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RESEARCH

Reproductive hormones and sex differences in relation to brachial-ankle pulse wave velocity in obese subjects: a retrospective case–control study

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Abstract

Background: Reproductive hormones may be a risk factor for cardiovascular disease (CVD), but their influence is often underestimated. Obesity can exacerbate the progression of CVD. Arterial stiffness (AS) is correlated with the risk of CVD. Brachial-ankle pulse wave velocity (baPWV) has served as a practical tool for assessing AS with broad clinical applications. This study aimed to investigate the association between reproductive hormones and baPWV in obese male and female subjects.

Methods: A retrospective case–control design was designed. AS was assessed using baPWV, with a baPWV ≥ 1400 cm/s indicating increased AS. Between September 2018 and October 2022, 241 obese subjects with increased AS were recruited from Ningbo Yinzhou No. 2 Hospital. The control group consisted of 241 obese subjects without increased AS. A 1:1 propensity score matching was performed to correct potential confounders by age and sex. We additionally performed a sex-based sub-analysis.

Results: Correlation analysis demonstrated that luteinizing hormone (LH) ($r = 0.214$, $P = 0.001$) and follicle-stimulating hormone (FSH) ($r = 0.328$, $P < 0.001$) were positively correlated with baPWV in obese male subjects. In the multivariate conditional logistic regression analysis, FSH (OR = 1.407, 95% CI = 1.040–1.902, $P = 0.027$) rather than LH (OR = 1.210, 95% CI = 0.908–1.612, $P = 0.194$) was independently and positively associated with increased AS in obese male subjects. However, there was no significant correlation between reproductive hormones and baPWV in women.

Conclusions: Our study identified FSH as a potential risk factor for arteriosclerosis in obese male subjects. This provides a novel and intriguing perspective on the pathogenesis of CVD in obese subjects.

Keywords: arterial stiffness; brachial-ankle pulse wave velocity; obese; reproductive hormones

Introduction

The prevalence of cardiovascular disease (CVD) among obese individuals has steadily increased over the past few decades, emerging as a global public health issue (1). Arteriosclerosis is an essential predictor of CVD events (2), which often manifests prior to the onset of CVD. The main reason is that arteriosclerosis leads to increased left ventricular afterload and insufficient coronary blood supply (3). Moreover, it can cause microvascular damage in vital organs such as the

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kidneys and brain due to compromised blood flow (4, 5). A healthy lifestyle, including regular physical activity (6), adherence to a Mediterranean diet (7) and cessation of smoking and drinking (8) can delay the onset of arteriosclerosis. In addition, genetic abnormalities significantly contribute to the development of arteriosclerosis (9). Various disease factors, such as abnormal glucose metabolism, aging, hypertension, hypercholesterolemia, obesity, and chronic kidney disease, can contribute to arteriosclerosis (10), with aging being the most prominent factor (11). Early detection of potential risk factors for arteriosclerosis may have clinical significance in preventing CVD and improving clinical outcomes.

Arterial stiffness (AS) serves as a critical indicator for assessing arteriosclerosis, commonly assessed through pulse wave velocity (PWV) (12). There are three modes of PWV, including carotid-femoral PWV (cfPWV), aortic PWV, and brachial-ankle pulse wave velocity (baPWV), each of which reflects the stiffness of different vascular segments. The accepted gold standard for assessing AS is cfPWV (13). However, large-scale clinical application remains challenging due to the high technical requirements, lengthy observation time, and expensive equipment (14). baPWV, in comparison with cfPWV, has gained broader clinical utilization owing to its ease of measurement, non-invasiveness, and excellent accuracy (15, 16). In addition, baPWV and cfPWV exhibit a strong correlation in the detection of AS (17). There is a growing recognition that baPWV can be used as a proxy for cfPWV. A prospective cohort study demonstrated that an increased baPWV was associated with an elevated risk of CVD (18). Thus, baPWV could serve as a practical tool for CVD risk prediction with broad clinical applications, and it was used as an indicator for the assessment of AS in our study.

Decades of research have demonstrated that sex hormone levels may determine the incidence of CVD. Several observational studies have reported that estradiol (E2) and testosterone are protective factors against CVD events in women and men, respectively (19, 20). The incidence of CVD was lower in premenopausal women than in men. However, in postmenopausal women (with the decrease of E2 level and the increase of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels), the incidence of CVD events significantly increased, becoming similar to that in men (21, 22). However, a growing body of evidence suggested that estrogen replacement therapy has not been successful in reducing the incidence of CVD-related diseases in postmenopausal women (23). Some studies have indicated that FSH or LH could potentially contribute to CVD events in addition to estrogen (24, 25).

Obesity raises the risk of CVD and shortens life expectancy, posing an inescapable challenge (26). Obesity-related oxidative stress potentially contributes to the development of vascular structural and functional disorders (27). Research has demonstrated that obese subjects not only exhibit significantly higher PWV (28) but also experience disrupted secretion of reproductive hormones (29). A prospective study found that the prevalence of secondary hypogonadism in moderately to severely obese men was 45% (30). Recent andrological guidelines emphasized the importance of evaluating reproductive hormones in obese individuals, with FSH and LH serving as crucial indicators to distinguish between subclinical and compensatory hypogonadism (31). Therefore, we hypothesize that reproductive hormones may play a significant role in the onset and progression of arteriosclerosis. It is necessary to conduct research on reproductive hormones in obese individuals in order to further clarify their potential effects on CVDs. To address these gaps, we designed this case–control study to further explore the association between reproductive hormones and baPWV in obese individuals in China and attempt to assess the differential roles of sex.

Materials and methods

Study subjects

This retrospective case–control study consecutively included obese subjects aged 18–50 years from Ningbo Yinzhou No. 2 Hospital between July 1, 2018, and August 5, 2022. The obesity diagnostic criteria advised by the WHO for Chinese people served as the inclusion criteria (32): a body mass index (BMI) ≥ 28 kg/m^2 was diagnosed as obesity. Another inclusion criterion was that all obese subjects were tested for AS, which was defined by PWV. The exclusion criteria were as follows: (i) subjects aged <18 or >50 years; (ii) a history of medication use that may affect reproductive hormone levels, including the contraceptive pill; (iii) postmenopausal women; (iv) a history of reproductive system diseases; (v) a history of extremity arterial disease, stroke, angina, myocardial infarction, cancer, or type 2 diabetes; and (vi) incomplete data. Obese subjects were divided into two groups according to the detected AS: control group (baPWV < 1400 cm/s) and case group (baPWV ≥ 1400 cm/s). We used the propensity score as a balancing score to adjust for confounding variables and match covariates between the two groups (Fig. 1). Age matching was necessary since age is the critical factor for increased AS. The study was endorsed by the ethics committee of Ningbo Yinzhou No. 2 Hospital (2022-P-013). The purpose was explained to the subjects, and informed written consent was subsequently obtained prior to enrollment in the study. All methods were performed in accordance with the relevant guidelines and regulations. The confidentiality of data was maintained as there were no personal identifiers used and neither the raw data nor the extracted data were passed to a third person.

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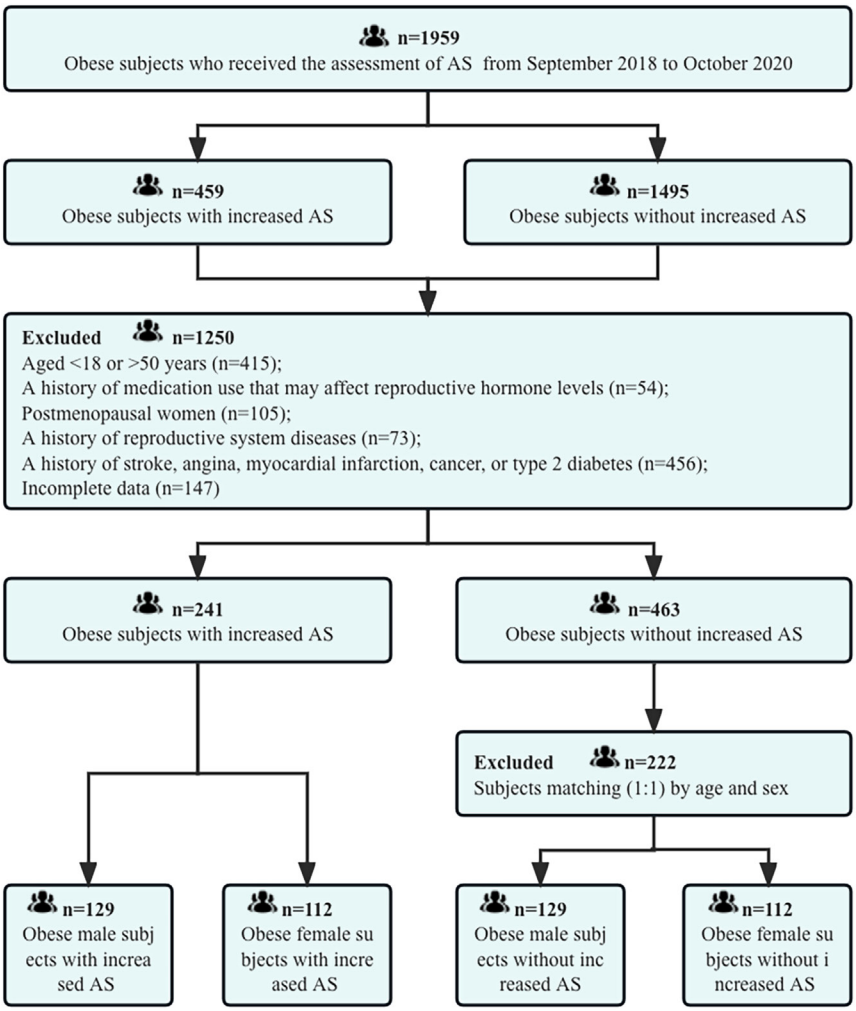

Figure 1

Flow chart of the sample size.

Clinical data collection

The general information was collected through a self-reported questionnaire, including age, sex, concomitant illnesses, and medical history. As part of the measurement, height and weight were taken standing up after the participants removed their shoes and wore light indoor clothing. The calculation of BMI was based on the weight (kg) divided by the height (m) squared (kg/m^2). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using an electronic sphygmomanometer on the right upper arm. Mean arterial pressure (MAP) was calculated based on the SBP and DBP. Waist circumference (WC) was measured using an inelastic measuring tape. Visceral fat area (VFA) and subcutaneous fat area (SFA) were determined by a dual bioelectrical impedance analyzer (HDS-2000, Omron Healthcare).

Laboratory assay

Blood samples were collected after an overnight fasting period in the morning before 10:00 h. Subsequently, all subjects were subjected to the following laboratory tests: fasting blood glucose (FBG), fasting plasma insulin (FINS), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), LH, FSH, E2, progesterone and testosterone. The degree of insulin resistance was assessed by the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR), which was calculated using the formula FBG × FINS/22.5. FBG was estimated by the glucose oxidase method, with the intra-assay coefficient of variation (CV) of 1.32%, the inter-assay CV of 2.65%, and the sensitivity of 0.11 mmol/L. FINS was estimated by electrochemical luminescence immunoassay, with intra- and inter-assay CVs of 4.4% and 5.1%, respectively, and a sensitivity of 0.1 mIU/L. Serum concentrations of TG, TC, HDL-C, and LDL-C were measured using an enzymatic colorimetric assay (Abbott). The intra-assay CVs ranged from 2.0% to 3.5%, the inter-assay CVs ranged from 3.0% to 4.5%, and the sensitivities were 0.2 mmol/L for TG, 0.12 mmol/L for TC, 0.08 mmol/L for HDL-C, and 0.18 mmol/L for LDL-C. Serum concentrations of LH, FSH, E2, progesterone, and

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testosterone were measured using chemiluminescent immunoassays (Abbott). The intra-assay CVs ranged from 4.0% to 8.0%, the inter-assay CVs ranged from 5.0% to 12.0%, and the sensitivities were 0.07 IU/L for LH, 0.05 IU/L for FSH, 10 pmol/L for E2, 0.1 nmol/L for progesterone, and 0.1 nmol/L for testosterone. Our study did not stratify female subjects' data by menstrual cycle phases. This decision was informed by previous literature indicating that PWV did not significantly vary across different menstrual cycle phases in females (33, 34, 35, 36).

Assessment of AS

The baPWV was measured with the assistance of an automatic waveform analyzer (BP-203 RPE III, Omron Healthcare). The arms and ankles were wrapped with pneumatic pressure cuffs after a rest period of 10 min and the distance between the brachial region and the ankle was considered the distance traveled by the pulse wave. The baPWV was automatically calculated by dividing the distance traveled by the pulse wave by the observed time interval. The average baPWV of each subject, measured bilaterally, was used for analysis. An increased AS was defined as a baPWV ≥ 1400 cm/s in our analysis (37, 38).

Statistical analysis

Statistical analyses were performed using SPSS software (SPSS Inc) in version 24.0 for Mac or R Studio version 2023.12.0 with R version 4.3.2. Propensity score matching (PSM) was used to balance measurable confounders between the control group and the case group. The propensity score was calculated by a logistic regression model with the covariates: age and gender. We performed a matched group analysis using 1:1 propensity matching with a 0.25 caliper. Prior to proceeding with the statistical analysis, all parameters were tested for a normal distribution using the Kolmogorov–Smirnov test. Normally distributed variables were presented as mean ± S.D. and compared using an independent sample *t*-test. Non-normally distributed variables were presented as the median (interquartile range) and compared using the Mann–-Whitney *U*-test. For skewed distribution data, 95% confidence intervals (CIs) of median difference were calculated by the Hodges–Lehmann estimate based on the Mann–Whitney *U*-test. Reproductive hormones were presented as quartiles, and linear regression analysis was employed to assess trends across groups. Non-normally distributed variables were naturally log-transformed into approximately normally distributed data prior to performing correlation analysis. Pearson's correlation analysis was employed to evaluate the relationship between baPWV and clinical parameters in males and females. Multivariate-adjusted conditional logistic regression analysis was conducted to assess the risk of AS in males and females. Odds ratios (ORs) and corresponding 95% CIs were calculated. A two-tailed *P* value < 0.05 was considered statistically significant.

Results

General characteristics of the study population

The present study included 241 cases with increased AS and 241 controls without increased AS. The characteristics of study subjects, both males and females, after PSM in a 1:1 ratio, are displayed in Table 1. There were 258 males and 224 females. The mean age of the study population was 34.2 ± 6.9 years. No differences were observed in age between males and females ($P > 0.05$). The case group of male subjects exhibited elevated MAP, VFA, LH, and FSH levels compared to controls. Additionally, the case group of female subjects exhibited elevated MAP, WC, and VFA compared to controls.

As shown in Fig. 2, obese male subjects with increased AS exhibited significantly higher LH (4.03 ± 1.75 IU/L vs 3.24 ± 1.16 IU/L, $P < 0.001$) and FSH (4.89 ± 1.7 IU/L vs 3.83 ± 1.19 IU/L, $P < 0.001$) levels than those without increased AS.

Incidence of increased AS in different quartiles of reproductive hormones in the males and females

The incidence of increased AS was categorized into four groups based on the quartiles of reproductive hormones. As shown in Fig. 3A, the incidence of baPWV ≥ 1400 cm/s was 40.0%, 37.9%, 50.8%, and 71.9%, respectively, according to the elevated LH quartiles in male subjects (P for trend < 0.001). Additionally, a subgroup analysis of men with normal testosterone levels (>12 nmol/L) revealed a similar conclusion: baPWV increased with elevated LH quartiles (Supplementary Figure 1, see the section on supplementary materials given at the end of this article). Similarly, the incidence of baPWV ≥ 1400 cm/s according to elevated FSH quartiles was 27.5%, 31.4%, 37.9%, and 58.4%, respectively (P for trend <0.001). However, as shown in Fig. 3B, the incidence of baPWV ≥ 1400 cm/s showed no statistically significant difference according to the elevated LH or FSH quartiles in female subjects (P for trend > 0.005).

Correlation between baPWV and clinical characteristics in obese subjects of males and females

Pearson correlation analysis was performed to examine the relationship between the baPWV and clinical characteristics in obese male and female subjects

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Table 1 Clinical characteristics of the obese subjects grouped by sex and baPWV. Data represent the mean ± S.D. or medians (interquartile ranges). For continuous data, the 95% CI of mean or median difference was assessed by the Student's *t*-test or the Hodges–Lehmann estimate based on the Mann–Whitney *U*-test.

	Males (*n* = 258)				**Females** (*n* = 224)			
Characteristic	**Control group** (*n* = 129)	**Case group** (*n* = 129)	*P*[a]	**95% CI**	**Control group** (*n* = 112)	**Case group** (*n* = 112)	*P*[b]	**95% CI**
Age (years)	33.0 ± 6.1	33.8 ± 8.9	0.442	−1.185–2.574	34.9 ± 3.8	35.5 ± 7.4	0.442	−0.794–2.095
MAP (mm Hg)	102.5 ± 11.7	112.9 ± 14.8	0.001	7.070–13.940	96.5 ± 10.4	105.4 ± 12.2	0.001	5.687–11.689
BMI (kg/m^2)	33.4 ± 4.2	34.2 ± 4.0	0.110	−0.174–1.846	32.4 ± 2.6	33.2 ± 4.1	0.081	−0.101–1.673
WC (cm)	108.2 ± 9.9	110.3 ± 9.2	0.074	−0.205–4.454	98.2 ± 6.6	101.1 ± 10.1	0.012	0.675–5.141
VFA (cm^2)	154.0 ± 46.9	169.2 ± 43.6	0.008	3.660–26.399	105.2 ± 22.1	119.0 ± 35.7	0.001	5.979–21.968
SFA (cm^2)	303.8 ± 67.9	318.2 ± 75.8	0.119	−4.566–31.777	299.4 ± 69.6	321.2 ± 90.0	0.053	−0.919–42.661
FBG (mmol/L)	5.39 ± 0.61	5.43 ± 0.57	0.674	−0.119–0.186	5.35 ± 0.54	5.41 ± 0.47	0.466	−0.079–0.187
HOMA-IR	5.59 (3.64, 8.91)	6.30 (4.52, 9.26)	0.086	−1.491–0.104	4.81 (3.45, 7.34)	5.39 (4.16, 7.19)	0.253	−0.992–0.265
TG (mmol/L)	1.91 (1.43, 2.80)	1.92 (1.51, 3.00)	0.952	−0.250–0.220	1.60 (1.07, 2.09)	1.57 (1.09, 1.93)	0.890	−0.170–0.190
TC (mmol/L)	5.55 ± 1.02	5.63 ± 1.13	0.513	−0.188–0.369	5.42 ± 1.01	5.45 ± 0.89	0.845	−0.239–0.271
HDL-C (mmol/L)	1.11 ± 0.21	1.14 ± 0.21	0.349	−0.028–0.080	1.21 ± 0.20	1.25 ± 0.23	0.200	−0.021–0.096
LDL-C (mmol/L)	3.64 ± 0.74	3.79 ± 0.79	0.144	−0.045–0.349	3.53 ± 0.77	3.59 ± 0.68	0.544	−0.134–0.246
LH (IU/L)	3.24 ± 1.16	4.03 ± 1.75	0.001	0.426–1.132	5.72 (3.41, 10.52)	5.20 (3.63, 9.11)	0.516	−0.610–1.310
FSH (IU/L)	3.83 ± 1.19	4.89 ± 1.70	0.001	0.692–1.396	5.86 (2.99, 7.12)	5.51 (4.11, 7.08)	0.584	−0.920–0.490
E2 (pmol/L)	109.56 ± 36.92	109.75 ± 46.59	0.974	−9.906–10.749	236.50 (123.00, 384.75)	219.50 (123.00, 397.75)	0.673	−30.000–48.000
Progesterone (nmol/L)	1.49 (1.02, 2.16)	1.58 (1.09, 2.20)	0.332	−0.300–0.090	2.23 (1.20, 10.61)	2.67 (1.27, 13.10)	0.467	−0.840–0.350
Testosterone (nmol/L)	11.56 ± 3.20	11.60 ± 3.30	0.904	−0.745–0.889	1.89 (1.51, 2.38)	1.87 (1.38, 2.52)	0.714	−0.170–0.230
baPWV (cm/s)	1236.9 ± 124.4	1588.8 ± 165.3	0.001	318.005–386.917	1196.8 ± 129.4	1523.4 ± 116.7	0.001	292.571–362.430

P[a], comparison between men and *P*[b], comparison between women.

baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; E2, estradiol; FBG, fasting blood glucose; FSH, follicle-stimulating hormone; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; LDL-C, low-density lipoprotein cholesterol; LH, luteinizing hormone; MAP, mean arterial pressure; SFA, subcutaneous fat area; TC, total cholesterol; TG, triglyceride; VFA, visceral fat area; WC, waist circumference.

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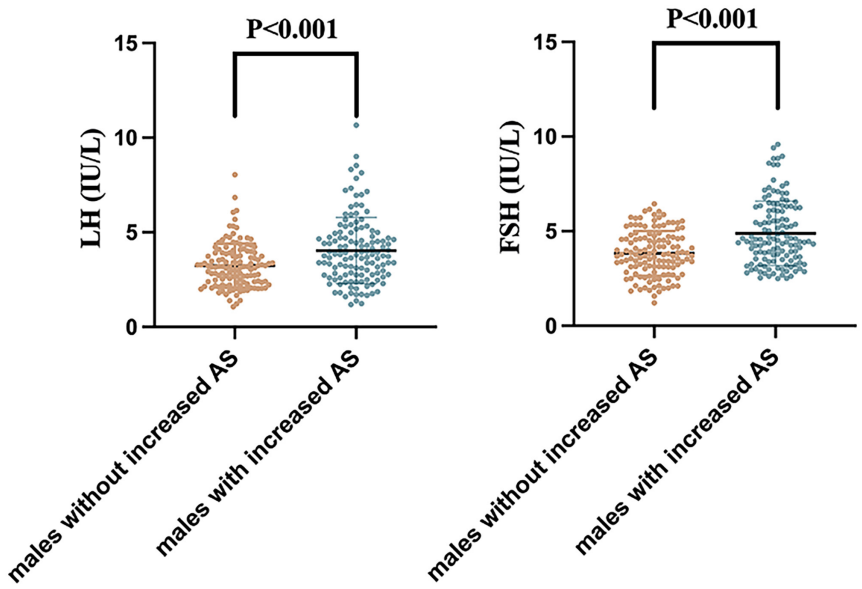

Figure 2

The relationship between LH or FSH and increased AS (baPWV ≥ 1400 cm/s) by independent *t*-test in obese male subjects.

(Table 2). In men, the Pearson correlation analysis showed that baPWV was positively correlated with age, MAP, VFA, HOMA-IR, LH, and FSH levels ($P < 0.05$). The scatter plot illustrates the correlations between baPWV and the reproductive hormones (Fig. 4A and B). In females, the Pearson correlation analysis showed that baPWV was positively correlated with MAP, WC, VFA, and SFA ($P < 0.05$).

Risk factor analysis for increased AS in obese male subjects

Multivariate conditional logistic regression analysis was conducted in males (Table 3). We used an increased AS, defined by baPWV ≥ 1400 cm/s, as the dichotomous outcome. Model 1, which included LH, age, MAP, WC, VFA, HOMA-IR, and TG levels as independent variables, showed that LH and MAP emerged as significant and independent factors associated with increased AS (OR = 1.392, 95% CI = 1.076–1.800, $P = 0.012$). Model 2, in which LH was replaced with FSH, demonstrated that FSH was significantly associated with increased AS (OR = 1.538, 95% CI = 1.163–2.034, $P = 0.003$). Furthermore, when LH and FSH were simultaneously included as independent variables in model 3, FSH (OR = 1.407, 95% CI = 1.040–1.902, $P = 0.027$) rather than LH (OR = 1.210, 95% CI = 0.908–1.612, $P = 0.194$) was related to the increased AS. Notably, the addition of FSH did not affect the significant

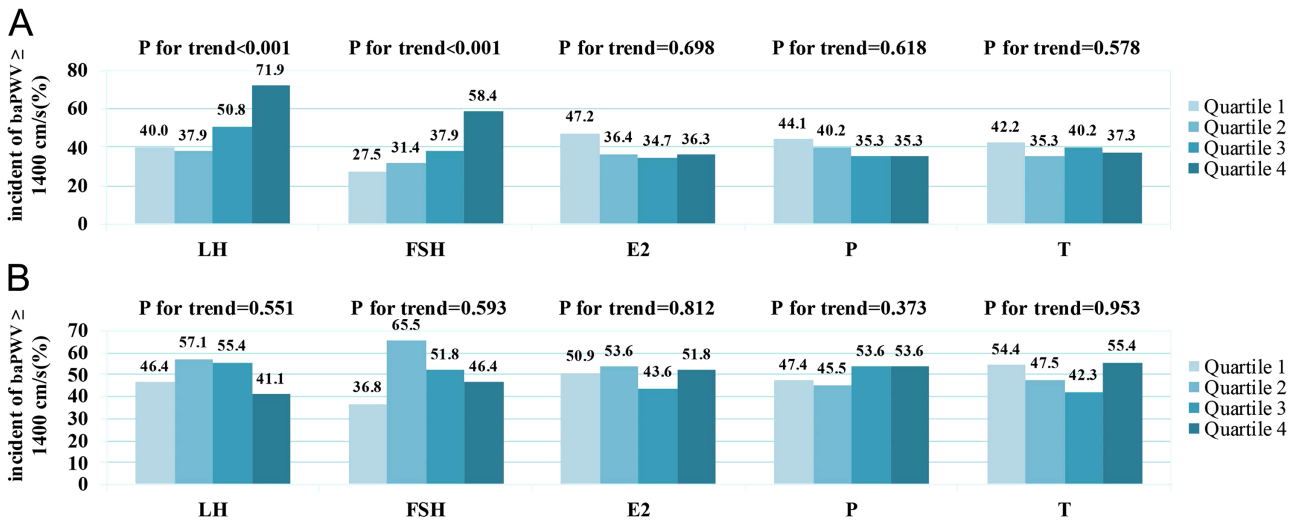

Figure 3

Incidence of baPWV ≥ 1400 cm/s in different quartiles of reproductive hormones in obese subjects.

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Table 2 Correlation between baPWV and clinical characteristics in obese subjects of males and females. Natural log-transformed HOMA-IR, TG, and progesterone were used for statistical analysis in men. Natural log-transformed HOMA-IR, TG, LH, FSH, E2, progesterone, and testosterone were used for statistical analysis in women.

	Males		Females	
Variable	r^a	P^a	r^b	P^b
Age (years)	0.149	0.017	0.054	0.423
MAP (mmHg)	0.475	<0.001	0.460	<0.001
BMI (kg/m^2)	0.082	0.191	0.121	0.071
WC (cm)	0.108	0.085	0.208	0.002
VFA (cm^2)	0.244	<0.001	0.215	0.002
SFA (cm^2)	0.039	0.539	0.139	0.041
FBG (mmol/L)	0.021	0.737	0.051	0.451
HOMA-IR	0.134	0.032	0.055	0.419
TG (mmol/L)	0.112	0.079	0.018	0.789
TC (mmol/L)	0.022	0.731	0.039	0.569
HDL-C (mmol/L)	−0.008	0.896	0.018	0.789
LDL-C (mmol/L)	0.061	0.339	0.061	0.373
LH (IU/L)	0.214	0.001	0.028	0.673
FSH (IU/L)	0.328	<0.001	0.098	0.142
E2 (pmol/L)	−0.009	0.881	−0.033	0.619
Progesterone (nmol/L)	0.014	0.823	0.034	0.617
Testosterone (nmol/L)	−0.027	0.665	−0.025	0.705

P^a, comparison between men, and P^b: comparison between women.
BMI, body mass index; E2, estradiol; FBG, fasting blood glucose; FSH, follicle-stimulating hormone; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; LDL-C, low-density lipoprotein cholesterol; LH, luteinizing hormone; MAP, mean arterial pressure; SFA, subcutaneous fat area; TC, total cholesterol; TG, triglyceride; VFA, visceral fat area; WC, waist circumference.

association of MAP. Additionally, we performed multivariate conditional logistic regression analysis on female subjects (Supplementary Table 1) to enhance the robustness of our findings. However, no statistically significant correlation was found between baPWV and reproductive hormones in females.

Discussion

In this retrospective case–control study, we provided evidence of the relationship between reproductive hormones and baPWV in obese subjects. After analyzing obese subjects of males and females, we found that a correlation between reproductive hormones and baPWV only exists in men, with no significant correlation observed in women. First, obese male subjects with increased AS exhibited higher LH and FSH levels. Furthermore, the incidence of baPWV ≥ 1400 cm/s gradually increased with increasing LH and FSH quartiles. Second, correlation analysis demonstrated that LH and FSH were positively correlated with baPWV in obese male subjects. Third, multivariate conditional logistic regression analysis further showed that FSH levels were independently and positively associated with increased AS in obese male subjects, whereas LH did not appear to be a determinant of increased AS risk.

Comparison with other studies

Our study demonstrated that MAP was a significant risk factor for baPWV in both males and females. Similar conclusions have been confirmed in the prospective

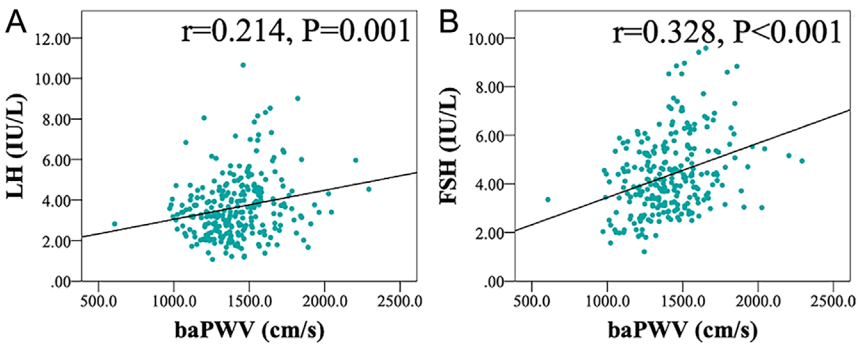

Figure 4

Scatter plot showing a significant correlation between LH or FSH levels and baPWV in obese male subjects.

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Table 3 Multivariate conditional logistic regression analysis of increased AS and reproductive hormones in obese male subjects. Model 1 included age, MAP, WC, VFA, HOMA-IR, TG, and LH as independent variables; model 2 included age, MAP, WC, VFA, HOMA-IR, TG, and FSH as independent variables; model 3 included age, MAP, WC, VFA, HOMA-IR, TG, LH, and FSH as independent variables.

	Model 1			Model 2			Model 3		
Variable	**OR**	**95% CI**	*P*	**OR**	**95% CI**	*P*	**OR**	**95% CI**	*P*
MAP	1.111	1.059–1.165	<0.001	1.114	1.060–1.170	<0.001	1.113	1.058–1.170	<0.001
LH	1.392	1.076–1.800	0.012				1.210	0.908–1.612	0.194
FSH				1.538	1.163–2.034	0.003	1.407	1.040–1.902	0.027

FSH, follicle-stimulating hormone; LH, luteinizing hormone; MAP, mean arterial pressure.

study (39). MAP represents the average pressure in the arteries during a single cardiac cycle, affecting the mechanical stress on arterial walls. Chronic elevation of MAP leads to increased arterial wall stress, promoting structural changes such as reduced elastin content, thereby contributing to greater AS (10). The relationship between MAP and baPWV underscores the importance of managing blood pressure to prevent or attenuate AS.

Previous studies on AS mostly focused on sex hormones (40). However, the effects of LH and FSH on AS were rarely addressed. We found some clues in the research concerning the correlation between reproductive hormones and CVD events. Research on the association between LH and CVD events in men was limited and controversial. In a study by Haring *et al.* (41), a prospective evaluation of 254 elderly men (mean age 75.5 years) revealed no association between baseline LH and FSH levels and their trajectories with CVD events during the follow-up period. Additionally, a prospective cohort study by Holmboe *et al.* (42), consisting of 5350 randomly selected men with up to 30 years of follow-up, found that elevated LH levels lead to increased cancer mortality rather than CVD mortality. However, it was interesting that LH and FSH levels were significantly elevated in men with a history of CVD events at the beginning of the study. Similarly, in a large cross-sectional study, Qu *et al.* (43) showed that LH was positively associated with the incidence of CVD but only in the grade 2 hypertension group. The association disappeared in patients with normal blood pressure and grade 1 hypertension. In our study, LH was positively correlated with baPWV in obese male subjects (Tables 1 and 2). However, this correlation disappeared (OR = 1.210, 95% CI = 0.908–1.612, $P = 0.194$) when FSH was included in conditional logistics regression analysis simultaneously. Subclinical hypogonadism was defined as normal testosterone (>12 nmol/L) and elevated LH (LH ≥ 9.4 IU/L) (44). However, subclinical hypogonadism is rarely reported in young males. One study reported a 9.5% prevalence of subclinical hypogonadism in aging men (average age 67.3 years), with age being a significant factor (relative risk ratio (95% CI) for each decade: 2.41 (2.08–2.79), $P < 0.001$) (45). Our study population consisted entirely of young people (average age 34.2 ± 6.9 years), which may explain the absence of this subgroup in our sample. Despite this, we analyzed males with normal testosterone levels across different LH levels. We divided them into quartiles based on LH levels (Supplementary Figure 1). The results showed that baPWV increased with higher LH quartiles among males with normal testosterone. This suggests that as LH levels exceed 12 IU/L, baPWV could be even higher. Therefore, it is reasonable to hypothesize that males with subclinical hypogonadism might have higher baPWV compared to healthy individuals. Research on the relationship between FSH and CVD events has been reported. In women, the more pronounced the increase in FSH levels during the menopausal transition, the higher the risk of atherosclerosis occurring after menopause (25). FSH levels were more predictive of metabolic disease in postmenopausal women than C-reactive protein, leptin, and adiponectin levels (46). Additionally, in male patients with prostate cancer undergoing androgen deprivation therapy, FSH can increase CVD events by promoting the formation of atherosclerotic plaque, insulin resistance, and metabolic syndrome (47). Similar to the aforementioned studies, our study supported that FSH was an independent risk factor for baPWV.

We also observed that the baPWV of premenopausal women seems to be lower than that of men (Table 1), which aligns with a previously reported study (48), indicating that baPWV may exhibit different physiological characteristics in males and females. In our study, the associations between LH and FSH with baPWV disappeared in obese female subjects. The observed gender differences may be attributed to the following reasons. First, estrogen, which fluctuates significantly during the menstrual cycle, has vasoprotective effects (21). High levels of estrogen during the follicular phase enhance endothelial function and reduce vascular resistance. This protective effect of estrogen may obscure any direct correlation between FSH, LH, and baPWV in women. Another critical factor is the disordered hormone levels. Our study included women in all menstrual cycle stages, resulting in significant fluctuations and skewed levels of reproductive hormones (Table 1). The inherent variability in hormone levels means that any potential impact of FSH or LH on AS may be transient and inconsistent. For instance, elevated FSH or LH levels

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during certain phases may have an atherogenic effect, but this can be rapidly mitigated by subsequent hormonal changes. The differences in reproductive hormone levels between premenopausal and postmenopausal women further support our speculation. Postmenopausal women, who have relatively stable and low levels of estrogen, might show different associations compared to premenopausal women. Previous studies have suggested a relationship between reproductive hormones and cardiovascular risk factors (25, 46). In conclusion, significant hormonal fluctuations during the menstrual cycle, the vasoprotective effects of estrogen, and menopausal status may explain the absence of a significant correlation between reproductive hormones and baPWV in women.

Although our study did not find a significant effect of sex hormones on baPWV, the effect of sex hormones on arteriosclerosis cannot be disregarded according to previous literature reports. Testosterone and estrogen regulate endothelial function by modulating nitric oxide release (49), which is partly similar to the mechanism of reproductive hormones. Compared to sex hormones, reproductive hormones may identify differences and assess CVD risk earlier. Previous studies often focused on sex hormones without incorporating reproductive hormones, so the specific interactions require verification through prospective studies.

LH and FSH play essential roles in regulating gonadal development, maturation, and function. LH and FSH perform their biological functions by binding to LH receptors (LHR) and FSH receptors (FSHR), respectively. Aside from the well-known reproductive tissues, LHR and FSHR are expressed in human umbilical vein endothelial cells (50, 51). However, the mechanisms underlying the effects of LH and FSH on AS remain unclear. Arteries have three layers of walls: endothelium, media, and adventitia. Abnormalities in any of these three layers can lead to arteriosclerosis. Animal experiments have confirmed that elevated LH inhibits the release of nitric oxide (NO) from human umbilical vein endothelial cells by blocking the PI3K/Akt/eNOS pathway (51). After 2 weeks of treatment with the nonspecific NO synthase inhibitor L-NAME, aged spontaneously hypertensive rats exhibited reduced NO levels and increased AS (52). These findings confirm that NO plays an important role in the onset of arteriosclerosis. Impaired NO release is a feature of endothelial dysfunction (53). Impaired NO release may mediate LH-induced endothelial dysfunction and arteriosclerosis. Additionally, in a mouse model, mice treated with GnRH/LHRH antagonists (exhibiting higher FSH levels but unchanged testosterone levels) had less fat mass and fewer atherosclerotic plaques than mice treated with agonists or orchiectomy (54), suggesting that FSH may be related to arteriosclerosis in the context of androgen deprivation therapy. It is worth noting that neovascularization plays a crucial role in the occurrence and development of arteriosclerosis. Angiogenesis is a physiological process dynamically regulated by angiogenic and angiostatic factors. Angiogenesis inhibitors have been shown to inhibit angiogenesis and plaque growth in mouse models (55), indicating that angiogenesis is related to the development of plaque. FSHR has been detected in human umbilical cord endothelial cells, and FSH can directly stimulate the process of angiogenesis in endothelial cells (56). FSH activates endothelial cells through FSHR/G αs/cAMP/PKA and PI3K/Akt/mTOR/NF-κB signaling pathways and expresses intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), thereby recruiting human monocytes to the endothelium and causing an inflammatory reaction (57).

The molecular mechanisms linking obesity to arteriosclerosis are intricate and multifactorial. There is a potential synergistic effect between obesity-related factors and reproductive hormones in promoting arteriosclerosis. Obesity represents a chronic low-grade inflammatory state, accompanied by an increase in inflammatory markers such as interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) (58). Both IL-6 and TNF-α can induce endothelial dysfunction and exacerbate arteriosclerosis by increasing ICAM-1 and VCAM-1 expression (59). Obesity contributes to arteriosclerosis by impacting NO availability. Excess free fatty acids and oxidative stress in obese individuals result in the production of reactive oxygen species, which react with NO, reducing its bioavailability (60). This reduction in NO, combined with endothelial NO synthase dysfunction, leads to endothelial dysfunction and contributes to the development of arteriosclerosis (61).

Strengths and limitations of the study

To our knowledge, this is the first retrospective case–control study to specifically address the relationship between reproductive hormones and baPWV in obese individuals of different sexes. Compared to previous studies, ours was unique for several reasons: first, we assessed both reproductive hormones and sex hormones in the subjects. Second, reproductive hormones may serve distinct physiological functions in males and females. Therefore, to investigate the correlation between reproductive hormones and baPWV in different sexes, age-matched men and women were compared. Finally, the incidence of obesity increases annually, and obesity is an independent predictor of future CVD events. Therefore, our study focused on obese subjects.

Although the strengths of our study lie in the analysis of sex-specific subjects and the inclusion of comprehensive reproductive hormone indices, there were some limitations to our study that need to be addressed. First, our study population comprised exclusively of Chinese subjects, with nearly all

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participants recruited from the outpatient department of a single hospital. Consequently, this selection may introduce potential biases and limit the generalizability of our findings to broader populations. Secondly, during a woman's monthly hormonal cycle, reproductive hormones fluctuate widely depending on the menstrual cycle. We did not further investigate the relationship between the menstrual cycle and baPWV. In addition, postmenopausal women were excluded from our study to ensure age comparability between males and females. Due to the younger age of the sample population, no men with subclinical hypogonadism were included. Thirdly, although baPWV shows great prospects, it remains a research tool and cannot replace the gold standard. We should be cautious about interpreting AS results measured by baPWV. Large-scale validation studies may transform baPWV from a research tool to a clinical standard, solidifying its role in cardiovascular health monitoring. Finally, a causal relationship between reproductive hormones and baPWV could not be established because of the case–control design. In the future, it is imperative that multi-center and large-scale prospective studies are conducted to determine whether modifying FSH levels reverses arteriosclerosis and reduces cardiovascular events.

Conclusion

In conclusion, the association of reproductive hormones with AS in obese individuals manifests differently between men and women. Our findings indicate that FSH is a risk factor for arteriosclerosis in obese male subjects but not in obese female subjects. This provides a novel and intriguing perspective on the pathogenesis of CVD in obese subjects. Clinically, identifying FSH as a risk factor for AS in obese men underscores the importance of considering sex-specific hormonal influences when assessing cardiovascular risk and developing targeted interventions. This could lead to personalized treatment strategies aimed at reducing cardiovascular risk in obese men by modulating FSH levels. Further studies are required to address the potential reproductive hormone-mediated mechanisms affecting AS in males and females.

Supplementary materials
This is linked to the online version of the paper at https://doi.org/10.1530/EC-24-0190.

Declaration of interest
The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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Data availability statement
Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

Author contribution statement
TL and ES conceptualized and designed the study while also planning, organizing, and supervising its execution. HJ conducted data collection. TL and YJ wrote the early and final draft of the manuscript. All authors thoroughly reviewed and approved the final version of the manuscript.

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