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ORIGINAL ARTICLE

Preconceptional maternal hyperandrogenism and metabolic syndrome risk in male offspring: a long-term population-based study

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Abstract

Purpose There is limited research on the effects of maternal hyperandrogenism (MHA) on cardiometabolic risk factors in male offspring. We aimed to compare the risk of metabolic syndrome (MetS) in sons of women with preconceptional hyperandrogenism (HA) to those of non-HA women in later life.

Methods Using data obtained from the Tehran Lipid and Glucose Cohort Study, with an average of 20 years follow-up, 1913 sons were divided into two groups based on their MHA status, sons with MHA (n = 523) and sons without MHA (controls n = 1390). The study groups were monitored from the baseline until either the incidence of events, censoring, or the end of the study period, depending on which occurred first. Age-scaled unadjusted and adjusted Cox regression models were utilized to evaluate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between MHA and MetS in their sons.

Results There was no significant association between MHA and HR of MetS in sons with MHA compared to controls, even after adjustment (unadjusted HR (95% CI) 0.94 (0.80–1.11), $P = 0.5$) and (adjusted HR (95% CI) 0.98 (0.81–1.18), $P = 0.8$). Sons with MHA showed a HR of 1.35 for developing high fasting blood sugar compared to controls (unadjusted HR (95% CI) 1.35 (1.01–1.81), $P = 0.04$), however, after adjustment this association did not remain significant (adjusted HR (95% CI) 1.25 (0.90–1.74), $P = 0.1$).

Conclusion The results suggest that preconceptional MHA doesn't increase the risk of developing MetS in sons in later life. According to this suggestion, preconceptional MHA may not have long-term metabolic consequences in male offspring.

Keywords Fetal programming · Maternal hyperandrogenism · Metabolic syndrome (MetS) · Son · Tehran Lipid and Glucose Study (TLGS)

Introduction

One of the most significant causes of disability and mortality worldwide is cardiovascular diseases (CVDs), which are more prevalent in men than in women. Metabolic syndrome (MetS), a group of metabolic disorders, is considered a risk factor for CVDs. Patients with MetS have a higher risk of death, stroke, and heart attacks compared to those without MetS [1]. The diagnosis of MetS requires the presence of at least three out of the following criteria including hypertension, impaired fasting glucose (impaired glucose tolerance/insulin resistance (IR)), central adiposity, decreased high-density lipoprotein cholesterol (HDL-C), and elevated triglycerides. The prevalence of MetS is increasing globally, even among children and young adults [1].

An adverse intrauterine environment may affect organ growth and development, potentially leading to diseases in later life. Evidence supports that some diseases, such as vascular diseases, hypertension, MetS, and type 2 diabetes mellitus (T2DM), may be programmed during the early stages of fetal development [2].

Excess androgen exposure during fetal development has been suggested as a factor contributing to metabolic diseases in later life. Evidence involving both animals and humans indicates that maternal androgen excess can result

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in metabolic disorders, such as impaired insulin secretion, IR, glucose intolerance, T2DM, dyslipidemia, and hypertension in offspring in later life [3–6]. However, most studies on the cardiometabolic effects of maternal hyperandrogenism (MHA) (androgen excess) have primarily focused on female offspring, with limited research on male offspring [3, 5–8].

Aim

Therefore, in this long-term population-based follow-up study, we aimed to examine the risk of MetS in sons of women with preconceptional hyperandrogenism (HA) compared to sons of women without HA in their later life.

Materials and methods

Study design

Tehran Lipid and Glucose Study (TLGS) is an ongoing prospective study with more than 2 decades of follow-up initiated in 1998 to explore the prevalence of non-communicable diseases risk factors among 15,005 males and females aged ≥ 3 years who were followed at 3-year intervals (seven phases including 6 follow-ups in addition to baseline). Follow-up included a general physical examination, demographic, anthropometric, and metabolic assessments, as well as blood sampling. The TLGS details have been published before [9]. For the present study, we used specific data collected in the context of reproductive aspects of TLGS the most detailed data was reported before [10].

Study population

From the total participants (mothers and sons) (n = 3512), all women who had defined HA status with at least one son were assessed to participate in the present study. We identified 1420 mothers with defined HA status and 2092 sons (Those who were not taking any medication that could affect their cardiometabolic parameters (blood sugar-lowering, blood lipid-lowering, and antihypertensive medications, as well as medications for weight loss/gain)). Sons who did not have at least one follow-up were excluded (n = 179). Finally, the total number of 1913 sons with at least one follow-up visit was divided into two groups including:

1. Sons of women with HA (sons with MHA) (n = 523)
2. Sons of women without HA (sons without MHA) (controls) (n = 1390).

The study's flowchart is shown in Fig. 1. From baseline to the first event, censoring, or end of follow-up, we monitored all sons in both groups.

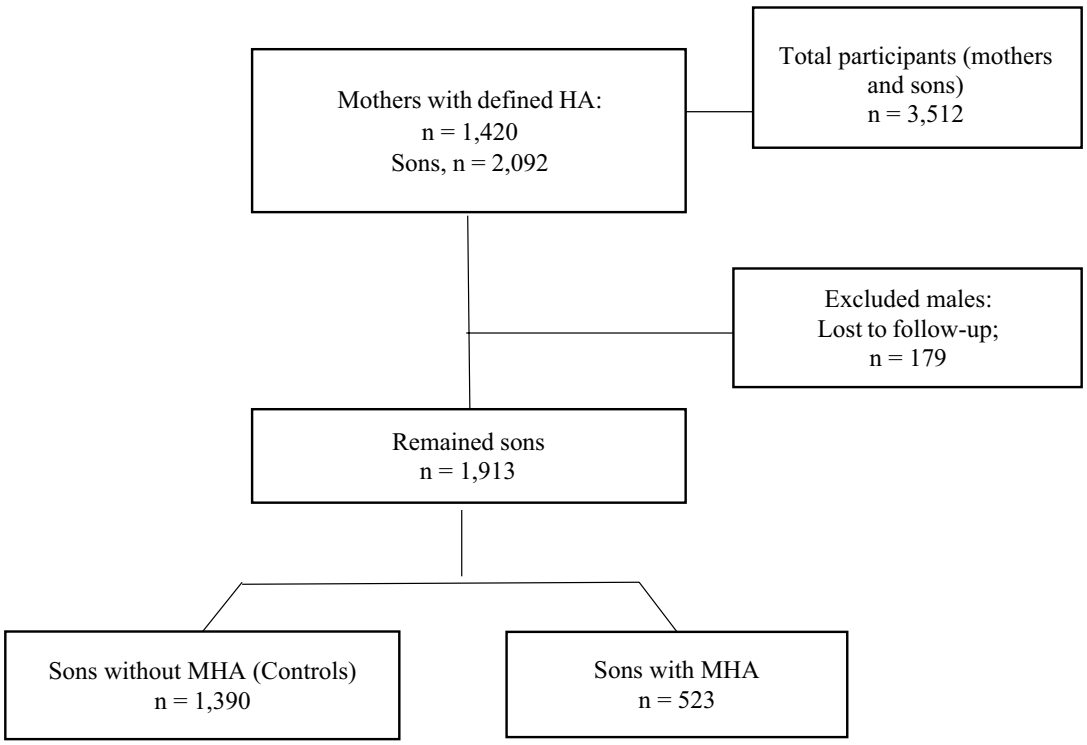

Fig. 1 Flowchart of the study, *HA* hyperandrogenism, *MHA* maternal hyperandrogenism

Measurements

A standard questionnaire was used during the face-to-face interview to collect all demographic data and family medical history. The educational level was categorized into 2 groups: those with formal education lasting less than 12 years, and those with greater than 12 years of education. During the interviews, a questionnaire was administered to assess reproductive variables, with a particular focus on the regularity of menstrual cycles, gynecological history, HA symptoms and family history of irregular menstrual cycles by trained midwives under the supervision of a gynecologist.

Data collection included the following clinical parameters body mass index (BMI), waist circumference (WC), systolic (SBP) and diastolic blood pressure (DBP), fasting blood sugar (FBS), HDL-C, triglyceride (TG), dehydroepiandrosterone sulfate (DHEAS), total testosterone (TT), androstenedione (A4) levels, and sex hormone-binding globulin (SHBG). All measurements were carried out by the standard protocol of the TLGS.

Using the modifiable activity questionnaire, participants were asked if they had physical activity in the past 12 months. Those who performed over 600 metabolic equivalent task minutes per week were classified into the moderate to high physical activity group. Subsequently, a blood sample was taken from each participant after an overnight fast. After centrifuging blood samples, the sera were separated and stored at −80 °C for subsequent measurements. The measurement of FBS was carried out using the glucose oxidase method. HDL-C was measured after precipitation of the apolipoprotein B (APO B)-containing lipoproteins with phosphotungstic acid. Using glycerol phosphate oxidase, TG was measured. Both intra- and inter-assay coefficient variation (CVs) were below 3% for FBS, HDL-C, and TG. Related kits were utilized for the analyses (Pars Azmon Inc., Tehran, Iran) and a selectra analyzer (Vital Scientific, Spankeren, Netherlands).

Maternal hormonal assessment includes Enzyme immunoassay (EIA) (Diagnostic Biochem Canada 1 Co. Ontario, Canada) was performed to measure DHEAS, TT, and A4 levels. Immunoenzymometric assay (IEMA) was used to measure SHBG (Mercodia, Uppsala, Sweden). A Sunrise ELISA Reader (Tecan Co., Salzburg, Austria) was used to perform all enzyme-linked immunosorbent assays (ELISAs). The free androgen index (FAI) was estimated using the formula below TT (nmol/L) × 100/SHBG (nmol/L). Inter-and intra-assay coefficients of variations (CVs) for all hormones were found to be below 7%.

Definition of exposure and outcome terms

Exposure

Hirsutism, acne, or androgenic alopecia are the characteristics that define clinical hyperandrogenism (CH) [6]. The modified Ferriman-Gallwey score was used to determine hirsutism (mF-G ≥ 8), and acne grading was determined based on its number, type, and distribution into four grades (mild, moderate, moderate to severe, severe) [6]. This study included women who had moderate/severe acne. Female hair loss was categorized into three severity levels, from mild to severe (I, II, III). In the present study, androgenic alopecia was defined by moderate to severe hair loss on the temples or diffuse thinning on the crown.

Biochemical hyperandrogenism (BH) was evaluated as an elevated serum levels of one or more androgens above the 95th percentile, including TT, A4, DHEAS, and free androgen index (FAI), determined in the selected healthy non-hirsute eumenorrheic women in the study population; specifically, the upper normal limits were 0.89 ng/mL, 2.9 ng/mL, 179 µg/dL and 5.39 for TT, A4, DHEAS and FAI, respectively [11].

Women who had regular and spontaneous menstrual cycles without CH and/or BH were considered control mothers (women without HA). The sons of women who did not have HA were considered as a control group.

Outcomes

In children and adolescents, MetS was defined according to the definition proposed by Cook et al. as 3 or more of the following:

(1) WC ≥ 90th percentile for age and sex according to national reference curves, (2) SBP and DBP ≥ 90th percentile for sex, age, and height based on the National Heart, Lung, and Blood Institute's recommended cut-off points, (3) FBS ≥ 100 mg/dL according to the recommendations of the American Diabetes Association, (4) fasting TGs ≥ 110 mg/dL, (5) HDL-C < 40 mg/dL [12].

MetS in adults (age > 18 years) was defined by having at least three of the criteria listed below. (1) elevated FBS (≥ 100 mg/dL or drug treatment), (2) elevated fasting TGs (≥ 150 mg/dL or drug treatment), (3) reduced fasting HDL-C (< 40 mg/dL or drug treatment), (4) elevated BP (≥ 130/85 mmHg or treatment with antihypertensive medications), (5) elevated WC (abdominal obesity) (≥ 89 cm) [12].

In this study, we also considered each component of MetS as an outcome variable.

Statistical analysis

Our study had the power of 81% to detect a HR of 1.30 for the effects of MHA on MetS at a 0.05 significance level, after adjusting for an expected event rate of 25% for MetS.

The one-sample Kolmogorov–Smirnov test was used to check the normality of continuous variables; and were presented as mean (standard deviation) if they had a normal distribution or median with inter-quartile range (IQ25-75) for variables with skewed distribution. Numbers and percentages were used to present categorical variables. Demographic and clinical characteristics of sons were compared according to their MHA status using the student's t-test or χ^2 test for continuous or categorical data, respectively. The Mann–Whitney test was applied to compare variables with skewed distribution.

The HRs and 95% confidence intervals (CIs) for the association of MHA with MetS and its components in sons were evaluated using the Cox regression model. The event date was considered as when the intended outcome occurred for the first time, and age at the event was computed. We used an attained age scale where the primary time variable in the Cox model is defined by study son's age at entry into the study (birth) and the age at which they experience an event or their follow-up is censored. The use of the attained age scale provides the most flexible control for age effects while avoiding the need to include an effect of age [13].

The multivariate Cox model included potential confounding factors including BMI_SDS (body mass index_standard deviation score), physical activity, and education status. Both unadjusted and adjusted cumulative hazard functions were also plotted. Missing data for repeated measurement data was imputed using the multiple imputation method considering the time trend of the variable with the Amelia package in R [14].

Furthermore, an adjusted generalized estimating equations method (GEE) was applied to investigate longitudinal trends of MetS components, including WC, HDL-C, TG, FBS, SBP, and DBP in study groups (sons with MHA and controls). It accounts for correlations within subjects through a working correlation matrix. It enables researchers to accurately estimate the effect size in case of incomplete data (missing variables in some repeated measures), which is common in cohort studies. The interaction between the MHA status and each phase of the study was checked; for this purpose, we entered the cross-product term (interaction term) in the model including both groups of study (sons with MHA and controls) and this analysis was performed on data of the first visit. An exchangeable working correlation matrix that accounts for correlations within subjects was implemented. All individuals were required to have data on at least one of the seven visits. Predictors were: time (follow-up years), MHA status, and an interaction of these two (follow-up years × MHA status).

Statistical analysis was performed using the software package STATA (version 13; STATA Inc., College station, TX, USA) and R version 4.0.3 the significance level was set at $P < 0.05$.

Results

After identifying 1420 mothers with defined HA status, 1913 eligible sons including 523 (27.3%) sons with MHA and 1390 (72.7%) sons without MHA as controls were recruited. Table 1 shows the characteristics of mothers and their sons according to MHA status. The mean ± SD of age at first visit for sons with MHA and controls was 11.12 ± 6.42 and 12.85 ± 7.50 years, respectively ($P < 0.001$). Sons with MHA and controls reached the mean age of 27.48 ± 8.58 and 29.19 ± 9.42 years at last follow-up, respectively ($P < 0.001$). Moreover, the mean ± SD of BMI at first visit for sons with MHA and controls was 18.5 ± 4.8 kg/m^2 and 19.3 ± 4.8 kg/m^2, respectively ($P < 0.001$). The percentage of moderate to high level physical activity at last follow-up for sons with MHA and controls was 52.9% and 46.2%, respectively ($P = 0.01$).

Figure 2 presents differences in the cumulative hazard curves for MetS according to the MHA status of sons.

Table 2 presents the results of Cox regression analysis regarding the association between the MHA and HR of MetS in their sons. There was no significant association between MHA and developing MetS in sons of these women compared to controls (HR (95% CI) 0.94 (0.80–1.11)), ($P = 0.5$) the result remained not significant after adjusting for potential confounders, including BMI_SDS, physical activity, and education status (HR (95% CI) 0.98 (0.81–1.18)), ($P = 0.8$)). The results of Cox regression analysis regarding the association between the maternal clinical hyperandrogenism (MCH) and HR of MetS in their sons are presented in Table 2. There was no significant association between MCH and developing MetS in sons of these women compared to controls (HR (95% CI), 1.01 (0.55– 1.87)), ($P = 0.9$); the result remained not significant after adjusting for potential confounders (HR (95% CI) 1.11 (0.56–2.23)), ($P = 0.8$)). Additionally, Table 2 shows the results of Cox regression analysis regarding the association between the maternal biochemical hyperandrogenism (MBH) and HR of MetS in their sons. There was no significant association between MBH and developing MetS in sons of these women compared to controls (HR (95% CI) 1.02 (0.74–1.41)), ($P = 0.8$); the result remained not significant after adjusting for potential confounders (HR (95% CI) 0.91 (0.64–1.30)), ($P = 0.6$)).

Table 3 summarizes the results of Cox regression analysis regarding the association between the MHA and HRs

Table 1 Characteristics of women (mothers) and their sons according to maternal hyperandrogenism (MHA) status

Mother's characteristics	Women with preconceptional HA (n = 368)	Women without HA (n = 1052)	*P*
Age at delivery (years)	23.8 (6.9)	22.2 (9.1)	**0.003**
Smoking history (past and current), n (%)	58 (15.8)	236 (22.4)	**0.01**
Parity	3.4 (2.5)	3.4 (1.0.19)	0.8
Mode of delivery (cesarean), n (%)	62 (16.8)	110 (10.5)	0.1
Education (diploma and upper), n (%)	287 (78)	782 (74.3)	0.2
T2DM, n (%)	130 (35.3)	372 (35.4)	0.9
GDM, n (%)	31 (8.4)	50 (4.7)	**0.01**
Total T (ng/mL)	0.4 (0.2, 0.75)	0.4 (0.2, 0.6)	**0.01**
SHBG (nmol/L)	46.6 (31.7, 64.0)	60.3 (46.0, 83.1)	**< 0.001**
FAI	0.97 (0.45, 1.67)	0.60 (0.3, 1.04)	**< 0.001**
DHEAS (µg/dL)	159 (89.2, 25.2)	122.8 (69.1,14.3)	**< 0.001**
A4 (ng/mL)	1.7 (1.0, 2.4)	1.1 (0.9,1.7)	**< 0.001**
Son's characteristics	Sons with MHA (n = 523)	Sons without MHA (Controls) (n = 1390)	*P*
Age at first visit (years)	11.12 (6.42)	12.85 (7.50)	**< 0.001**
Age at last follow up (years)	27.48 (8.58)	29.19 (9.42)	**< 0.001**
BMI at first visit (kg/m^2)	18.5 (4.8)	19.3 (4.8)	**< 0.001**
BMI at last follow up (kg/m^2)	25.9 (5.2)	26.4 (5.3)	0.06
Physical activity at first visit (moderate to high), n (%)	322 (64.5)	794 (59.8)	0.06
Physical activity at last follow up (moderate to high), n (%)	264 (52.9)	614 (46.2)	**0.01**
Education level at last follow up (diploma and upper), n (%)	258 (50.5)	679 (50.1)	0.8

Values are presented as mean (SD), median (interquartile range) or number (percentage) as appropriate. *P* is calculated by independent-samples *t*-test or Mann–Whitney test for continuous, and χ^2 test for categorical data as appropriate for between group comparisons

HA hyperandrogenism, *MHA* maternal hyperandrogenism, *T2DM* type 2 diabetes mellitus, *GDM* gestational diabetes mellitus, *Total T* total testosterone, *SHBG* sex hormone binding globulin, *FAI* free androgen index, *DHEAS* dehydroepiandrosterone sulfate, *A4* androstenedione, *BMI* body mass index

P value in bold signifies a statistically significant difference

of the components of MetS (high WC, low HDL, high TG, high BP, and high FBS) in study groups. Sons with MHA showed a HR of 1.35 for developing high FBS compared to controls (HR 1.35, 95% CI 1.01–1.81, $P = 0.04$), however, this association did not remain significant after adjustment (HR 1.25, 95% CI 0.90–1.74, $P = 0.1$). Table 4 and Fig. 3 **a–f** present the trends of the components of MetS during the study, according to the MHA status; the mean changes of MetS components were not significantly different between the sons with MHA and controls.

Discussion

In our population-based study with a long-term follow-up, we found that the risk of developing MetS did not increase in sons of women with HA (sons with MHA) compared to sons of women without HA in later life. This finding persisted even after accounting for CH and BH status, where no significant association was detected.

An unfavorable intrauterine milieu during critical fetal development stages can affect the embryo's growth and differentiation, and predisposes the embryo to developing chronic non-communicable diseases, such as cardiovascular, metabolic, psychiatric, and other chronic diseases in later life [15–17]. As demonstrated by the evidence, the fetal endocrine, nutritional, and metabolic milieu have been found to influence cardiometabolic risk in adulthood [18, 19]. Especially, prenatal exposure to sex steroid hormones affects disease susceptibility in later life. Recent attention has been focused on the role of the maternal androgen milieu because of the increase in environmental endocrine disruptors, which may interact with the androgen receptor and its signaling [20].

Preclinical studies suggest that exposure to high levels of androgen during fetal development can increase the risk of cardiometabolic diseases in later life. Numerous animal

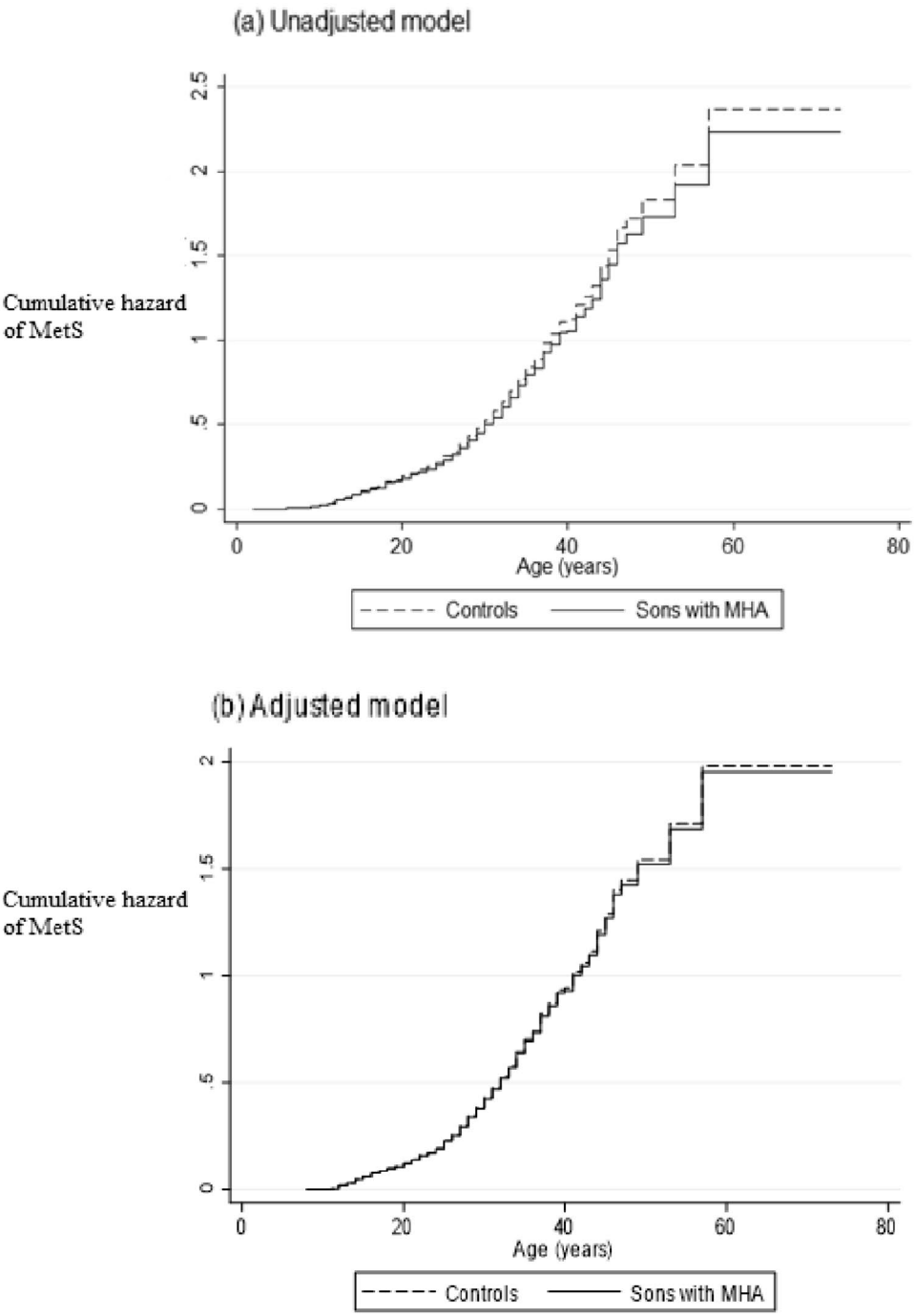

Fig. 2 Unadjusted (**a**) and adjusted (**b**) cumulative hazard plots for sons with maternal hyperandrogenism (MHA) (sons of women with hyperandrogenism) and controls. Adjusted variables are body mass index_standard deviation score (BMI_SDS), physical activity, and education status

studies have indicated that prenatal androgen excess exposure can lead to cardiometabolic changes, including IR, impaired glucose tolerance, T2DM, hypertension, adiposity and obesity in later life [21–26]. However, the mechanisms by which prenatal androgen exposure contributes to metabolic dysfunction and CVDs in humans remain unclear. Human studies on offspring prenatally exposed to androgens due to congenital adrenal hyperplasia or virilizing tumors, and also children born to women with polycystic ovary syndrome (PCOS) and HA report worse metabolic outcomes including central obesity, overweight, IR, increased serum fasting glucose and insulin levels, more prone to prediabetes, T2DM and higher body weight and body mass index Z-scores in their later life [5, 27–32]. Notably, most research on the metabolic effects of the maternal androgen excess on metabolic disorders has focused on female offspring. One study conducted on male offspring reported that maternal androgen excess is not associated with increased risk for incident MetS in adult life [33], on contrary, Risal, et al. (2023) have indicated that maternal androgen excess can

Table 2 Association between MHA, MCH, MBH and hazard ratio of MetS in their sons

Variables	MHA(ref.controls)				MCH(ref.controls)				MBH (ref controls)			
	Unadjusted model		Adjusted model		Unadjusted model		Adjusted model		Unadjustable model		Adjusted model	
	HR(95% CI)	*P*	HR(95% CI)	*P*	HR(95% CI)	*P*	HR(95% CI)	*P*	HR(95% CI)	*P*	HR(95% CI)	*P*
	0.94(0.80–1.11)	0.5	0.98(0.81–1.18)	0.8	1.01(0.55–1.87)	0.9	1.11(0.56–2.23)	0.8	1.02(0.74, 1.41)	0.8	0.91(0.64, 1.30)	0.6
BMI_SDS	–	–	1.37 (1.27–1.47)	< 0.001	–	–	1.12 (0.79–1.58)	0.5	–	–	1.28(1.11–1.48)	< 0.001
Physical activity (moderate to high)	–	–	0.91 (0.78–1.07)	0.2	–	–	1.04 (0.60–1.79)	0.8	–	–	1.03(0.74–1.44)	0.8
Education (diploma and upper)	–	–	0.81 (0.74–0.88)	< 0.001	–	–	0.83 (0.62–1.12)	0.2	–	–	0.85(0.70–1.02)	0.09

Adjusted variables are BMI_SDS, physical activity, and education status, Cox regression model was applied to assess the hazard ratios and 95% confidence intervals

MHA maternal hyperandrogenism, *MCH* maternal clinical hyperandrogenism, *MBH* maternal biochemical hyperandrogenism, *MetS* metabolic syndrome, *HR* hazard Ratio, *CI* confidence interval, *BMI_SDS* body mass index_standard deviation score, *Controls* sons without MHA, without MCH and without MBH

lead to metabolic dysfunction through the male germline [34]. Additionally, Siemienowicz, et al. (2019) found that sons of PCOS patients might be at risk for intrahepatic cholestasis-like condition and impairment of metabolic health [35].

Contrary to the present study, we reported an elevated risk of MetS in daughters of women with HA, within the same cohort [6]. This finding is consistent with the results of a cohort study conducted by Huang and colleagues [33]. This research revealed that elevated maternal androgen levels were associated with a greater likelihood of MetS in adult offspring, with a pronounced effect observed in female offspring but not for male [33]. These findings suggest that fetal programming alterations in adult cardiometabolic risk due to androgen exposure may be sex-dependent [33].

Cardiometabolic diseases such as MetS, T2DM, and hypertension are known to have sexual dimorphism in their development [36], which could be partially attributed to variations in hypothalamic neurocircuitry and the expression of androgen receptor (AR) in the hypothalamus. The hypothalamus is a critical brain region that regulates both energy and glucose homeostasis and it is influenced by testosterone, leading to differences in reproductive behavior and physiology between genders [37]. The differences in hypothalamic neurocircuitry suggest that androgen interacting with AR in the hypothalamic regions may exert different effects on metabolic functions in males and females.

There is substantial evidence supporting the alteration of cardiometabolic function in female offspring as a consequence of exposure to androgen excess during prenatal development [3, 5–8, 33]. Animal studies indicated that exposure to androgen excess during critical periods of development through increased sympathetic activity following the central testosterone action leads to increased norepinephrine turnover in white adipose tissue and metabolic dysfunction such as obesity and increased fat mass in adulthood in female animals [25, 38, 39]. Interestingly, human exposed to testosterone from their male co-twin's testes during prenatal life exhibit masculinized eating habits in later life [40]. It is well-established that males and females inherently exhibit distinct consumption patterns. Consequently, the eating behavior of females and males diverges significantly. Males tend to will consume more calorie foods, reflecting their masculine traits, while females are more likely to exhibit characteristics associated with femininity [41]. On the other hand, exposure to excess testosterone during the perinatal period leads to a decrease in food intake in male offspring, what is observed in female littermates is not the same as this [25]. These observations are in line with our findings in terms of the lack of increase in the risk of MetS in sons of women with HA, despite perceiving a higher risk of MetS in daughters who were exposed to MHA during their prenatal life, in

Table 3 Association between MHA and hazard ratio of MetS' components in their sons

Response variable	Variables	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
High WC	MHA (ref: control)	1.01 (0.88–1.16)	0.8	1.08 (0.92–1.27)	0.3
	BMI_SDS	–	–	1.37 (1.28–1.47)	< 0.001
	Physical activity (moderate to high)	–	–	0.92 (0.80–1.06)	0.2
	Education (diploma and upper)	–	–	0.77 (0.71–0.83)	< 0.001
Low HDL-C	MHA (ref: control)	0.80 (0.64–1.00)	0.05	0.83 (0.62–1.11)	0.2
	BMI_SDS	–	–	1.23 (1.1–1.39)	< 0.001
	Physical activity (moderate to high)	–	–	1.16 (0.9–1.49)	0.2
	Education (diploma and upper)	–	–	0.85 (0.74–0.99)	0.03
High TG	MHA (ref: control)	0.87 (0.73–1.04)	0.1	0.97 (0.79–1.18)	0.7
	BMI_SDS	–	–	1.12 (1.02–1.22)	0.01
	Physical activity (moderate to high)	–	–	0.97 (0.82–1.15)	0.7
	Education (diploma and upper)	–	–	0.82 (0.75–0.91)	< 0.001
High BP	MHA (ref: control)	0.82 (0.65–1.03)	0.1	0.89 (0.69–1.14)	0.3
	BMI_SDS	–	–	1.17 (1.05–1.30)	0.003
	Physical activity (moderate to high)	–	–	0.98 (0.80–1.21)	0.9
	Education (diploma and upper)	–	–	0.75 (0.67–0.84)	< 0.001
High FBS	MHA (ref: control)	1.35 (1.01–1.81)	0.04	1.25 (0.90–1.74)	0.1
	BMI_SDS	–	–	0.86 (0.73–1)	0.06
	Physical activity (moderate to high)	–	–	0.91 (0.69–1.2)	0.5
	Education (diploma and upper)	–	–	0.80 (0.69–0.93)	0.003

Adjusted variables are BMI_SDS, physical activity and education status. Reference group for MHA is controls (sons without MHA), Cox regression model was applied to assess the hazard ratios and 95% confidence intervals

MHA maternal hyperandrogenism, *MetS* metabolic syndrome, *HR* hazard ratio, *CI* confidence interval, *WC* waist circumference, *HDL-C* high-density lipoprotein-cholesterol, *TG* triglyceride, *BP* blood pressure, *FBS* fasting blood sugar, *BMI_SDS* body mass index_standard deviation score

Table 4 Estimation of the generalized estimating equation (GEE) model in sons with MHA *vs*. controls after adjusting for confounding variables

Variable		Coefficient*	95% CI	*P*
WC (cm)	MHA group	−0.85	−2.35,0.65	0.2
	Time (years)	3.24	3.10,3.39	< 0.001
	MHA group *Time	0.03	−0.22,0.29	0.7
HDL-C (mmol/L)	MHA group	0.05	0.01,0.08	< 0.01
	Time (years)	0.01	0.01,0.01	< 0.001
	MHA group *Time	−0.004	−0.01,0.002	0.2
TG (mmol/L)	MHA group	−0.16	−0.31,−0.01	0.03
	Time (years)	0.09	0.08,0.10	< 0.001
	MHA group *Time	0.01	−0.01,0.03	0.3
SBP (mmHg)	MHA group	0.10	−1.73,1.95	0.9
	Time (years)	0.95	0.77,1.13	< 0.001
	MHA group *Time	−0.17	−0.5,0.14	0.2
DBP (mmHg)	MHA group	0.19	−1.23,1.62	0.7
	Time (years)	1.57	1.43,1.71	< 0.001
	MHA group *Time	−0.11	−0.37,0.14	0.3
FBS (mmol/L)	MHA group	0.05	−0.007,0.12	0.08
	Time (years)	0.04	0.03,0.04	< 0.001
	MHA group *Time	−0.005	−0.01,0.005	0.3

Adjusted variables are BMI_SDS (body mass index_standard deviation score), physical activity, and education status. Reference group for MHA is controls (sons without MHA)

MHA maternal hyperandrogenism, *CI* confidence interval, *WC* waist circumference, *HDL-C* high-density lipoprotein-cholesterol, *TG* triglyceride, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FBS* fasting blood sugar

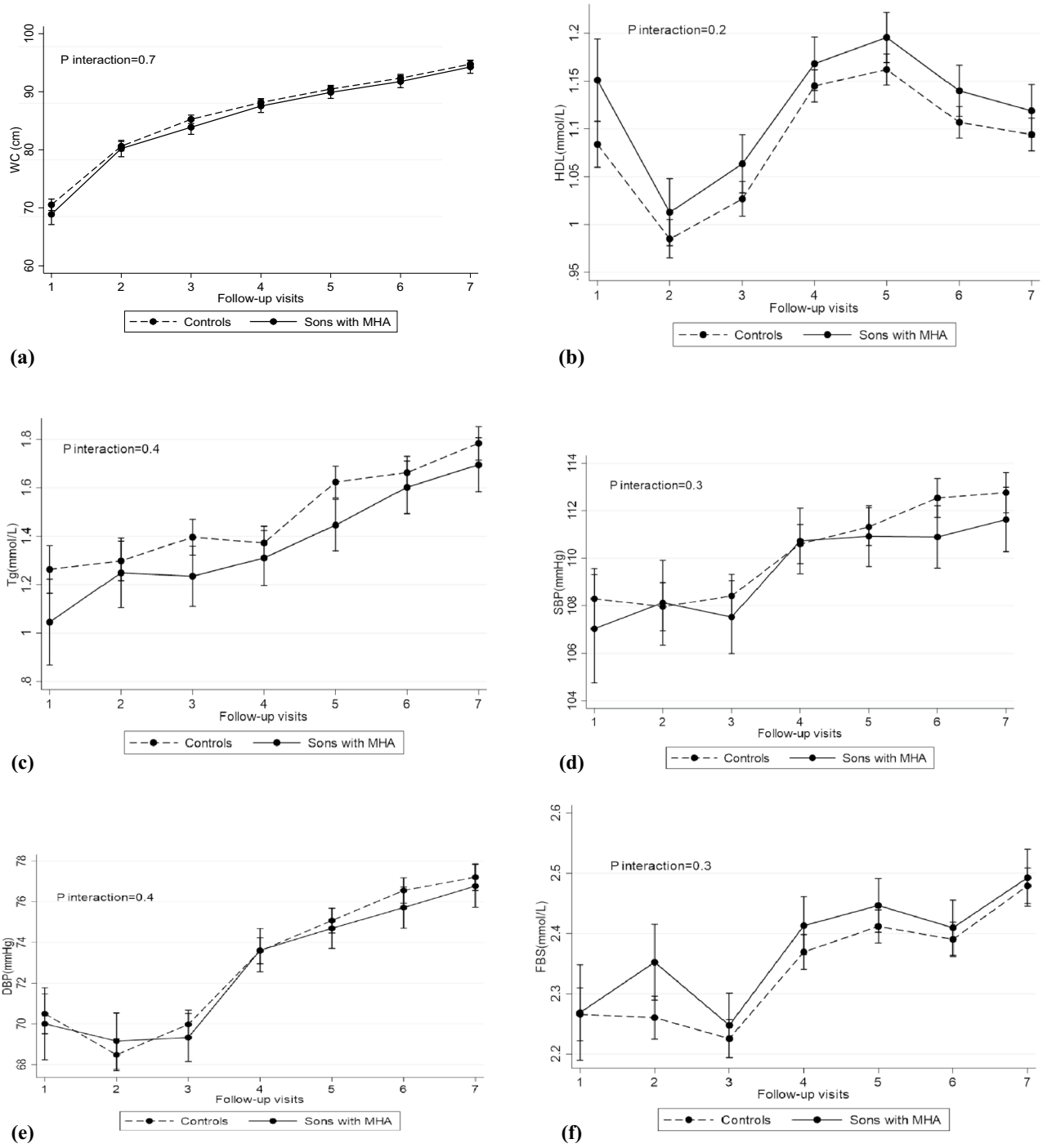

Fig. 3 **a–f** Generalized estimating equation (GEE) measures. Mean of changes within follow-ups between sons with maternal hyperandrogenism (MHA) (sons of women with hyperandrogenism) and controls assuming the interaction between time and study group and also adjusting for confounding variables (body mass index_standard deviation score (BMI_SDS), physical activity, and education status)

the same population [6]. This inconsistency may also be partly explained by the different effects of androgen on metabolic disorders in men and women; although higher androgen levels increase the risk of MetS in women, lower levels are associated with a higher risk in men [42]. Moreover, men with testosterone deficiency are at a higher risk of IR, obesity, MetS, T2DM, and CVDs, as evidenced by studies [43–47]. It seems that androgen deficiency in men can be associated with obesity due to the loss of testosterone action in neurons of the central nervous system,

which decreases energy expenditure, and increases leptin resistance. Conversely, women with androgen excess are more prone to IR, adiposity, and T2DM [43, 46, 48]. Notably, the association between testosterone levels and cardiometabolic consequences varies by gender, and these gender-specific effects may be partly explained by distinct roles of testosterone in modulating glucose and energy homeostasis [43]. In males, the loss of central AR action decreases energy expenditure and predisposes them to adiposity and IR. In contrast, females experience adverse effects on metabolic homeostasis due to androgen excess during the perinatal period or adulthood.

Furthermore, the metabolism of female rodents, nonhuman primates, and even humans can be influenced by transient perinatal androgen excess, potentially altering their genetic predisposition to obesity and MetS in adulthood [25–28, 39, 49, 50].

In addition to the different effects of androgens on the metabolic homeostasis in men and women, sex differences in physiology of men and women may arise from differences in sex chromosomes. Genes expressed on the X chromosome can significantly impact metabolic parameters. These genes contribute to various aspects, including body weight and adiposity [51–53]. Notably, excess abdominal adiposity and an elevated risk of T2DM have been observed in men with Klinefelter syndrome, who possess two X chromosomes, therefore metabolic dysfunction is promoted by an additional X chromosome [54, 55]. Moreover, increased fasting insulin levels, IR, elevated liver triglycerides, enhanced expression of fatty acid oxidation enzymes, and increased fat mass are observed in XX animals with 2 X chromosomes when exposed to a high-fat diet [51]. Collectively, these findings suggest that the X chromosome may indeed impair metabolic function. Additionally, some genes on the X chromosome escape inactivation and maintain expression levels in tissues such as adipose and liver [56]. These genes could contribute to phenotypic differences between males and females, impacting metabolic outcomes. Recent research, utilizing the four core genotypes mouse model, highlights the independent role of sex chromosome complement (regardless of gonadal sex) [56]. This complement influences various aspects, including adiposity, feeding behavior, fatty liver, and glucose homeostasis. Potential mechanisms for the effects of sex chromosome complement include differential gene dosage from X chromosome genes that escape inactivation and distinct genomic imprints on X chromosomes inherited from maternal or paternal parents [56]. In summary, understanding the interplay between sex chromosomes and metabolic function is a fascinating area of research. While existing studies primarily correlate metabolic parameters with hormonal milieu, further investigations specifically addressing the correlation between the X chromosome and metabolic traits are still required.

The variation in metabolic parameters between males and females may be caused by dosage of androgen exposure during prenatal life. Previous research has indicated that testosterone exposure during fetal life can lead to a dose-dependent reduction in the birth weight among fetuses [57].

Strengths and limitations

This is a long-term prospective population-based study involving a cohort of sons with MHA and controls, possibly demonstrating more accurate results and facilitating the assessment of the incidence of Mets over time. Using a standardized and exact definition for HA, the presence of the control group that is not HA and adjustment for some potential confounders that may affect each outcome were strengths of the present study that helped us achieve valuable results. Additionally, the study's population-based framework enables us to evaluate the impact of MHA on subsequent cardiometabolic disorders in male offspring. The population-based approach enhances the generalizability of our findings beyond the study cohort.

There are some limitations in our study. First, we did not directly measure androgen levels in pregnant women during gestational period, therefore, the assessing the dose-dependent effects of androgen exposure during prenatal life remains challenging. The most common cause of HA in reproductive-aged women is PCOS [58]. While the status of HA is believed to originate during fetal life and persists throughout the lifespan of affected women, we did not re-evaluate its status during pregnancy [59, 60]. Moreover, the concept of maternal PCOS has often been served as a paradigm for exploring the impact of prenatal androgen exposure on the disease pathogenesis in offspring [61], notwithstanding the absence of subsequent reassessment of androgen excess during the gestational period. Recent findings indicate that women with HA linked to PCOS exhibit elevated concentrations of androgens in umbilical cord blood compared to non-PCOS counterparts, leading to increased fetal exposure to maternal-origin androgens [62–64]. Studies have revealed structural and molecular abnormalities in the placentae of mothers with PCOS [65, 66], resulting in compromised placental aromatase activity that fails to shield the fetus from the adverse effects of androgen excess. Moreover, research indicates that maternal androgens play a role in regulating placental and fetal steroidogenesis, influencing in utero androgen levels [67, 68]. Furthermore, a recent study has highlighted alterations in key enzymes involved in steroid synthesis (3β-HSD-1 and P450) among pregnant women with PCOS, potentially contributing to heightened androgen production during pregnancy [66]. Notably, placental tissue emerges as a potential source of androgen production in women with PCOS. While direct assessment of maternal hyperandrogenic status during pregnancy was not conducted,

it is plausible that male offspring of hyperandrogenic mothers were exposed to elevated androgens during their prenatal development. Second, our study lacked adjustment for lifestyle modifications, including dietary habits. Third, we did not assess specific medications used by mothers during the preconception period, as well as the birth weight, and the androgen levels in these male offspring during their adulthood. Future studies may benefit from incorporating such measurements to enhance the comprehensiveness and accuracy of the results. Forth, our analysis focused solely on an urban population, limiting the generalizability of results to rural populations. All participants were limited to the Asian subjects, further studies should be performed among other ethnicities. Finally, it should be kept in mind that, in this study, the lack of statistical significance may be attributed to sample size limitations, the absence of some covariates related to metabolic disorders (such as small for gestational age neonates), and the definition of exposure.

Conclusion

Over two decades of follow-up, our study reveals that preconceptional MHA does not significantly increase the risk of MetS development in male offspring in their later life. However, to validate these findings and unravel the intricate mechanisms underlying sex-specific developmental programming of MetS influenced by androgens, further comprehensive, population-based studies are essential. These investigations should encompass all relevant parameters, enhancing our understanding of this complex interplay.

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Author contributions Mahsa Noroozzadeh, Fahimeh Ramezani Tehrani, and Fereidoun Azizi contributed to the study conception and design. Material preparation, data collection and analysis were performed by Mahsa Noroozzadeh, Maryam Rahmati and Fahimeh Ramezani Tehrani. Mahsa Noroozzadeh, Fahimeh Ramezani Tehrani, Mina Amiri, and Marzieh Saei Ghare Naz involved in reviewing the manuscript and critical discussion. The first draft of the manuscript was written by Mahsa Noroozzadeh and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare that there are no conflicts of interest.

Ethical approval The study proposal received approval from the ethics review board of the Research Institute for Endocrine Sciences (approval number IR.SBMU.ENDOCRINE.REC.1401.059). By following the ethical standards of the Declaration of Helsinki, this study aimed to promote respect for all humans and protect their health and rights.

Informed consent All participants received adequate explanations about this study, and written informed consent was obtained from all of them.

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