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Association between uric acid/high-density lipoprotein cholesterol ratio and testosterone deficiency in adult American men: findings from the national health and nutrition examination survey 2011–2016

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Abstract

Background Testosterone deficiency (TD) is a globally recognized health concern, closely linked to disruptions in uric acid and lipid metabolism. Recently, the uric acid to high-density lipoprotein cholesterol ratio (UHR) has emerged as a comprehensive index for assessing the impact of inflammation and metabolic disturbances on disease risk. Therefore, we intended to explore the association of UHR with total testosterone levels and the risk of TD among US male adults.

Methods The analysis was based on data from the National Health and Nutrition Examination Survey (NHANES) conducted between January 2011 and December 2016. All eligible participants were males aged 20 and older who had complete data for UHR and testosterone levels. The associations between UHR and total testosterone levels and the risk of TD were examined using weighted multivariable linear and logistic regression analysis, respectively. To visually demonstrate the linear relationship between them, weighted regression using generalized additive models and smooth curve fits were applied. Furthermore, subgroup analyses with interaction tests were executed to evaluate the stability of the outcomes.

Results Finally, a total of 2,844 men were enrolled in the study with the weighted mean age of 47.72 ± 0.42 years. Of these, 592 were diagnosed with TD. After controlling for potential confounders, the continuous UHR exhibited a

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positive linear correlation with the risk of TD (OR = 1.08, 95%CI: 1.04–1.11, $P < 0.001$) and a negative linear correlation with total testosterone levels (β=-7.82, 95%CI: -10.47 to -5.17, $P < 0.0001$). When UHR was categorized into quartiles, with Q1 as the reference, participants in Q4 had significantly lower total testosterone levels (β = -96.64, 95% CI: -129.39 to -63.90, $P < 0.0001$) and a higher risk of TD (OR = 2.35, 95%CI: 1.45–3.80, $P = 0.001$). These associations remained stable in subgroup analyses without significant interaction (all P for interaction > 0.05).

Conclusions The study indicates that, among adult males, higher UHR is negatively correlated with total testosterone levels and positively associated with the risk of TD. This suggests its potential value for early disease diagnosis and intervention. However, further clinical studies are needed to validate these findings.

Keywords Uric acid/High-density lipoprotein cholesterol ratio, Testosterone deficiency, Total testosterone level, NHANES database, Cross-sectional study

Introduction

Testosterone, an essential male sex hormone, is primarily produced by the Leydig cells in the testes and is predominantly regulated by the negative feedback mechanism of the hypothalamic-pituitary-gonadal axis (HPGA) [1]. Beyond its crucial role in reproductive and sexual functions, maintaining normal testosterone levels in men is vital for regulating various aspects such as cognitive functions, metabolic processes, and cardiovascular health [2-6]. Normal testosterone levels in men range from 300 to 1000 ng/dL, while testosterone deficiency (TD) is defined as levels below 300 ng/dL and is associated with specific symptoms [7]. TD is a prevalent condition among men, with incidence increasing with age and certain common diseases, such as obesity, diabetes, and hypertension [8]. In the United States, 20–50% of men are affected by TD, with approximately 500,000 new diagnoses each year [9]. As a global health concern, TD presents not only common sexual symptoms like erectile dysfunction, decreased libido, and difficulty achieving orgasm but also serious nonsexual symptoms, including obesity, depression, decreased bone mineral density, and cardiovascular diseases (CVD), all of which negatively impact a man's quality of life [1, 10, 11, 12]. Therefore, investigating modifiable risk factors to mitigate the incidence of TD, is critical in improving the long-term prognosis for patients and enhancing their quality of life.

Uric acid (UA), a byproduct of purine metabolism, plays a dual role in the body. At physiological concentrations, it acts as an antioxidant and anti-inflammatory agent. However, when elevated abnormally, it triggers chronic inflammation and oxidative stress, which may contribute to various diseases [13, 14]. Uric acid-induced high oxidative stress leads to increased insulin resistance and reduced insulin sensitivity, which in turn results in decreased synthesis of sex hormone-binding globulin (SHBG) in the liver [15]. Meanwhile, oxidative stress can directly affect Leydig cells, impairing the activity of 17β-hydroxysteroid dehydrogenase and cytochrome P450 enzymes, as well as mitochondrial function, thereby reducing testosterone production [16, 17]. Additionally, elevated UA can contribute to an increased conversion of testosterone to estradiol by stimulating aromatase activity [18]. A Mendelian randomization study suggests that elevated UA can mediate the decrease in testosterone levels through its effect on SHBG. In other words, elevated UA reduces SHBG levels, and SHBG further contributes to the decline in total testosterone levels [19]. Studies by Tan et al. and Han et al. further corroborate this negative correlation between serum uric acid (SUA) and total testosterone levels [20, 21]. Serum high-density lipoprotein cholesterol (HDL-C) protects the heart and lowers the risk of CVD because it aids in reverse cholesterol transfer, anti-oxidation, and anti-inflammation [22]. Previous research has repeatedly shown that low HDL-C levels are associated with low testosterone levels [23, 24]. However, UA and HDL-C individually reflect their respective influences. Recently, the ratio of UA to HDL-C (UHR) has emerged as a novel biomarker for more comprehensive assessment of inflammation and metabolic function [25]. To the best of our knowledge, a number of recent case-control studies have established the association between UHR and metabolic syndrome (MS), uncontrolled hypertension, diabetic nephropathy, Hashimoto's thyroiditis, and non-alcoholic fatty liver disease (NAFLD) [26-29]. Furthermore, as a promising biomarker, UHR exhibits superior assessment capabilities in diseases such as MS, type 2 diabetes, hypertension, and coronary artery disease, compared to the independent evaluation of HDL-C and UA [30-32]. Mechanistically, UHR better reflects the body's inflammation, oxidative stress, and lipid metabolism dysregulation, which are key pathological factors that may contribute to the development of TD. Therefore, studying the relationship between UHR and testosterone levels as well as TD in adults is meaningful, and this remains a research gap.

The aim of this study is to fill this knowledge gap using a nationally representative sample of adults in the United States. We hypothesize that higher UHR is negatively correlated with total testosterone levels and positively associated with the risk of TD in adult males.

Materials and methods

Study population and survey description

NHANES is an ongoing series of cross-sectional surveys conducted by the National Center for Health Statistics (NCHS) within the US Centers for Disease Control and Prevention. Since 1999, NHANES has been conducted in two-year cycles. The survey employs laboratory testing, physical examinations, and interviews to assess the general health and nutritional status of Americans across all age groups. Using a multiperiod probability-based sampling method, NHANES generates a nationally representative sample of the non-institutionalized civilian population in the United States. The study methods were reviewed and approved by the NCHS Research Ethics Review Board, and written informed consent was obtained from all participants.

Only three data cycles from NHANES January 2011 to December 2016 were utilized to fully represent our study population, as these cycles included simultaneous measurements of testosterone levels and UHR evaluations. The final cohort comprised 6,103 adult male participants after excluding female participants ($N = 15,151$), males under the age of 20 ($N = 6,506$), and those lacking data on testosterone levels ($N = 836$), UHR measurements ($N = 27$), medication use for testosterone (T)/HDL-C/uric acid (UA) ($N = 85$), and potential covariates ($N = 1,194$) from a total of 29,902 participants in the selected NHANES cycles. Figure 1 illustrates the comprehensive procedure for selecting samples.

Exposure and outcome variables' definition

The UHR, designed as the exposure variable, was calculated by dividing UA (mg/dL) by HDL-C (mg/dL) and multiplying by 100%. Blood samples collected from fasting participants in the morning were analyzed for UA and HDL-C, with UA measured using multi-channel analyzers (Hitachi Model 704, Beckman Synchron LX20, Beckman UniCel DxC800 Synchron, and Roche Cobas 6000) and HDL-C determined using the ARCHITECT automatic analyzer with Abbott reagent kits. The detailed measurement protocols are available at https://www.cdc.gov/nchs/nhanes/index.htm. UHR was used as both a continuous variable and as a quartile-based categorical variable in the analysis.

Morning serum samples were also obtained after an overnight fast to measure testosterone levels and minimize biological variability. Serum testosterone levels were measured using isotope dilution liquid chromatography tandem mass spectrometry (ID-LC-MS/MS), with a lower limit of detection of 0.75 ng/ml. Further details regarding the NHANES laboratory techniques for testosterone measurement can be found on the official NHANES website: https://www.cdc.gov/nchs/nhanes/index.htm. According to the American Urological Association, TD is defined as a total testosterone level of less than 300 ng/dL [7].

Assessment of study covariates

The research identified and adjusted for potential covariates based on existing literature related to testosterone levels. The demographic characteristics included age, body mass index (BMI), poverty-income ratio (PIR) (< 1, ≥ 1), race (Mexican American, Non-Hispanic White, Non-Hispanic Black, Other Race), educational level, and marital status. These demographic data were collected primarily through physical examinations and interviews. Additionally, significant health risk factors were considered, including estimated glomerular filtration rate (eGFR), smoking status, alcohol consumption, hypertension, DM, hyperlipidemia, and CVD. The eGFR was calculated using an equation based on serum creatinine levels [33].

Participants were classified into three groups based on smoking status: those who had smoked at least 100 cigarettes in their lifetime and were currently smoking were classified as 'currently smoking'; those who had smoked fewer than 100 cigarettes in their lifetime and were not currently smoking were classified as 'never smoking'; and those who had smoked at least 100 cigarettes in their lifetime but were not currently smoking were classified as 'former smoking'. Participants were classified as drinkers if they consumed 12 or more alcoholic beverages per year, and as non-drinkers if they consumed fewer. Hypertension was defined by a blood pressure ≥ 140/90 mmHg, self-reported hypertension, or antihypertensive medication use. DM was diagnosed based on self-report, insulin or oral medication use, or meeting at least one criterion: HbA1c ≥ 6.5%, FBG ≥ 126 mg/dL, or plasma glucose ≥ 200 mg/dL after OGTT. Prediabetes was defined by HbA1c between 5.7% and 6.4%, FBG between 100 and 125 mg/dL, or 2-hour plasma glucose between 140 and 199 mg/dL after OGTT, in the absence of diabetes. CVD was indicated by a history of coronary heart disease, angina, congestive heart failure, or heart attack. Hyperlipidemia was identified by total cholesterol > 240 mg/dL, hypercholesterolemia medication use, or a medical diagnosis of high cholesterol.

Statistical analyses

Given the NHANES complex multistage cluster survey design and the use of sample weighting, all statistical analyses in this study were conducted using appropriate sampling weights. Continuous variables were reported as weighted mean ± standard error (SE), while categorical variables were expressed as weighted percentages with SE. To assess baseline characteristic differences across UHR quartiles, survey-weighted linear regression was used for continuous variables, and survey-weighted

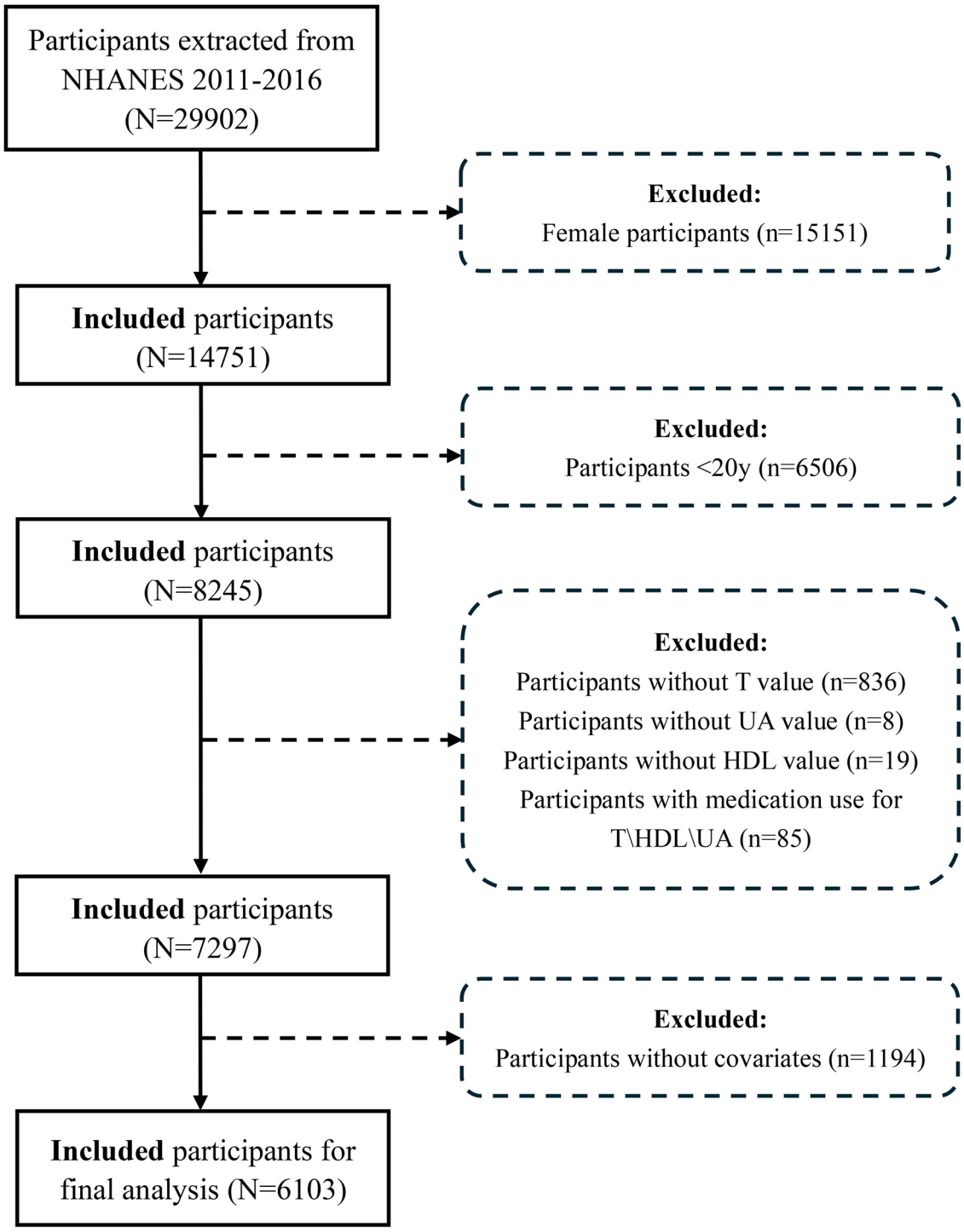

Fig. 1 Flow chart of the selection process for study population from NHANES 2011–2016. NHANES: National Health and Nutrition Examination Survey; T: testosterone; UA, uric acid; HDL, high-density lipoprotein cholesterol

Chi-square tests were applied for categorical variables. Two regression analyses were performed: (1) a multivariate linear regression analysis to evaluate the relationship between UHR and total testosterone levels, with results presented as β (95% confidence interval [CI]), and (2) a multivariate logistic regression analysis to assess the association between UHR and TD, with results expressed as odds ratios (OR) (95% CI). In Model 1, no covariates were adjusted. Model 2 adjusted for age, race, education, PIR, and marital status. Model 3 included additional adjustments based on Model 2, incorporating BMI, eGFR, TC, smoking status, alcohol consumption,

hypertension, DM, hyperlipidemia, and CVD. When UHR was treated as a quartiles-categorical variable, trend tests were performed.

To investigate the linear association between UHR and total testosterone levels, as well as the prevalence of TD, we employed smooth curve fitting and generalized GAM (Generalized Additive Models). GAM were used in this study to explore the nonlinear relationships between variables. It is a flexible statistical method that allows for the modeling of complex, non-linear relationships by incorporating smooth functions of continuous predictors. This approach is particularly useful when the relationship between the independent variables and the outcome is not strictly linear. The GAM analysis provides a more accurate understanding of these relationships and enhances the robustness of our findings. Additionally, we utilized stratified multivariate regression models for subgroup analyses to explore the associations between UHR and both total testosterone levels and TD in specific categories. The log-likelihood ratio test was applied to evaluate interaction terms, assessing heterogeneity among various subgroups, including age, BMI, DM, smoking status, hyperlipidemia, and CVD. A two-sided P-value < 0.05 was considered statistically significant. All statistical analyses were performed using R software (Version 4.0.2) and the R package (http://www.R-project.org, The R Foundation) [39]. Furthermore, the EmpowerStats program (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA) significantly contributed to our research.

Results

Baseline characteristics of study participants

Ultimately, 6,103 men aged 20 years or older were enrolled in the study. Table 1 summarizes the categories of TD status as part of the study population's baseline characteristics. The weighted mean age of the study population was 46.84 ± 0.39 years, with 25.19% of participants over 60. Among the participants, 1,674 were diagnosed with TD, while 4,429 were not. Compared to the non-TD group, those with TD were older (49.74 ± 0.60 years vs. 45.79 ± 0.46 years), had a higher probability of obesity (54.64% vs. 28.58%), and exhibited a greater prevalence of hypertension, pre-DM, DM, hyperlipidemia, and CVD. Conversely, compared to TD patients, non-TD people scored higher on eGFR, normal weight, alcohol use, and current smoking. It is noteworthy that TD individuals had greater UA (6.29 ± 0.04 mg/dl vs. 5.93 ± 0.02 mg/dl) and lower HDL (43.88 ± 0.46 mg/dl vs. 50.00 ± 0.40 mg/dl). Furthermore, the most satisfying finding is that people with TD had higher UHR levels than those without TD (15.30 ± 0.19 vs. 12.83 ± 0.11). Nevertheless, neither the TC nor the LDL markers were statistically significant ($P > 0.05$) (Table 1). Additionally, we compared total testosterone levels across different age groups, BMI, DM, and CVD status, with significant differences observed between the groups, as shown in Fig. 2.

Associations of UHR with testosterone level and TD

To better understand the relationships between total testosterone levels, the UHR, and the risk of TD, we conducted detailed multivariate regression analyses. The results are presented in Table 2. First, in every model, weighted linear regression analysis demonstrated a consistent negative association between UHR and total testosterone levels: Model 1 (β = -11.02, 95% CI: -12.16, -9.87, $P < 0.0001$), Model 2 (β = -11.18, 95% CI: -12.36, -10.01, $P < 0.0001$), and Model 3 (β = -6.30, 95% CI: -7.57, -5.02, $P < 0.0001$). Similarly, when we categorized continuous UHR into quartiles, the negative association remained statistically significant across all models. In the fourth quartile (Q4), total testosterone levels were lower compared to the first quartile (Q1): Model 1 (β = -136.01, 95% CI: -150.39, -121.62), Model 2 (β = -137.43, 95% CI: -152.37, -122.49), Model 3 (β = -75.09, 95% CI: -91.90, -58.28), all with $P < 0.0001$. Next, the relationship between UHR and the risk of TD was also explored using weighted logistic regression analysis. All three models showed a positive association between UHR and the risk of TD: Model 1 (OR = 1.11, 95% CI: 1.10, 1.13, $P < 0.0001$), Model 2 (OR = 1.12, 95% CI: 1.10, 1.14, $P < 0.0001$), and Model 3 (OR = 1.07, 95% CI: 1.05, 1.09, $P < 0.001$). After adjusting for all possible variables, participants in the Q4 had a 111% higher risk of TD compared to those in the first quartile (Model 3, OR = 2.11, 95% CI: 1.64, 2.71, $P = 0.001$). Finally, smooth curve fittings were used to visualize the nonlinear relationships between UHR and testosterone levels (Fig. 3). Specifically, UHR was negatively correlated with total testosterone levels (Fig. 3A), while UHR showed a positive association with TD risk (Fig. 3B) Table 3.

Subgroup analysis

Table 3 presents the results of subgroup analyses stratified by age group, BMI, smoking status, DM, hyperlipidemia, and CVD, considering UHR as a continuous variable. With the exception of the age and DM subgroups, most other subgroups demonstrated a significant negative association between UHR and total testosterone levels. No significant interactions were observed across any subgroups (all P for interaction > 0.05). In the age subgroup, participants older than 20 years exhibited a significant negative association: 20-40y (β = -11.23, 95% CI: -15.49, -6.96, $P < 0.0001$); 40-60y (β = -6.73, 95% CI: -9.68, -3.78, $P < 0.0001$); >60y (β = -3.13, 95% CI: -7.38, 1.12, $P = 0.14$). In the DM subgroup, a consistent negative association was observed only in participants without DM and those with borderline DM (No diabetes: β

Table 1 Baseline characteristics of the research population stratified by TD status, weighted

Characteristics	Total participants (*N* = 6103)	History of TD		*P* value
		No (*N* = 4429)	Yes (*N* = 1674)	
Age, years	46.84 ± 0.39	45.79 ± 0.46	49.74 ± 0.60	< 0.0001
BMI, kg/m^2	28.84 ± 0.13	27.69 ± 0.12	32.03 ± 0.28	< 0.0001
TC, mg/dl	189.00 ± 0.87	188.82 ± 0.91	189.48 ± 1.47	0.65
HDL, mg/dl	48.37 ± 0.33	50.00 ± 0.40	43.88 ± 0.46	< 0.0001
UA, mg/dl	6.02 ± 0.02	5.93 ± 0.02	6.29 ± 0.04	< 0.0001
eGFR	93.63 ± 0.47	94.57 ± 0.50	91.01 ± 0.66	< 0.0001
UHR	13.49 ± 0.11	12.83 ± 0.11	15.30 ± 0.19	< 0.0001
Total testosterone, ng/dl	416.79 ± 3.60	485.89 ± 3.39	225.35 ± 1.62	< 0.0001
Age group, %				< 0.0001
20-40y	37.22	40.10	29.26	
40-60y	37.59	36.21	41.38	
≥ 60y	25.19	23.69	29.36	
BMI, %				< 0.0001
Normal (< 25 kg/m^2)	26.30	31.60	11.61	
Overweight (25–30 kg/m^2)	38.22	39.83	33.75	
Obese (≥ 30 kg/m^2)	35.49	28.58	54.64	
PIR, %				0.15
< 1	13.83	14.28	12.59	
>=1	86.17	85.72	87.41	
Race, %				0.18
Mexican American	8.73	8.76	8.66	
Non-Hispanic White	68.50	68.00	69.88	
Non-Hispanic Black	9.34	9.77	8.16	
Other Race	13.43	13.48	13.31	
Education, %				0.86
Less than high school	14.78	14.63	15.18	
High school	22.40	22.56	21.97	
More than high school	62.82	62.81	62.85	
Marital status, %				< 0.0001
Solitude	33.50	36.19	26.06	
Cohabitation	66.50	63.81	73.94	
Smoke, %				< 0.0001
Never	49.94	50.27	49.03	
Former	28.84	26.55	35.20	
Current	21.22	23.18	15.77	
Alcohol, %				< 0.0001
No	21.55	19.62	26.89	
Yes	78.45	80.38	73.11	
Hypertension, %				< 0.0001
No	60.93	64.17	51.93	
Yes	39.07	35.83	48.07	
Diabetes, %				< 0.0001
No	74.80	77.63	66.98	
Prediabetes	9.78	9.98	9.22	
Yes	15.42	12.40	23.79	
Hyperlipidemia, %				< 0.0001
No	31.99	36.04	20.76	
Yes	68.01	63.96	79.24	
CVD, %				< 0.0001

Table 1 (continued)

Characteristics	Total participants (*N* = 6103)	History of TD		*P* value
		No (*N* = 4429)	Yes (*N* = 1674)	
No	90.79	91.74	88.16	
Yes	9.21	8.26	11.84	

Abbreviations TD, testosterone deficiency; BMI, body mass index; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; UA, uric acid; eGFR, estimated glomerular filtration rate; UHR, serum uric acid/high-density lipoprotein cholesterol ratio; PIR, poverty-income ratio; CVD: cardiovascular diseases

Statistical tests:

Continuous variables were presented as mean ± standard error ($\bar{x}$±SE), and the categorical variables were expressed as weighted percentages (%). The survey-weighted linear regression and weighted chi-square test were used to compare the differences between the two groups for continuous variables and categorical variables, respectively. Results were considered significant when $p < 0.05$

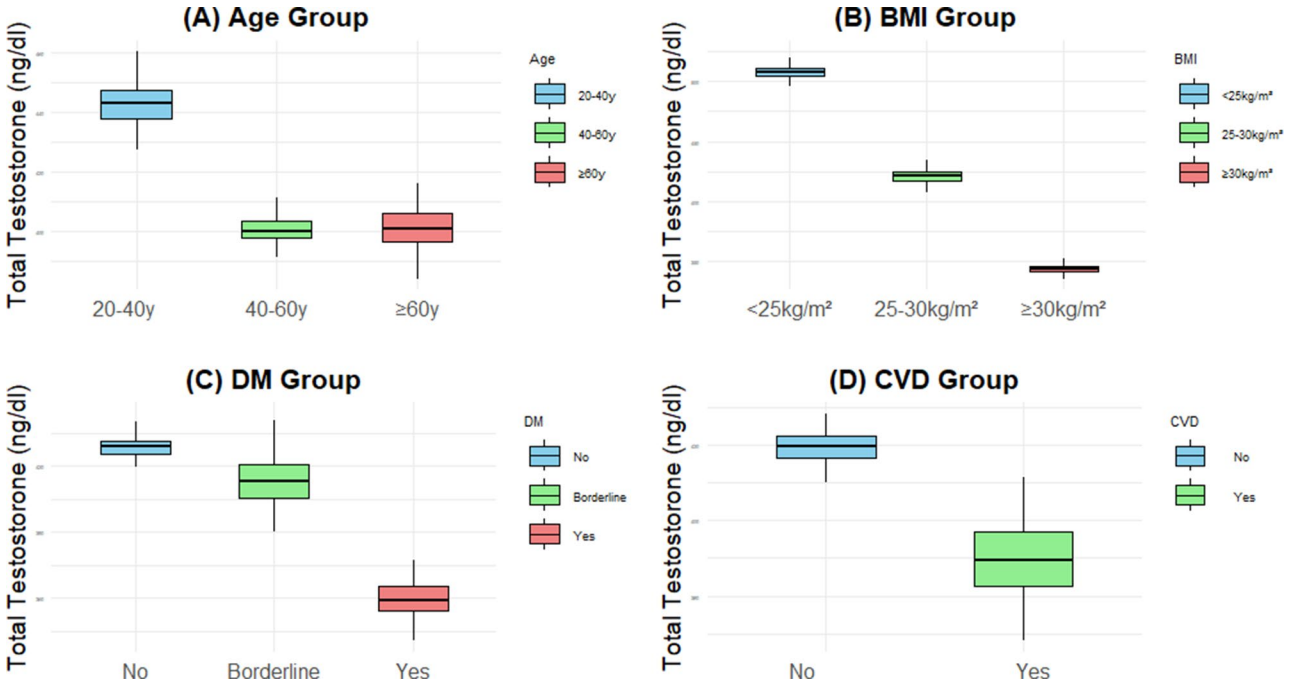

Fig. 2 Differences in total testosterone levels according to clinical characteristics. (**A**) Distribution of total testosterone levels across age groups; (**B**) Total testosterone levels stratified by body mass index (BMI) categories; (**C**) Total testosterone levels in subjects with different diabetes mellitus (DM) status; (**D**) Total testosterone levels in subjects with or without cardiovascular disease (CVD). Total testosterones were presented as mean ± standard error ($\bar{x}$±SE)

= -8.76, 95% CI: -11.38, -6.14, $P < 0.0001$; Borderline DM: β = -9.03, 95% CI: -12.30, -5.76, $P < 0.0001$). Similarly, the positive association between UHR and the risk of TD remained significant in the hyperlipidemia and CVD subgroups, with no interaction effects detected (all P for interaction > 0.05) (Fig. 4).

Following the division of the UHR into quartiles, Table 4; Fig. 5 present the results of the subgroup analysis. With the exception of the DM subgroup, the negative association between UHR quartiles and total testosterone levels was consistent. In the DM subgroup, the negative association was significant only among participants without DM and those with borderline DM: No DM (Q4 vs. Q1: β = -96.32, 95% CI: -131.30, -61.35, $P < 0.0001$); Borderline DM (Q4 vs. Q1: β = -108.56, 95% CI: -158.21, -58.91, $P < 0.001$). Similarly, with the exception of the age, smoking, and DM subgroups, the positive relationship between UHR quartiles and the risk of TD remained consistent across all other subgroups. For these associations, no interaction effects were observed (all P for interaction > 0.05).

Discussion

To our knowledge, this is the first large-scale study using nationally representative data, specifically NHANES 2011–2016, to explore the relationship between UHR, total testosterone levels, and the risk of TD. Our study demonstrates that UHR is linearly negatively correlated with total testosterone levels and positively correlated with the risk of TD in adult men. These relationships remain consistent when UHR is converted into four categories. Subgroup analysis and interaction tests confirmed that these associations hold stable across different subgroups.

Although no study has explored the relationship between UHR and testosterone levels, its association with

Table 2 Association between UHR and total testosterone and risk of TD, weighted

	Model 1	Model 2	Model 3
	Total testosterone (ng/dl)-β (95%CI) p-value		
Continuous UHR	-11.02(-12.16, -9.87), < 0.0001	-11.18(-12.36, -10.01), < 0.0001	-6.30(-7.57, -5.02), < 0.0001
Q1	Reference	Reference	Reference
Q2	-34.48(-54.54, -14.43), 0.001	-35.97(-55.41, -16.54), < 0.001	-15.66(-34.35, 3.04), 0.10
Q3	-79.06(-95.10, -63.01), < 0.0001	-79.66(-95.68, -63.65), < 0.0001	-40.25(-55.74, -24.77), < 0.0001
Q4	-136.01(-150.39, -121.62), < 0.0001	-137.43(-152.37, -122.49), < 0.0001	-75.09(-91.90, -58.28), < 0.0001
P for trend	< 0.0001	< 0.0001	< 0.0001
	Testosterone deficiency-OR (95% CI) p-value		
Continuous UHR	1.11(1.10,1.13), < 0.0001	1.12(1.10,1.14), < 0.0001	1.07(1.05,1.09), < 0.0001
Q1	Reference	Reference	Reference
Q2	1.29(0.96,1.75), 0.09	1.33(0.98,1.83), 0.07	1.03(0.74,1.44), 0.84
Q3	2.07(1.58,2.72), < 0.0001	2.14(1.63,2.82), < 0.0001	1.35(1.03,1.78), 0.03
Q4	3.83(3.10,4.74), < 0.0001	4.07(3.27,5.07), < 0.0001	2.11(1.64,2.71), < 0.0001
P for trend	< 0.0001	< 0.0001	< 0.0001

Abbreviations UHR, serum uric acid/high-density lipoprotein cholesterol ratio; TD, testosterone deficiency; β: effect size for linear regression; OR, odds ratios; CI, confidence interval. PIR, poverty-income ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; TC, total cholesterol; CVD: cardiovascular diseases; Q1-Q4, Quartile 1-Quartile 4

Statistical tests:

In Model 1, no covariates were adjusted

Model 2 adjusted for age, race, education, PIR, and marital status

Model 3 included additional adjustments based on Model 2, incorporating BMI, eGFR, TC, smoking status, alcohol consumption, hypertension, diabetes, hyperlipidemia, and CVD

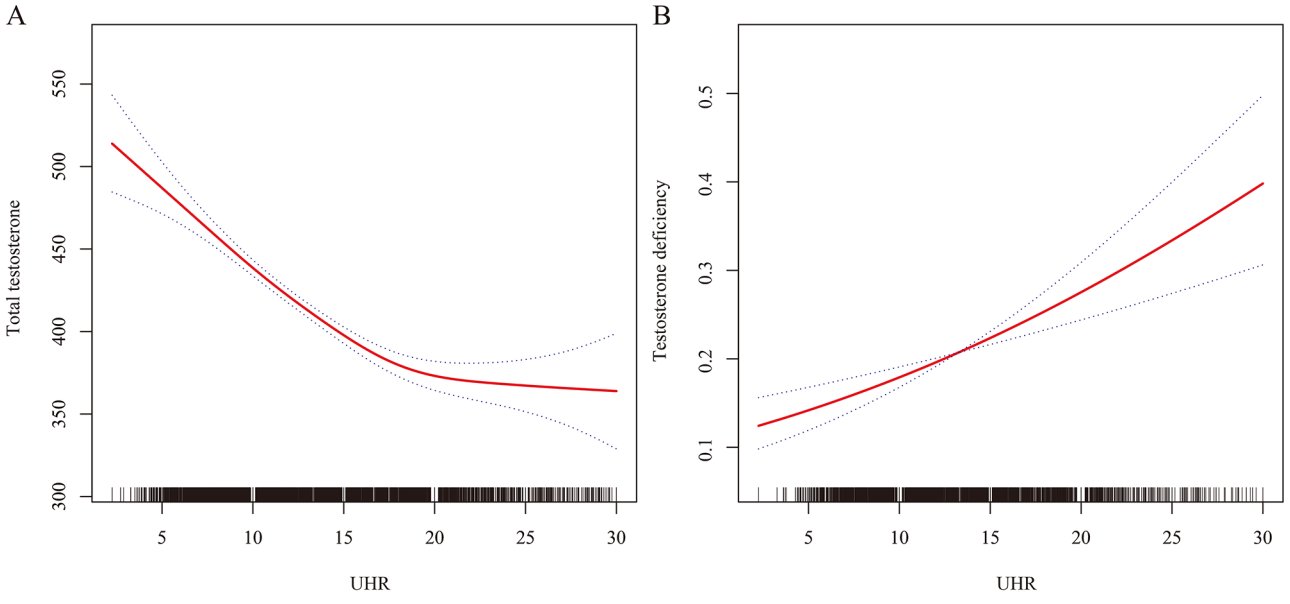

Fig. 3 Graphics of smooth curve fittings between UHR and total testosterone level and risk of TD. (**A**) Total testosterone levels; (**B**) Risk of TD. All analyses were adjusted in Model 3, including age, race, education, PIR, marital status, BMI, eGFR, TC, smoking status, alcohol consumption, hypertension, DM, hyperlipidemia, and CVD. The red solid line represents ORs, and the black dashed line represents 95% CI. TD, testosterone deficiency; OR, odds ratio; CI, confidence interval; PIR, poverty-income ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; TC, total cholesterol; DM, diabetes mellitus; CVD: cardiovascular diseases

various other metabolic diseases has been well established. Zhou et al. provided strong evidence showing a positive association between UHR and insulin resistance [34]. Kocak et al. showed that UHR outperformed all other established markers in identifying MetS [35]. Additionally, UHR is closely associated with NAFLD, based on the relationship between MetS and hepatic steatosis [36]. However, these metabolic disturbances have been consistently identified as key contributors to TD [37, 38]. Therefore, our findings are consistent with the established literature, demonstrating the interconnections between metabolic disturbances and TD. Previously, Han

Table 3 Subgroup analysis of the association between continuous UHR and total testosterone level, weighted

Subgroup	β (95%CI)	*P* value	*P* for interaction
Age group			0.09
20-40y	-11.23(-15.49, -6.96)	< 0.0001	
40-60y	-6.73(-9.68, -3.78)	< 0.0001	
>60y	-3.13(-7.38, 1.12)	0.14	
BMI			0.07
Normal (< 25 kg/m^2)	-15.84(-20.94, -10.75)	< 0.0001	
Overweight (25–30 kg/m^2)	-7.38(-11.29, -3.47)	< 0.001	
Obese (> 30 kg/m^2)	-6.77(-9.85, -3.69)	< 0.001	
Smoke			0.39
Never	-6.79(-9.36, -4.22)	< 0.0001	
Former	-7.66(-10.60, -4.72)	< 0.0001	
Current	-9.52(-15.07, -3.97)	0.002	
DM			0.12
No	-8.76(-11.38, -6.14)	< 0.0001	
Borderline	-9.03(-12.30, -5.76)	< 0.0001	
Yes	-2.75(-7.61, 2.10)	0.26	
Hyperlipidemia			0.06
No	-12.98(-19.77, -6.18)	< 0.001	
Yes	-6.29(-8.53, -4.05)	< 0.0001	
CVD			0.31
No	-7.81(-10.33, -5.30)	< 0.0001	
Yes	-5.79(-9.46, -2.11)	0.004	

Abbreviations UHR, serum uric acid/high-density lipoprotein cholesterol ratio; β: effect size for linear regression; CI, confidence interval. PIR, poverty-income ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; TC, total cholesterol; DM, diabetes mellitus; CVD: cardiovascular diseases

Statistical tests:

Analyses were conducted in Model 3, with full adjustment for all covariates except the subgroup variable itself. The Model 3 was adjusted with age, race, education, PIR, marital status, BMI, eGFR, TC, smoking status, alcohol consumption, hypertension, DM, hyperlipidemia, and CVD

et al. demonstrated the relationship between elevated uric acid levels and low testosterone levels [21]. However, their study had several limitations. First, they did not take HDL-C into consideration. Second, they only examined the effect of uric acid on testosterone levels without addressing TD. In fact, there exists a positive interrelationship between HDL-C levels and testosterone. Several studies have consistently demonstrated a positive correlation between HDL-C and testosterone levels [23]. In addition, studies have revealed that uric acid exerts an influence on HDL-C levels. Previous research has demonstrated that dietary components, particularly used frying oils, can significantly influence oxidative stress and inflammation, which are key pathways implicated in metabolic dysfunction and hormonal imbalances [39]. Evidence has also shown that increased uric acid levels are significantly associated with reduced HDL-C concentrations (OR: 0.774; 95% CI: 0.709–0.846) [40]. Therefore, the use of UHR offers a more comprehensive approach to evaluate the impact of metabolic dysregulation and inflammation on both testosterone levels and TD risk, providing more valuable clinical implications for patient management.

While our evidence demonstrates that elevated UHR regulates testosterone levels, the potential reverse causality of testosterone level affecting UHR deserves careful consideration. Epidemiological evidence from previous studies provides some insights into this potential reverse relationship. In a 5-year interventional study, Yamamoto et al. demonstrated that monthly testosterone injections significantly reduced triglyceride levels in hypogonadal men compared to untreated controls [41]. A meta-analysis of seven RCTs involving 612 hypogonadal men with T2DM revealed that testosterone supplementation significantly reduced total cholesterol (MD: -6.44 mg/dL, 95% CI: -11.82 to -1.06) and triglycerides (MD: -27.94 mg/dL, 95% CI: -52.33 to -3.54), while improving HDL-C levels (MD: 2.79 mg/dL, 95% CI: 0.73 to 4.86) [42]. Additionally, a cross-sectional study by Chao found a significant inverse relationship between uric acid and testosterone in males with T2DM [15]. A follow-up study examining androgen replacement in hypogonadal patients found that weekly administration of testosterone enanthate effectively reduced serum uric acid concentrations compared to untreated controls over a 4-month intervention period [43]. Testosterone has been shown to suppress xanthine oxidase activity in hepatocytes through the androgen receptor-mediated pathway, thereby reducing uric acid production [44]. Additionally, testosterone enhances ATP-binding cassette transporter A1 expression in macrophages and hepatocytes, promoting HDL-C synthesis and reverse cholesterol transport [45, 46]. These molecular pathways provide mechanistic support for the inverse association between low testosterone level and elevated UHR.

Several molecular mechanisms may explain how elevated UHR affects testosterone levels. High uric acid, a key component of UHR, induces oxidative stress and promotes inflammatory responses in Leydig cells through activation of the NLRP3 inflammasome pathway, thereby impairing testosterone synthesis [47, 48]. Specifically, uric acid triggers mitochondrial dysfunction and endoplasmic reticulum stress in Leydig cells, leading to reduced expression of steroidogenic enzymes including StAR and P450scc [49]. Meanwhile, reduced HDL-C levels compromise cholesterol delivery to Leydig cells, as HDL-C serves as the preferred cholesterol source for steroidogenesis via the SR-BI-mediated selective uptake pathway. HDL-C also exhibits anti-inflammatory properties by suppressing pro-inflammatory cytokine production in testicular macrophages through the ABCA1/STAT3 signaling axis, and its reduction may exacerbate inflammatory damage to Leydig cells [50]. The combined effect of elevated uric acid and decreased HDL-C

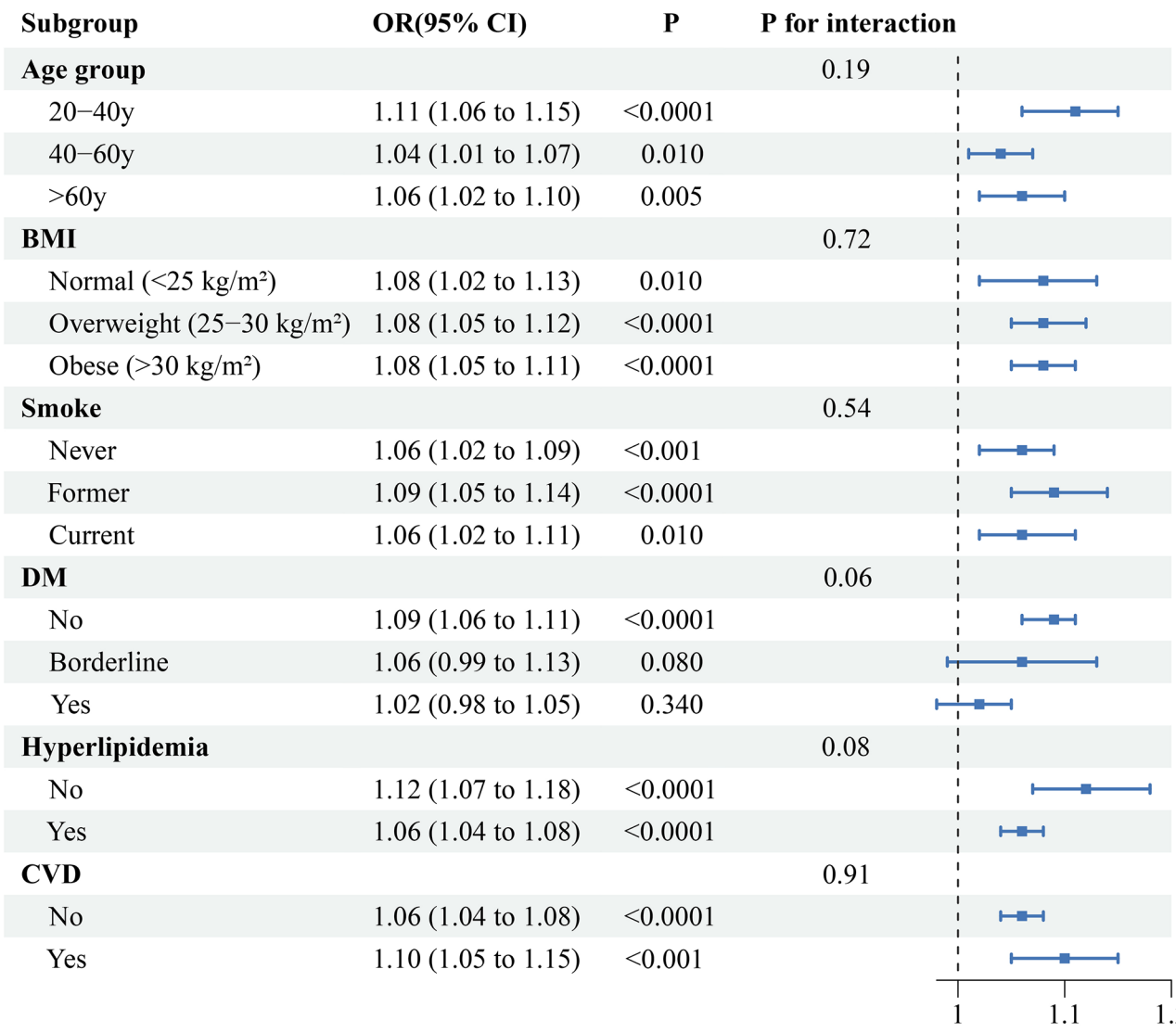

Fig. 4 Subgroup analysis of the association between continuous UHR and risk of TD, weighted. All analyses were adjusted for all variables included in Model 3, except for the stratifying variables. This includes adjustments for age, race, education, PIR, marital status, BMI, eGFR, TC, smoking status, alcohol consumption, hypertension, DM, hyperlipidemia, and CVD. TD, testosterone deficiency; OR, odds ratios; CI, confidence interval; UHR, serum uric acid/high-density lipoprotein cholesterol ratio; PIR, poverty-income ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; TC, total cholesterol; DM, diabetes mellitus; CVD: cardiovascular diseases

creates a detrimental microenvironment characterized by enhanced oxidative stress and inflammation, ultimately leading to impaired testosterone production. Moreover, the persistent inflammatory state induced by high UHR may lead to Leydig cell apoptosis through activation of the caspase cascade, resulting in a progressive decline in testosterone production capacity.

Further discussion is needed on some of the findings from the subgroup analyses. As observed in earlier studies, the decline in total testosterone levels associated with each unit increase in the uric acid to high-density lipoprotein ratio (UHR) was not statistically significant in obese individuals (BMI ≥ 30 kg/m²) [8]. The observed link may be weakened because individuals with higher BMI are more likely to engage in physical activity and dietary restriction to lose weight, which can increase testosterone levels. Our findings were consistent with previous research on the smoking status subgroup [8, 74]. Among smokers, the decline in total testosterone levels per unit increase in UHR was less pronounced, and the risk of TD was not statistically significant. This could be due to several factors: exposure to nicotine and other toxins in smokers may directly impair testicular function, leading to lower testosterone levels [75]. Additionally, smoking and eating may compete as reward mechanisms, resulting in lower food consumption and, consequently, lower rates of obesity among smokers [76]. This may explain the

Table 4 Subgroup analysis of the association between UHR quartiles and total testosterone level, weighted

Subgroup	Q1	Q2	Q3	Q4	*P* for trend	*P* for interaction
Age group						0.12
20-40y	Ref	-50.68(-82.21, -19.14)	-93.68(-130.17, -57.20)	-133.02(-186.29, -79.75)	< 0.0001	
40-60y	Ref	-22.68(-67.96, 22.59)	-56.8(-87.91, -25.70)	-61.36(-103.39, -19.33)	0.003	
>60y	Ref	0.18(-52.29,52.65)	0.87(-45.38,47.11)	-54.94(-103.71, -6.17)	0.07	
BMI						0.38
Normal (< 25 kg/m^2)	Ref	-42.86(-87.02, 1.31)	-59.9(-105.55, -14.25)	-164.16(-226.01, -102.31)	< 0.0001	
Overweight (25–30 kg/m^2)	Ref	-22(-62.82, 18.83)	-65.7(-101.24, -30.16)	-79.54(-130.00, -29.08)	< 0.001	
Obese (> 30 kg/m^2)	Ref	0.29(-46.50, 47.07)	-22.55(-67.99, 22.88)	-63.69(-109.80, -17.58)	0.001	
Smoke						0.61
Never	Ref	-29.78(-63.04, 3.48)	-55.7(-87.95, -23.45)	-77.8(-112.45, -43.16)	< 0.0001	
Former	Ref	-7.74(-60.38, 44.89)	-43.62(-77.89, -9.35)	-85.44(-127.94, -42.95)	< 0.0001	
Current	Ref	-48.57(-92.49, -4.65)	-88.78(-134.95, -42.61)	-108.55(-170.69, -46.41)	0.001	
DM						0.16
No	Ref	-33.91(-63.69, -4.12)	-55.8(-82.17, -29.42)	-96.32(-131.30, -61.35)	< 0.0001	
Borderline	Ref	-57.89(-107.77, -8.00)	-88.22(-141.59, -34.86)	-108.56(-158.21, -58.91)	< 0.001	
Yes	Ref	68.24(-9.75,146.23)	-13.16(-71.94, 45.61)	-4.69(-70.39, 61.01)	0.20	
Hyperlipidemia						0.45
No	Ref	-2.42(-47.82, 42.98)	-53.66(-98.41, -8.91)	-95.54(-175.34, -15.75)	0.01	
Yes	Ref	-31.65(-62.29, -1.00)	-53.03(-83.03, -23.02)	-82.47(-111.29, -53.65)	< 0.0001	
CVD						0.06
No	Ref	-20.24(-47.70, 7.21)	-59.28(-83.95, -34.60)	-85.01(-116.62, -53.40)	< 0.0001	
Yes	Ref	-73.58(-122.31, -24.84)	-64.27(-114.55, -13.99)	-85.33(-133.26, -37.40)	0.003	

Abbreviations UHR, serum uric acid/high-density lipoprotein cholesterol ratio; β: effect size for linear regression; CI, confidence interval. PIR, poverty-income ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; DM, diabetes mellitus; CVD, cardiovascular diseases; Q1-Q4, Quartile 1-Quartile 4

Statistical tests:

Analyses were conducted in Model 3, with full adjustment for all covariates except the subgroup variable itself. The Model 3 was adjusted with age, race, education, PIR, marital status, BMI, eGFR, TC, smoking status, alcohol consumption, hypertension, DM, hyperlipidemia, and CVD

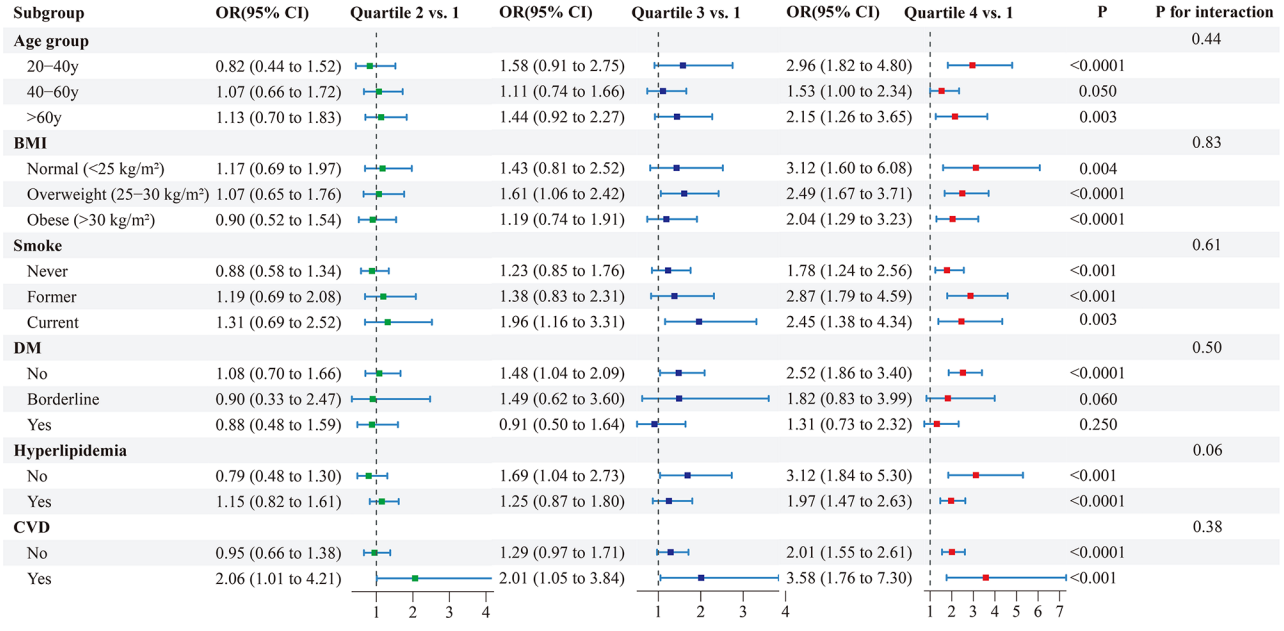

Fig. 5 Subgroup analysis on the association of quartile UHR with risk of TD, weighted. All analyses were adjusted for all variables included in Model 3, except for the stratifying variables. This includes adjustments for age, race, education, PIR, marital status, BMI, eGFR, TC, smoking status, alcohol consumption, hypertension, DM, hyperlipidemia, and CVD. TD, testosterone deficiency; OR, odds ratios; CI, confidence interval; UHR, serum uric acid/high-density lipoprotein cholesterol ratio; PIR, poverty-income ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; TC, total cholesterol; DM, diabetes mellitus; CVD: cardiovascular diseases

weaker correlation between testosterone levels and UHR in smokers and the increased risk of TD in this group.

However, several limitations must be considered when interpreting our findings. First, while cross-sectional studies are valuable for hypothesis generation, they do not establish temporal or causal relationships between UHR and TD risk. Second, despite adjusting for several key confounders, we were unable to account for additional variables, such as medication history and occupational exposure, which may also influence testosterone levels. Third, our diagnosis of TD was based solely on a total testosterone level of < 300ng/dL, excluding symptoms and signs of TD due to NHANES database constraints. Lastly, caution is needed when generalizing our findings globally, as they may not be fully applicable to other populations. These limitations should be carefully considered in the interpretation of our findings and the design of future studies.

Conclusion

Our study found a negative correlation between UHR and total testosterone levels, and a positive correlation between UHR and the risk of TD in a nationally representative US sample. These results suggest that UHR could be a valuable indicator of testicular health and help identify the risk of TD in men, enabling early detection and intervention. However, further research with experimental or longitudinal designs and more diverse populations is needed to confirm these findings and improve their generalizability.

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Author contributions
Wei Xia, Pinpeng Xie and Qianfeng Zhuang contributed to conceptualization, investigation, data analysis, and writing editing and reviewing. Wei Xia and Mingran Zhang were involved in the methodology, software, image processing, and writing reviewing. Naiyuan Shao, Yiming Chen and Xingliang Feng contributed to project administration, resources, and supervision. All authors contributed to the article and approved publication.

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Data availability
The datasets used and analyzed during the current study are available from the NHANES database (https://www.cdc.gov/nchs/nhanes/index.htm). Detailed data can be requested from the corresponding author upon reasonable request.

Declarations

Ethical approval and consent to participate
This study was conducted in accordance with the ethical standards of the National Center for Health Statistics (NCHS) Ethics Review Board. All procedures and experimental protocols of NHANES were reviewed and approved by the NCHS Ethics Review Board in advance. Participants were fully informed about the benefits and risks associated with the study, and all provided written informed consent prior to participation.

Consent for publication
Not appliable.

Competing interests
The authors declare no competing interests.

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