 2020;45(5):100396. doi:https://doi.org/10.1016/j.cpcardiol.2018.09.003
14. Streed CG, Harfouch O, Marvel F, Blumenthal RS, Martin SS, Mukherjee M. Cardiovascular Disease Among Transgender Adults Receiving Hormone Therapy. *Annals of Internal Medicine*. 2017/08/15 2017;167(4):256-267. doi:10.7326/M17-0577
15. Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*. 2014/07/01/ 2014;63(25, Part B):2935-2959. doi:https://doi.org/10.1016/j.jacc.2013.11.005
16. van Zijverden LM, Wiepjes CM, van Diemen JJK, Thijs A, den Heijer M. Cardiovascular disease in transgender people: a systematic review and meta-analysis. *European Journal of Endocrinology*. 2024;190(2):S13-S24. doi:10.1093/ejendo/lvad170

17. Rossouw JE, Manson JE, Kaunitz AM, Anderson GL. Lessons Learned From the Women's Health Initiative Trials of Menopausal Hormone Therapy. *Obstetrics & Gynecology*. 2013;121(1):172-176. doi:http://10.1097/AOG.0b013e31827a08c8
18. van Velzen DM, Paldino A, Klaver M, et al. Cardiometabolic Effects of Testosterone in Transmen and Estrogen Plus Cyproterone Acetate in Transwomen. *The Journal of Clinical Endocrinology & Metabolism*. 2019;104(6):1937-1947. doi:10.1210/jc.2018-02138
19. Klaver M, van Velzen D, de Blok C, et al. Change in Visceral Fat and Total Body Fat and the Effect on Cardiometabolic Risk Factors During Transgender Hormone Therapy. *The Journal of Clinical Endocrinology & Metabolism*. 2022;107(1):e153-e164. doi:10.1210/clinem/dgab616
20. Klaver M, de Blok CJM, Wiepjes CM, et al. Changes in regional body fat, lean body mass and body shape in trans persons using cross-sex hormonal therapy: results from a multicenter prospective study. *European Journal of Endocrinology*. 2018;178(2):163-171. doi:10.1530/EJE-17-0496
21. Lagraauw HM, Kuiper J, Bot I. Acute and chronic psychological stress as risk factors for cardiovascular disease: Insights gained from epidemiological, clinical and experimental studies. *Brain, Behavior, and Immunity*. 2015/11/01/ 2015;50:18-30. doi:https://doi.org/10.1016/j.bbi.2015.08.007
22. Parent MC, Arriaga AS, Gobble T, Wille L. Stress and substance use among sexual and gender minority individuals across the lifespan. *Neurobiology of Stress*. 2019/02/01/ 2019;10:100146. doi:https://doi.org/10.1016/j.ynstr.2018.100146
23. Denby KJ, Cho L, Toljan K, Patil M, Ferrando CA. Assessment of Cardiovascular Risk in Transgender Patients Presenting for Gender-Affirming Care. *The American Journal of Medicine*. 2021;134(8):1002-1008. doi:10.1016/j.amjmed.2021.02.031
24. Balsa C, Vital C, Urbano C. V Inquérito Nacional ao Consumo de Substâncias Psicoativas na População Geral, Portugal 2022. Relatório final. SICAD – Serviço de Intervenção nos Comportamentos Aditivos e nas Dependências; 2023.
25. Maraka S, Singh Ospina N, Rodriguez-Gutierrez R, et al. Sex Steroids and Cardiovascular Outcomes in Transgender Individuals: A Systematic Review and Meta-Analysis. *The Journal of Clinical Endocrinology & Metabolism*. 2017;102(11):3914-3923. doi:10.1210/jc.2017-01643
26. Quintela-Castro FCdA, Pereira TSS, Alves DB, et al. Lipid profile and risk of cardiovascular disease in adult transgender men receiving cross-sex hormone therapy: a systematic review. *Nutrition Reviews*. 2023;81(10):1310-1320. doi:10.1093/nutrit/nuad003
27. Velho I, Fighera TM, Ziegelmann PK, Spritzer PM. Effects of testosterone therapy on BMI, blood pressure, and laboratory profile of transgender men: a systematic review. *Andrology*. 2017;5(5):881-888. doi:https://doi.org/10.1111/andr.12382
28. Suppakitjanusant P, Ji Y, Stevenson MO, et al. Effects of gender affirming hormone therapy on body mass index in transgender individuals: A longitudinal cohort study. *Journal of Clinical & Translational Endocrinology*. 2020/09/01/ 2020;21:100230. doi:https://doi.org/10.1016/j.jcte.2020.100230
29. Banks K, Kyinn M, Leemaqz SY, Sarkodie E, Goldstein D, Irwig MS. Blood Pressure Effects of Gender-Affirming Hormone Therapy in Transgender and Gender-Diverse Adults. *Hypertension*. 2021;77(6):2066-2074. doi:doi:10.1161/HYPERTENSIONAHA.120.16839

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Exma. Sra. Francisca Neto Palma
Estudante do ICBAS

ASSUNTO: Trabalho Académico - MIM - **"Impacto da terapêutica hormonal de afirmação de género nos fatores de risco cardiovascular em indivíduos transgénero"** - N/ REF.ª 2023.241(203-DEFI/193-CE)

O Conselho de Administração do Santo António, na reunião de 10 de janeiro de 2024, emitiu a seguinte Deliberação: "Autorizado" para a realização do estudo acima mencionado, a realizar no Serviço de Endocrinologia desta Instituição e tendo como Investigador Principal Francisca Neto Palma, estudante do ICBAS.
O estudo foi previamente analisado pela Comissão de Ética do Santo António |ICBAS, pelo Gabinete de Projetos de Investigação do CAC, pela Direção do Centro Académico Clínico ICBAS|CHUdSA e pelo Presidente do Conselho de Administração, tendo obtido parecer favorável.

Cumprimentos,

Assinado por: **Cláudia Alexandra Oliveira Santos**
Num. de Identificação: 11089889
Data: 2024.01.11 10:12:15+00'00'

CHAVE MÓVEL

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