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Research Article

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Posted Date: March 25th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9203321/v1

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Additional Declarations: No competing interests reported.

Association of Testosterone-to-Estradiol Ratio and Coronary Heart Disease: A NHANES-Based Study with the Weight-Adjusted Waist Index as a Potential Mediator

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ABSTRACT

Objectives

Sex differences in coronary heart disease (CHD) are well known, but the impact of sex hormone balance on cardiovascular risk is still unclear. We studied how the testosterone-to-estradiol ratio (TT/E2) relates to CHD and investigated whether abdominal fatness mediates this relationship across different sexes and menopausal states.

Methods

We included 9,558 adults aged ≥ 30 years from the 2013–2016 National Health and Nutrition Examination Survey (NHANES). Serum total testosterone and estradiol levels were measured using isotope-dilution liquid chromatography–tandem mass spectrometry. The TT/E2 ratio was log-transformed and standardized. CHD was defined as a self-reported physician diagnosis. Survey-weighted logistic regression models with multiple imputation estimated odds ratios

(ORs) and 95% confidence intervals (CIs), adjusting for demographic and cardiometabolic variables. Interaction terms evaluated effect modification by sex and menopausal status. Restricted cubic splines assessed dose–response relationships. A counterfactual mediation analysis was used to examine the mediating effect of the weight-adjusted waist index (WWI).

Results

In fully adjusted models, a higher log(TT/E2) was associated with a lower odds of CHD in men (OR per 1-SD increase: 0.81; 95% CI 0.70–0.94), but this association was not observed in women overall. There were significant interactions with sex (p_interaction = 0.017) and menopausal status (p_interaction = 0.009). Stratified analysis revealed an inverse relationship in premenopausal women (OR 0.73; 95% CI 0.56–0.95), but not in postmenopausal women. Spline analyses showed a mainly linear inverse association in men. WWI partially mediated the link in men (indirect effect $p = 0.019$), but not in premenopausal women.

Conclusions

A higher TT/E2 ratio was inversely associated with CHD in men and premenopausal women, with partial mediation by abdominal adiposity in men. These findings underscore the context-dependent role of sex hormone balance in cardiovascular risk.

Highlights

- A higher log-transformed testosterone-to-estradiol ratio (TT/E2) was inversely associated with coronary heart disease (CHD) in men after multivariable adjustment.
- A significant interaction was observed between TT/E2 and sex, indicating sex-specific heterogeneity in the hormone–CHD association.

- Among women, TT/E2 was inversely associated with CHD in premenopausal women but not in postmenopausal women.
- A predominantly linear inverse dose–response relationship between TT/E2 and CHD risk in men.
- Weight-adjusted waist index (WWI) partially mediated the association between TT/E2 and CHD in men, but not in premenopausal women.

Keywords

Coronary heart disease， Testosterone-to-estradiol ratio， Sex differences， Abdominal adiposity， NHANES

Plain Language Summary

Coronary heart disease (CHD) remains one of the leading causes of death worldwide, and its risk differs between men and women. Sex hormones such as testosterone and estrogen are thought to play an important role in these differences. However, it is still unclear whether individual hormone levels or the balance between them is more important for heart disease risk.

In this study, we analyzed data from a nationally representative sample of U.S. adults to examine whether the testosterone-to-estradiol ratio (TT/E2) was associated with CHD. We also explored whether abdominal fat, measured using the weight-adjusted waist index (WWI), could partly explain this relationship.

We found that a higher TT/E2 ratio was linked to a lower likelihood of CHD in men and in premenopausal women, but not in postmenopausal women. In men, part of this protective

association appeared to operate through lower levels of abdominal fat. In contrast, this indirect pathway was not observed in women.

These findings suggest that the balance between sex hormones—rather than testosterone or estrogen alone—may be important for heart health. Importantly, the relationship between hormone balance and CHD differs by sex and reproductive stage. Understanding these differences may help improve prevention strategies tailored to men and women at different life stages.

INTODUCTION

Coronary heart disease (CHD) remains a leading cause of death and disability globally, posing a significant public health challenge. [1] Population and clinical studies have well-established sex differences in CHD. These studies show apparent variations in the occurrence, presentation, and outcomes of CHD between men and women. [2,3,4] Typically, occurrence and death rates of CHD are higher among men. However, after menopause, the risk for women can notably increase, approaching that of men over 45 years old. [5] Evidence indicates that these sex-specific variations are driven by factors including hormones, genetics, vascular biology, and inflammation, with sex steroid hormones long recognized as pivotal. [6,7]

At normal physiological levels, both estrogen and testosterone protect the vascular system. [8] Estrogen exerts beneficial effects on the vessel by decreasing inflammation, reducing the expression of adhesion molecules, and inhibiting smooth muscle cell proliferation. [9] Such effects retard intimal thickening and plaque development, at least in part, underpinning the later and less frequent incidence of CHD in women before menopause than in men. [10] However, androgens and heart disease are a relatively complicated issue, one that cannot be narrowly defined. Although the specific mechanism is not yet clear, there have been some cross-sectional studies suggesting that men with low testosterone levels are more likely to have CHD, and patients display lower circulating testosterone compared with healthy controls.[11,12] Because estrogen and testosterone influence many biological and disease processes together, some researchers propose that the testosterone-to-estradiol ratio (TT/E2) may be a better indicator of cardiovascular risk than either hormone alone. [13] In this study, the authors reported that

higher levels of testosterone or estrogen alone were associated with a lower risk of myocardial infarction with UK biobank data. However, these associations weaken after adjusting for other covariates. Instead, the TT/E2 ratio persists as an independent predictor of CHD risk, suggesting that sex hormone balance may be more important than absolute levels in predicting CHD. [13]

In addition to their effects on cardiovascular conditions, sex hormones play a prominent role in lipid metabolism and body fat distribution. [14,15] In women, both estrogen deficiency (notably due to menopause) and increased androgen production (e.g., in polycystic ovary syndrome) lead to visceral and abdominal fat deposition. [15,16] Typically, estrogen increases fat deposits in the hips and thighs in women. [17] However, the postmenopausal reduction of estrogen is linked to visceral adiposity and an androgen-like fat pattern.[17] Normal testosterone and estrogen levels in men control fat accumulation as follows: Higher testosterone or lower estrogen levels reduce total and abdominal fat, whereas higher estrogen levels correlate with more overall (and apple) fat. [14,18] These observations suggest that the TT/E2 ratio may better represent the combined effects of sex hormones on fat distribution in both sexes.

Visceral adiposity is an independent risk factor for CHD, affecting health through pathways such as endothelial dysfunction, inflammation, and insulin resistance. [19, 20] It also exacerbates traditional cardiovascular risks, including hypertension, diabetes, and dyslipidemia. [21] The WWI normalizes waist circumference by dividing it by the square root of body weight. [22] It can provide a better reflection of central obesity than classical measures such as BMI and waist circumference. [22] Furthermore, it shows a stronger correlation with adverse

cardiovascular events and better predictive performance. [23] So far, it is known that hormonal imbalance promotes visceral fat accumulation, [24,25] and visceral adiposity is strongly linked to CHD development. Therefore, the accumulation of visceral fat may play a role in the process by which hormonal imbalance leads to CHD. However, as a feasible and straightforward indicator of visceral fat accumulation, no research has yet thoroughly examined whether WWI mediates the link between TT/E2 imbalance and CHD, or whether this mediation varies by sex or menopausal status.

Overall, evidence suggests that the TT/E2 ratio may more accurately reflect hormonal balance than individual hormone levels. Meanwhile, visceral adiposity is likely a significant intermediate link in the association between changes in hormone levels and CHD, with WWI serving as a convenient marker of visceral fat in large population studies. The present study aims to investigate, using a representative sample of the U.S. population, the association between the TT/E2 ratio and CHD risk. It also examines whether WWI serves as a mediator in the relationship between the TT/E2 ratio and CHD. By reviewing these associations across the whole population and in sex- and menopause-stratified subgroups, this will yield a greater understanding of sex differences in CHD and inform early CHD prevention efforts by targeting hormonal and metabolic pathways.

METHOD

Study population

Data for this study were obtained from the 2013–2014 and 2015–2016 NHANES cycles, nationally representative surveys with a complex, multistage sampling design conducted to

assess the health and nutritional status of the civilian, noninstitutionalized U.S. population. The National Center approved the study protocol for Health Statistics Research Ethics Review Board, and all participants provided written informed consent. Initially, 20,146 individuals were identified. Individuals under 30 years old (n = 10588) were excluded, leaving 9,558 adults eligible for analysis. Several variables had missing data, which were handled using multiple imputation to reduce bias and maintain analytical efficiency. (Fig 1) The final dataset comprised all 9,558 eligible participants: 4,577 men (383 with CHD and 4,194 without) and 4,981 women (242 with CHD and 4,739 without). In women, menopausal status was determined using the reproductive health questionnaire, with 2,031 premenopausal and 2,950 postmenopausal individuals.

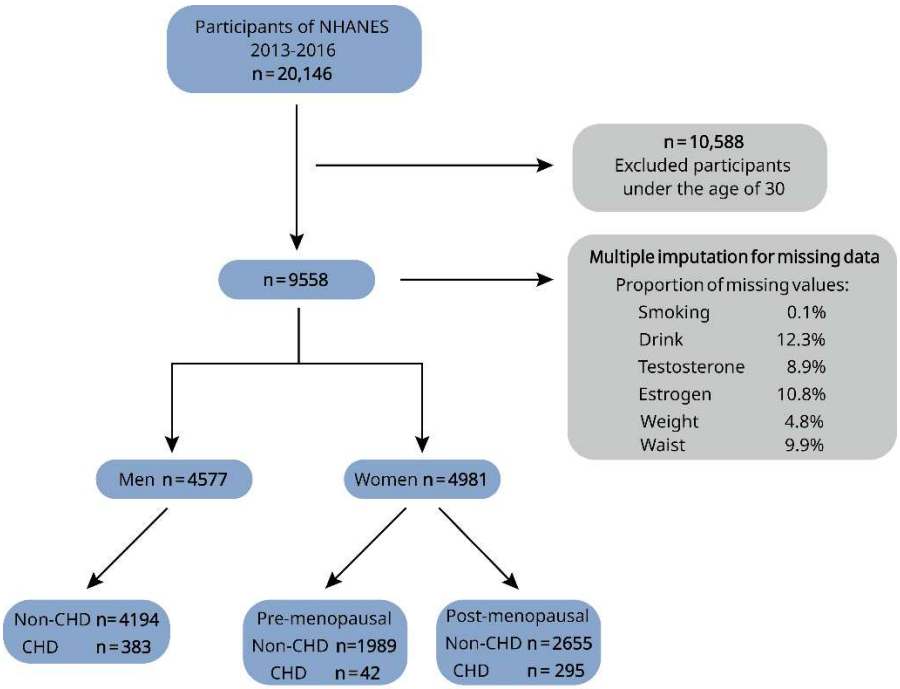


Fig.1 Flow chart of participant selection and the process of missing values

VARIABLES

Exposure: Sex Hormone Ratio

Serum concentrations of total testosterone and estradiol were determined by isotope-dilution high-performance liquid chromatography-tandem mass spectrometry (ID-LCMSMS). Hormone data were obtained from the NHANES TST_H and TST_I files, which contain LBXTST (total testosterone, ng/dL) and LBXEST (estradiol, pg/mL). For values below the detection limit, we replaced them with the reported detection limit divided by the square root of 2, as specified in the NHANES analytical protocol. The testosterone-to-estradiol ratio (TT/E2) was calculated as total testosterone divided by estradiol after cross-cycle standardization. Because the distribution of TT/E2 was right-skewed, we natural log-transformed the values for analyses modeling exposure as a continuous variable.

Outcome: Coronary Heart Disease (CHD)

The history of CHD was ascertained from self-reported physician diagnoses collected via the NHANES Medical Conditions Questionnaire. Three questionnaire items were extracted: whether participants had ever been told they had coronary heart disease, angina/angina pectoris, or a heart attack. CHD was coded as present if any of these conditions were reported; participants with all responses missing were coded as having a missing CHD status. The final variable was analyzed as a binary outcome (yes/no).

Mediator: Weight-Adjusted Waist Index (WWI)

Waist circumference and body weight measurements were taken from the NHANES body measures examination. Based on these data, the WWI was calculated by dividing waist circumference (cm) by the square root of body weight (kg) [22], as defined below:

171 $$WWI = \frac{WAIST}{\sqrt{WEIGHT}}$$

172 In the present study, WWI was treated as a continuous variable and served as the mediator to
173 evaluate the indirect pathway linking disturbances in the testosterone-to-estradiol ratio (TT/E2)
174 to the development of CHD.

175 **Covariates**

176 At baseline, demographic characteristics, lifestyle behaviors, and medical history were gathered
177 through standardized interviews conducted by trained NHANES staff. Covariates included age,
178 sex, race (Mexican American, Non-Hispanic White, Non-Hispanic Black, or Other), education
179 level (less than high school or high school and above), marital status (married and living with
180 a partner or not), smoking history (lifetime consumption of at least 100 cigarettes or fewer),
181 alcohol intake (≥12 drinks in the past year or not), and family socioeconomic status, determined
182 using the poverty–income ratio and classified as poor (≤1.3) or not poor (>1.3).

183 Anthropometric and biochemical parameters were collected through standard physical
184 examinations and laboratory tests. Cardiometabolic comorbidities were identified by
185 integrating survey responses with clinical and laboratory data. Hypertension was defined as
186 elevated blood pressure (mean systolic ≥140 mm Hg or diastolic ≥90 mm Hg), a self-reported
187 physician diagnosis. Diabetes was characterized by fasting plasma glucose ≥126 mg/dL,
188 glycated hemoglobin ≥ 6.5%, use of insulin or oral hypoglycemic agents, or a documented
189 diagnosis by a healthcare provider. Hyperlipidemia was defined as a reported history of high
190 cholesterol or abnormal lipid levels at screening, including elevated total cholesterol,
191 triglycerides, or LDL cholesterol, and low HDL cholesterol. In women, menopausal status was

assessed using responses to the reproductive health questionnaire and age (>55 years) to distinguish between premenopausal and postmenopausal states.

Statistical Analysis

All statistical analyses were conducted in RStudio (2025.09.1+401). The NHANES multistage complex sampling design was incorporated by using sample weights, strata, and primary sampling units (PSUs). Summary statistics described baseline characteristics: continuous data were expressed as means with standard deviations or medians with interquartile ranges, while categorical data were presented as survey-weighted frequencies and percentages. To compare the CHD and non-CHD groups, differences in continuous variables were tested with survey-weighted t-tests (Mann–Whitney U tests) and differences in categorical variables with design-adjusted chi-square tests.

Since several variables contained missing data, we applied multiple imputation by chained equations (MICE) to produce 20 complete datasets before analysis. All variables were incorporated into the analytic models during imputation, ensuring the NHANES design features were maintained. The regression estimates from these imputations were combined following Rubin's rules.

Log-transformed TT/E2 was analyzed in the survey-weighted logistic regression model for CHD, controlling for potential confounders in the population as a whole and in women and men separately. For women, supplementary analyses were conducted within premenopausal and postmenopausal subgroups. Log-transformed TT/E2 was treated as a continuous variable to assess linear trends with CHD. We investigated effect modification by sex and menopausal

status by including interaction terms with log (TT/E2).

Restricted cubic spline (RCS) models were applied to evaluate potential nonlinear associations between TT/E2 and CHD. Spline analyses were restricted to subgroups in which continuous associations were statistically significant in fully adjusted models—namely, men and premenopausal women.

We conducted a counterfactual-based causal mediation analysis within a survey-weighted multiple-imputation framework to assess whether WWI mediates the association between log(TT/E2) and CHD. Survey-weighted linear and logistic models were fitted to each imputed dataset and pooled using Rubin's rules. We estimated the average causal mediation effect (ACME), the average direct effect (ADE), and the total effect. Statistical uncertainty was evaluated via parametric Monte Carlo simulation (5,000 replications), and the proportion mediated was computed as ACME divided by the total effect.

To evaluate the robustness of our findings, sensitivity analyses were performed using complete-case datasets by excluding participants with missing values. Survey-weighted logistic regression models were re-estimated in the complete-case samples, and additional unweighted models were fitted to assess the influence of the complex sampling design. The consistency of the results was examined in comparison with the primary analyses based on multiple imputation. In addition, interaction effects were re-evaluated in complete-case weighted models to confirm their stability.

All statistical tests were two-sided, and p-values < 0.05 were considered statistically significant.

RESULTS

Baseline characteristics of the study population

Table 1 presents the baseline characteristics of the 9,558 eligible participants included in the final analysis. The study population comprised 825 participants with prevalent CHD and 8,733 without CHD.

Participants with CHD were older than those without CHD, with median ages of 67 years (IQR: 58, 76) and 51 years (IQR: 40, 62), respectively ($p < 0.001$). The sex composition also differed between groups, with men comprising a larger share of the CHD group than the non-CHD group (57.2% vs. 46.9%; $p < 0.001$). Statistically significant differences were also observed in race, educational attainment, marital status, and poverty-income ratio (PIR) between the two groups ($p < 0.05$).

Regarding lifestyle factors, smoking was more prevalent among participants with CHD than among those without CHD (62.0% vs. 44.6%; $p < 0.001$). In contrast, alcohol consumption did not differ significantly between the two groups ($p = 0.504$).

Participants with CHD had a higher prevalence of cardiometabolic comorbidities than those without CHD. Specifically, diabetes (36.7% vs. 15.5%), hypertension (76.0% vs. 43.2%), and hyperlipidemia (86.7% vs. 72.5%) were more prevalent in the CHD group ($p < 0.001$). In addition, WWI values were higher among participants with CHD [11.59 (11.15, 12.11)] than among those without CHD [11.09 (10.57, 11.64)] ($p < 0.001$).

Table 1. Baseline characteristics of the study participants

Variables	Non-CHD (n= 8733)	CHD (n= 825)	*p*-value
Age, median (IQR), years	51 (40, 62)	67 (58, 76)	<0.001
Gender, n (%)			<0.001
Men	4089 (46.9%)	488 (57.2%)	
Women	4644 (53.1%)	337 (42.8%)	
Race, n (%)			<0.001
Mexican American	1357 (8.5%)	88 (4.6%)	
Non-Hispanic White	3258 (66.3%)	418 (74.1%)	
Non-Hispanic Black	1810 (11.0%)	155 (9.5%)	
Other	2308 (14.1%)	164 (11.8%)	
Education, n (%)			0.003
Below high school	2060 (15.0%)	239 (19.6%)	
High School or above	6673 (85.0%)	586 (80.4%)	
Marital status, n (%)			<0.001
Yes	5578 (68.5%)	447 (56.9%)	
No	3155 (31.5%)	378 (43.1%)	
PIR, n (%)			<0.001
Poor	2488 (20.3%)	314 (30.0%)	
Not poor	5387 (79.7%)	435 (70.0%)	
Drinking, n (%)			0.504
Yes	5285 (76.1%)	527 (74.5%)	
No	2355 (23.9%)	217 (25.5%)	
Smoking, n (%)			<0.001
Yes	3800 (44.6%)	503 (62.0%)	
No	4922 (55.4%)	321 (38.0%)	
Diabetes, n (%)			<0.001
Yes	1695 (15.5%)	340 (36.7%)	
No	7038 (84.5%)	485 (63.3%)	
Hypertension, n (%)			<0.001
Yes	4017 (43.2%)	653 (76.0%)	
No	4716 (56.8%)	172 (24.0%)	
Hyperlipemia, n (%)			<0.001
Yes	6183 (72.5%)	692 (86.7%)	
No	2550 (27.5%)	133 (13.3%)	
WWI, median (IQR), NA	11.09 (10.57, 11.64)	11.59 (11.15, 12.11)	<0.001

Categorical variables are presented as unweighted counts and survey-weighted percentages. Data are column-normalized proportions, weighted by the survey; sums within each column equal 100%. Differences between groups for continuous variables were tested with survey-weighted Mann–Whitney U tests (svyranktest), while categorical variables were compared using design-adjusted chi-square tests with the Rao–Scott correction (svychisq). PIR, family poverty-income ratio; WWI, the Weight-adjusted Waist Index.

252 **Association of continuous log (TT/E2) with CHD across sex and menopausal status**

Survey-adjusted multiple logistic regression with multiple imputation was performed to investigate the association between the continuous log-transformed TT/E2 value and CHD across four subgroups: men, women, premenopausal women, and postmenopausal women. (Table 2). Log (TT/E2) was standardized, and odds ratios are presented for a 1-SD increment.

Table 2. Association of continuous log (TT/E2) with CHD across sex and menopausal status

Group	Model 1 OR (95% CI)	*P* value (M1)	Model 2 OR (95% CI)	*P* value (M2)	Model 3 OR (95% CI)	*P* value (M3)
Men	0.72 (0.63–0.82)	<0.001	0.75 (0.65–0.86)	<0.001	0.81 (0.70–0.94)	0.006
Women	1.79 (1.58–2.02)	<0.001	1.05 (0.91–1.21)	0.485	1.08 (0.93–1.24)	0.323
Pre-menopause	0.83 (0.62–1.10)	0.191	0.77 (0.59–1.01)	0.059	0.73 (0.56–0.95)	0.020
Post-menopause	1.30 (1.14–1.49)	<0.001	1.05 (0.91–1.21)	0.502	1.11 (0.95–1.29)	0.200

Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using survey-weighted logistic regression models with multiple imputation. Log (TT/E2) was standardized, and ORs are reported per 1-standard deviation (SD) increase.

Model 1 was adjusted for age only.

Model 2 was further adjusted for race, education level, marital status, PIR, smoking status, and alcohol consumption.

Model 3 was additionally adjusted for diabetes, hypertension, and hyperlipidemia. All *P* values are two-sided.

Among men, there was a consistent inverse relationship between higher log (TT/E2) and CHD. In the fully adjusted model (Model 3), each 1-SD increase in log (TT/E2) was associated with a 19% lower CHD odds (OR 0.81, 95% CI 0.70–0.94; $p = 0.006$).

Among women, the unadjusted model (Model 1: OR 1.79, 95% CI 1.58–2.02; $p < 0.001$) showed a positive association between log (TT/E2) and CHD. However, after adjusting for confounders, the association was attenuated and no longer statistically significant in the fully adjusted model (Model 3: OR 1.11, 95% CI 0.93–1.24; $p = 0.323$).

When women were stratified by menopausal status, a significant inverse association was observed among premenopausal women but not among postmenopausal women. Among premenopausal women, the fully adjusted model showed that each 1-SD increase in log (TT/E2) was associated with a 27% lower odds of CHD (OR 0.73, 95% CI 0.56–0.95; $p = 0.020$). Among

postmenopausal women, the positive association observed in the minimally adjusted model (Model 1: OR 1.30, 95% CI 1.14–1.49; $p < 0.001$) was no longer significant after full adjustment (Model 3: OR 1.11, 95% CI 0.95–1.29; $p = 0.200$).

Interaction Effects of Sex and Menopausal Status on the Association Between log (TT/E2) and CHD

Interaction between log (TT/E2) and gender on CHD

To assess whether the link between sex-hormone balance and CHD differs by sex, an interaction term between log (TT/E2) and sex was incorporated into survey-weighted logistic regression models using multiple-imputation pooling (Figure 2A). A significant interaction was detected (β for interaction = 0.31; OR = 1.36; 95% CI, 1.06–1.76; $p = 0.017$). Predicted probabilities from the fully adjusted model showed distinct association patterns for men and women across the log (TT/E2) spectrum.

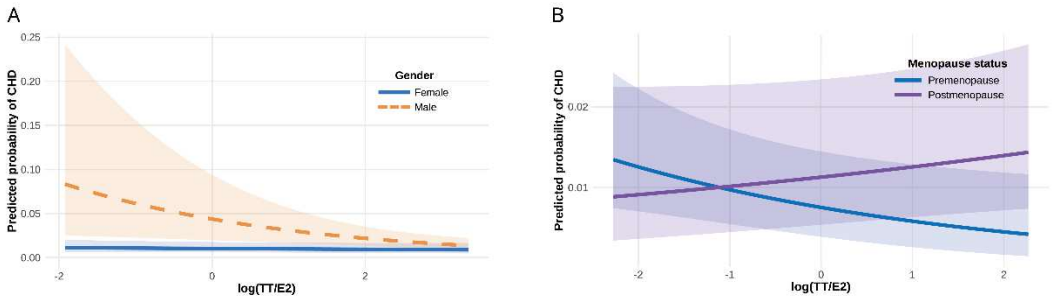


Fig.2 Interaction between log (TT/E2) and gender（A） / menopausal status (B) on the predicted probability of CHD.

Predicted probabilities were derived from survey-weighted logistic regression models that used multiple imputation and included an interaction term between log (TT/E2) and sex or menopausal status. The models were adjusted for age, race, education level, marital status, PIR, smoking status, alcohol consumption, diabetes, hypertension, and hyperlipidemia. Shaded areas represent 95% confidence intervals. Other covariates were held constant at their mean values or reference categories. The x-axis shows the standardized log-transformed TT/E2 ratio within the 5th-95th percentile range.

Interaction between TT/E2 and Menopausal Status among Women

To formally assess whether the associations between log (TT/E2) and CHD differed by menopausal status, an interaction term between log (TT/E2) and menopausal status was further examined among women (Figure 2B). A statistically significant interaction was detected (β for interaction = 0.35; OR = 1.42; 95% CI, 1.09–1.86; p = 0.009). Predicted probability curves differed between premenopausal and postmenopausal women across the range of log (TT/E2) in the fully adjusted model.

Restricted Cubic Spline

In men, restricted cubic spline analysis (Fig. 3A) showed a significant overall association between log (TT/E2) and CHD risk (p for overall association = 0.043). Although the test for non-linearity was statistically significant (p = 0.038), the spline curve indicated a largely monotonic inverse relationship, with no apparent threshold or risk reversal across the observed range of log (TT/E2).

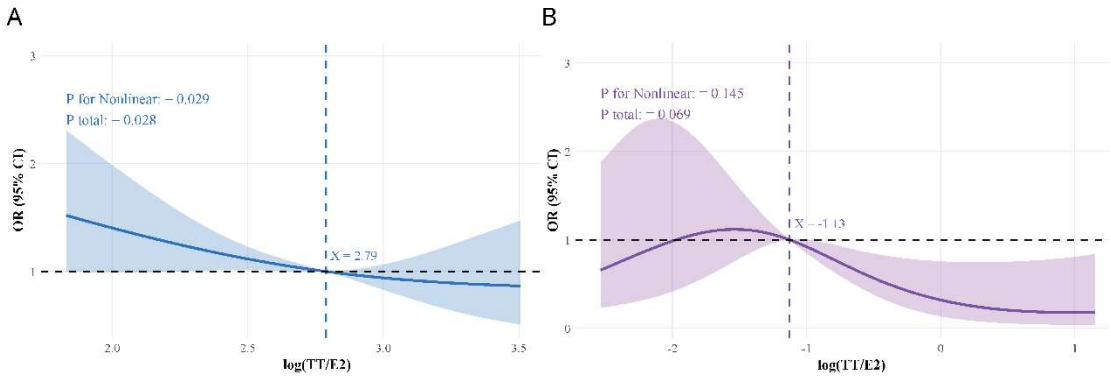


Fig 3. Restricted cubic spline of log (TT/E2) and CHD in men and premenopausal women

Restricted cubic spline curves illustrating the association between log-transformed TT/E2 and the odds of CHD. Models were fitted using survey-weighted logistic regression with multiple imputation and adjusted for age, race, education level, marital status, poverty–income ratio, smoking status, alcohol consumption, diabetes, hypertension, and hyperlipidemia. The dashed vertical line marks the median log (TT/E2) value, and shaded areas denote 95% confidence intervals.

In premenopausal women, restricted cubic spline analysis (Fig. 3B) did not reveal a statistically significant association between log (TT/E2) and CHD. Both the overall association (p total = 0.061) and the test for non-linearity (p nonlinear = 0.124) were non-significant. Although minor fluctuations appeared in the curve at the distributional extremes, these were driven by sparse data and did not represent meaningful non-linear patterns.

The mediating role of WWI in the association between log (TT/E2) and CHD

In men, WWI demonstrated a significant mediating role in the association between log (TT/E2) and CHD. As shown in Fig. 4A, a higher log (TT/E2) was associated with a lower risk of CHD, and part of this association was transmitted through WWI. The indirect effect through WWI was statistically significant (β = −0.106, p = 0.019). Although WWI accounted for 36.9% of the total impact, the proportion mediated did not reach statistical significance (p = 0.777).

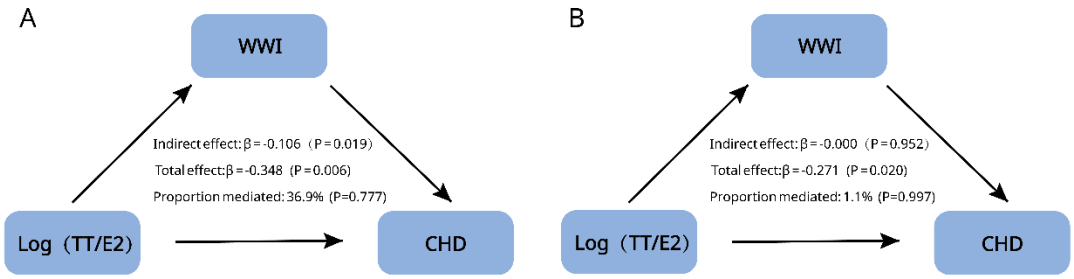


Fig 4. Mediation analysis of waist-weight index (WWI) in the association between log-transformed TT/E2 and CHD in men （A） and premenopausal women

All mediation models were fitted using survey-weighted multiple imputation regression and adjusted for age, race, education level, marital status, poverty–income ratio, smoking status, alcohol consumption, diabetes, hypertension, and hyperlipidemia.

On the other hand, WWI did not alter the association between log (TT/E2) and CHD in premenopausal women. The indirect effect was null and non-significant (β = 0.000, p = 0.952), and the proportion of mediation was minimal (1.1%, p = 0.997). When the total effect of log (TT/E2) on CHD was calculated, it remained statistically significant (β = −0.271, p = 0.020).

Sensitivity analyses using complete-case weighted and unweighted models yielded results broadly consistent with the primary findings.

Sensitivity

Sensitivity analyses using complete-case weighted and unweighted models yielded results broadly consistent with the primary findings (Supplementary Table S6 and Figure S2). Similar patterns were observed for the interaction terms (Supplementary Table S7 and Figure S3).

DISCUSSION

We examined the association between sex hormone balance and CHD, focusing on sex and menopausal status as effect modifiers and abdominal obesity as a potential mediator. In multivariable-adjusted logistic regression analyses, there was an inverse association between log (TT/E2) and CHD risk among men but not among women overall. Additional subgroup analysis by menopausal status revealed a consistent inverse relationship between log (TT/E2) and CHD risk in premenopausal women, whereas no significant association was observed in postmenopausal women. P-values for the interaction between sex and menopausal status with log (TT/E2) in the CHD association were derived from interaction analyses to formally assess effect modification. Restricted cubic spline analysis provided additional support for these results, demonstrating a more potent inverse dose–response association between log (TT/E2) and CHD risk in men. In contrast, the association was noticeably weaker among premenopausal women. In addition, mediation analyses indicated that the association between log (TT/E2) and CHD risk in men was partially mediated through WWI. However, no such mediating effect was observed among premenopausal women. Taken together, these findings demonstrate

considerable heterogeneity in the log (TT/E2)-CHD relationship by sex and female reproductive status, and suggest that abdominal obesity may be a key intermediate mechanism linking hormonal imbalance to CHD risk in men.

Sex Hormone and CHD

This study conducted a systematic analysis of the associations between sex hormones and CHD using NHANES data. We observed an inverse relationship between androgen levels and CHD risk in men (Supplementary Materials: Table S1), consistent with prior cross-sectional studies. [26] Notably, both log-transformed testosterone [log (TT)] and log (TT/E2) were independently associated with CHD in their respective multivariable-adjusted models. To compare the relative predictive contributions of these indicators, we fitted joint models that included both log (TT) and log (TT/E2). (Supplementary Materials: Table S2) As expected, given their mathematical dependence [log (TT/E2) = log (TT) − log(E2)], substantial collinearity was observed, and neither variable retained independent statistical significance after mutual adjustment. Based on the above findings, in men, both log (TT) and log (TT/E2) showed similar effectiveness in predicting CHD risk. While these results highlight the important role of androgens in male CHD development, log (TT/E2) is more comprehensive and may be better suited for future cross-sex comparisons.

In women, it has traditionally been assumed that the vascular protective effects of estrogen explain the lower incidence of CHD in premenopausal women compared with age-matched men. [27] However, in the present study, log(E2) was not significantly associated with CHD risk among premenopausal women. Instead, log (TT/E2) correlated similarly to that in men.

Conversely, among postmenopausal women with markedly lower E2 levels, log (TT/E2) was no longer predictive, whereas log(E2) remained inversely associated with CHD risk. (Supplementary Materials: Table S3 and Fig S1) These findings differ from those of an extensive prospective study, which reported that a higher log (TT/E2) ratio was significantly associated with increased CHD risk in postmenopausal women and emphasized the long-term importance of sex hormone balance for cardiovascular health in this population.[28] Given the observational nature and limited sample size of the present study, our results are insufficient to refute those conclusions. If prospective evidence is considered definitive, it would further underscore the importance of log (TT/E2) in predicting CHD risk.

Overall, log (TT/E2), as a representative indicator of hormonal balance, moves beyond the traditional view of testosterone or estrogen as sex-specific hormones and may more closely reflect the underlying endocrine milieu than either hormone alone. [29]

Sex Differences in the Predictive Value of Sex Hormone Balance for CHD

In men, the predictive relationship between sex hormone balance and CHD risk appears relatively straightforward. When analyzed as a continuous variable, log (TT/E2) was significantly inversely associated with CHD risk, and restricted cubic spline analyses indicated that this association was directionally consistent throughout the exposure range, suggesting an approximately linear dose–response relationship. A lower T/E2 ratio has also been reported in cross-sectional studies of the CHD population compared with controls and was inversely associated with inflammatory and stress-related markers, such as GDF-15 and sgp130. [30,31] Experimental data also suggest that testosterone and estradiol may have a synergistic effect on

396 the suppression of GDF-15 or the promotion of sgp130, thereby inhibiting inflammation and
397 the progression of atherosclerosis. Taken together, these findings indicate that the impact of the
398 sex hormone ratio on CHD risk in men may operate through relatively direct and stable
399 biological mechanisms, with limited interference from other factors, resulting in a strong,
400 partially nonlinear association between the hormone ratio and CHD.

401 In contrast, CHD risk in women is influenced by a broader array of biological and contextual
402 factors. Sex hormone balance may represent only one of multiple pathways contributing to
403 CHD risk. Interaction analyses in the present study confirmed that both sex and menopausal
404 status significantly modified the association between log (TT/E2) and CHD. The presence of a
405 sex interaction indicates substantial heterogeneity in the log (TT/E2)–CHD relationship
406 between men and women, suggesting that the same ratio may reflect distinct endocrine–
407 metabolic contexts in the two sexes. [32] The menopausal interaction further refines this
408 heterogeneity among women, indicating that reproductive stage transitions represent a critical
409 juncture at which hormone–cardiovascular relationships are reweighted. Although log (TT/E2)
410 exhibited a linear association with CHD in premenopausal women, the spline analyses indicated
411 a relatively weak effect size. This finding suggests that, in addition to sharing traditional CHD
412 risk factors with men, women are also affected by sex-specific risk factors. Conditions such as
413 polycystic ovary syndrome, gestational diabetes, preeclampsia, infertility or recurrent
414 pregnancy loss, and premature menopause have all been linked to elevated future CHD risk.
415 [33]Moreover, inflammatory and autoimmune diseases, including systemic lupus
416 erythematosus and rheumatoid arthritis, are more prevalent in women and substantially increase

CHD risk. [34] Psychosocial and mental health factors also play a non-negligible role in the development of CHD among women. [35]

Mediating Role of Abdominal Obesity and Sex Differences

Through further mediation analyses, we systematically evaluated the potential mediating role of abdominal obesity—operationalized using the WWI—in the relationship between sex hormones and CHD risk. The results revealed pronounced sex differences in mediation patterns. In men, WWI had a partial mediating effect, with a statistically significant effect on the relationship between log (TT/E2) and the risk of CHD, implying that the hormone imbalance could indirectly increase the risk of CHD by favoring abdominal fat deposition and aggravating metabolic and inflammatory load. Previous research has demonstrated that testosterone deficiency or hormonal imbalance can drive the redistribution of fat toward visceral depots. [29] Visceral adipose tissue is highly metabolically active and promotes atherosclerosis through multiple pathways, including pro-inflammatory cytokine secretion, insulin resistance, and dyslipidemia. [36,37]The partial mediating role of WWI in the association observed in our study is consistent with a relatively direct and stable path (the "sex hormone balance–abdominal obesity–CHD" sequence) in men.

In contrast, among women, WWI did not show a stable or significant mediating role in the associations of either log (TT/E2) or log(E2) with CHD risk (Supplementary Materials: Figs. S4 and S5). Even though previous studies have shown that postmenopausal estradiol levels are negatively correlated with overall and central obesity (e.g., BMI, waist circumference, and waist-to-hip ratio), all of which are key determinants of WWI.[38,39] And estrogen may reduce

CHD risk through direct vascular-protective, anti-inflammatory, and endothelial effects, as well as through an adverse metabolic effect mediated by altered fat distribution.[40] Taken together, this series of results from our mediation analysis suggests that abdominal obesity is a central intermediate causal pathway linking sex hormone dysregulation to CHD risk in men. It does not operate predominantly through body fat distribution.

Strengths and limitations

This study's strengths mainly stem from its sampling design and analytical approach. Data collection employed a complex, multistage probability sampling strategy, with all analyses adjusting for survey weights, stratification, and PSUs, which improves population representativeness. The statistical methods were detailed and systematic: initially, weighted multivariable logistic regression estimated key associations; then, interaction terms for sex and menopausal status assessed effect modification; restricted cubic splines explored possible dose–response relationships; and mediation analyses were performed within a multiple-imputation framework that incorporated survey weights. Sensitivity analyses using complete cases also tested the robustness of the results.

Several limitations should be acknowledged. Although the overall sample size was relatively large, stratified subgroup analyses substantially reduced the number of CHD cases, potentially limiting statistical power. Hormone levels were measured at a single time point; in particular, estradiol levels fluctuate across the menstrual cycle in premenopausal women, which may reduce the stability of exposure assessment. Missing data were addressed using multiple imputation, but this approach relies on assumptions about the missing-data mechanism and does

not eliminate the possibility of residual confounding. Both CHD status and menopausal status were primarily determined through self-reported questionnaire data, introducing potential misclassification. Finally, the cross-sectional design precludes the verification of causal relationships among variables.

Perspectives and significance

The relationship between sex hormone balance and CHD risk is highly context-dependent, with considerable stratification by sex and female reproductive stage. Higher log (TT/E2) was inversely associated with CHD risk in men and premenopausal women but not in postmenopausal women. This association was only partially mediated by abdominal adiposity in men and was not a dominant pathway among women. These results provide initial evidence that endocrine cardiovascular risk differences between men and women are likely driven by numerous, interconnected non-metabolic and biological mechanisms rather than by a unique metabolic axis. In conclusion, our findings emphasize the importance of an analytic approach that jointly considers sex, reproductive stage, and female-specific risk profiles when assessing the effects of endocrine factors on CHD risk

Supplementary Information

Supplymentary materials: **Table S1.** Association between standardized log-transformed total testosterone [log (TT)] and coronary heart disease (CHD), stratified by sex and menopausal status. **Table S2.** Joint association of log (TT) and log (TT/E2) with CHD in men. **Table S3.** **Figure S1.** Restricted cubic spline analysis of the association between log (E2) and CHD in postmenopausal women. The solid line represents adjusted odds ratios (ORs) and the shaded

area indicates 95% confidence intervals (CIs). Association between standardized log-transformed estradiol [log(E2)] and CHD by sex and menopausal status. **Table S4.** Mediation analysis of the association between log (TT/E2) and CHD with weight-adjusted waist index (WWI) as a mediator in premenopausal women. **Table S5.** Mediation analysis of the association between log(E2) and CHD with WWI as a mediator in postmenopausal women. **Table S6.** Sensitivity analyses for the association between log (TT/E2) and CHD across sex and menopausal subgroups. **Table S7.** Sensitivity analyses for the interaction of log (TT/E2) with sex and menopausal status in relation to CHD. **Figure S2.** Sensitivity analyses for the association between log (TT/E2) and CHD across sex and menopausal subgroups. Odds ratios (ORs) with 95% confidence intervals (CIs) are presented on a logarithmic scale for the primary analysis (multiple imputation with survey weighting), complete-case weighted models, and complete-case unweighted models. **Figure S3.** Sensitivity analyses for the interaction between log (TT/E2) and sex and between log (TT/E2) and menopausal status. Interaction odds ratios (ORs) with 95% confidence intervals (CIs) are presented for the primary analysis and complete-case weighted models.

Acknowledgements

We thank the participants and staff of the National Health and Nutrition Examination Survey (NHANES) for their valuable contributions to this study. We also acknowledge the data statistics support from the Key Laboratory of Precision Diagnosis and Treatment of Heart Failure, Shanxi Cardiovascular Hospital.

Author contributions

Author contributions

Yifan Li conceptualized the study and drafted the manuscript. Weiwei Chen performed the statistical analyses. Ningning Liu provided methodological guidance. Jicheng Xi critically revised the manuscript. All authors contributed to data interpretation and approved the final version of the manuscript.

Funding

This study was supported by the Four "Batches" Innovation Project of Invigorating Medical through Science and Technology of Shanxi Province (Grant No. 2023XM053), awarded to Jicheng Xi.

Availability of data and materials

The datasets analyzed during the current study are publicly available from the National Health and Nutrition Examination Survey (NHANES) database at https://www.cdc.gov/nchs/nhanes/.

Declarations

Ethics approval and consent to participate

The National Health and Nutrition Examination Survey (NHANES) was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board, and all participants provided written informed consent. The present study used publicly available de-identified data and was therefore exempt from additional ethical approval.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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