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Potential links between serum uric acid levels and testosterone levels in adult males: a cross-sectional study

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Given the controversial conclusion on the relationship between serum uric acid (SUA) levels and testosterone (T) levels in adult males, the purpose of this study is to explore the association between SUA levels and T levels in adult males. We conducted a cross-sectional study using data from the National Health and Nutrition Examination Survey (NHANES) spanning from 2011 to 2016. The association was estimated using multiple linear regression model and results are presented as β with its 95% confidence intervals (95% CIs). This study enrolled 7791 males aged 18 years or older and found a negative correlation between serum uric acid levels and testosterone levels after controlling for confounding factors. Additionally, a non-linear association was observed, with an infection point of 4.4 mg/dL for serum uric acid levels. The effect sizes on the left and right sides of the inflection point were determined as 17.93 (− 3.61 to 39.48) and − 14.73 (− 18.51 to − 10.95), respectively. Elevated SUA levels were found to be linked to decreased T levels, even after controlling for confounders. Moreover, non-linear pattern in the relationship between SUA levels and T levels was also identified.

Keywords Serum uric acid, Testosterone, NHANES, Metabolic syndrome

Abbreviations

NHANES	National Health and Nutrition Examination Survey
NCHS	National Center for Health Statistics
BMI	Body mass index
PIR	Poverty-to-income ratio
ASCVD	Atherosclerotic cardiovascular disease
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CKD	Chronic kidney disease
CI	Confidence interval

Serum uric acid (SUA) is the final product of purine nucleotide metabolism. It plays a role in scavenging oxygen free radicals, thus contributing to the restoration of normal body functioning. Moreover, SUA acts as a crucial antioxidant, aiding in the maintenance of stable blood pressure and combating oxidative stress[1]. In the United States, the prevalence of hyperuricemia was 21.2% and 21.6% in males and females, respectively[2]. A large number of studies have found that high serum uric acid levels have been linked to metabolic disorders including obesity, type 2 diabetes, cardiovascular disease, hepatic steatosis and insulin resistance[3–5]. Previous studies have confirmed that serum uric acid plays a role in the pathogenesis of metabolic syndrome, chronic kidney disease (CKD) and cardiovascular disease (CVD). This is achieved by disrupting biological processes such as oxidative stress, chronic inflammation, mitochondrial dysfunction, endothelial dysfunction, proliferation of vascular smooth muscle cells, and activation of the renin-angiotensin system[3,6,7]. A Mendelian randomization study conducted on a population of 10,000 individuals found that elevated SUA levels may increase the risk of metabolic syndrome. This increased risk is attributed to the elevation of blood pressure and triglyceride levels, as well as the reduction in HDL-C levels[8]. Another Mendelian randomization study, involving 3315 patients,

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revealed a causal association between SUA levels and adverse cardiovascular outcomes, including coronary artery disease, cardiovascular mortality and sudden cardiac death[9].

Testosterone, secreted by Leydig cells in the testes, is essential for male reproductive organ maturation and the development of secondary sexual characteristics[10]. Testosterone deficiency has become an increasingly concerning and controversial issue worldwide, affecting approximately 7% of men at the age of 50 and exhibiting a higher prevalence with advancing age[10]. Research has shown that there is a common occurrence of low testosterone levels in individuals with obesity, metabolic syndrome, and insulin resistance[11–13]. Additionally, testosterone deficiency is associated with an increased risk of developing type 2 diabetes[10,11]. Studies have also indicated that long-term testosterone replacement therapy can significantly reduce body mass index (BMI), improve insulin resistance, and enhance blood glucose control[14–16]. Furthermore, testosterone therapy has been found to improve metabolic control, leading to decreased blood glucose values and lower mean glycated hemoglobin levels in men with type 2 diabetes and visceral obesity[16].

Based on the association of serum uric acid levels and testosterone levels with metabolic syndrome, there have been studies investigating their relationship, but the results are controversial. Some studies show a negative correlation[17,18], while others indicate a positive association between serum uric acid levels and testosterone levels[19,20]. Therefore, we hypothesize that the relationship between serum uric acid levels and testosterone levels is more complex than a simple linear association, and this relationship may be modulated by factors such as age, metabolic status, and lifestyle. While testosterone levels tend to stabilize in adult males and reach a peak at 18 years of age[21,22], other factors may influence these levels thereafter. Thus, we conducted an analysis of the National Health and Nutrition Examination Survey (NHANES) dataset, including male adults aged 18 years and older, to explore the relationship between serum uric acid levels and serum testosterone levels in adult males.

Results

General characteristics

The weighted demographic characteristics are shown in Table 1. A total of 7791 eligible subjects were included in this study Fig. 1. The mean age was 47.62 ± 18.51 years, the mean serum testosterone level was 417.32 ± 189.56 ng/dL, and the mean SUA level was 6.02 ± 1.30 mg/dL. SUA levels were categorized based on SUA quartiles: Q1 (0.40 < SUA ≤ 5.00 mg/dL), Q2 (5.10 < SUA ≤ 5.80 mg/dL), Q3 (5.90 < SUA ≤ 6.70 mg/dL), and Q4 (6.80 < SUA ≤ 11.70 mg/dL). Significant differences were noted in the four groups in terms of age, race, BMI, waist circumference, PIR, smoking status, drinking status, ALT, AST, hsCRP, BUN, SCr, cholesterol, triglyceride, eGFR (estimated glomerular filtration rate), prevalence of hypertension, diabetes, hyperlipidemia, ASCVD, gout and CKD (all $P < 0.05$). In addition, we found that with increasing SUA quartiles, the serum testosterone levels gradually decreased ($P < 0.01$).

Associations between serum uric acid and testosterone

Table 2 reveals the association between serum uric acid levels and testosterone levels. In the crude model, testosterone levels is negatively correlated with serum uric acid levels (β = − 30.22, 95% CI − 33.97 to − 26.46, $P < 0.0001$). After adjusting for age, race and BMI in model I, the relationship between serum uric acid levels and testosterone levels was still robust (β = − 15.56, 95% CI − 19.73 to − 11.39, $P < 0.0001$). In model II, we further adjusted for ALT, AST, hypertension, diabetes, hyperlipidemia, ASCVD, CKD, smoking status and drinking status, their association persisted (β = − 15.66, 95% CI − 19.76 to − 11.55, $P < 0.0001$). This similar trend was seen when we treated SUA levels as a quartile in the sensitivity analysis (P for trend < 0.0001).

Non-linear relationship between uric acid and testosterone

In the present work, we looked at the possibility of a non-linear connection between SUA levels and testosterone levels by utilizing smooth curve fits (Fig. 2), we observed a non-linear connection between SUA levels and testosterone levels (after adjusting age, race, BMI, ALT, AST, hypertension, diabetes, hyperlipidemia, ASCVD, CKD, smoking status and drinking status). Using a two-piecewise linear regression model, we were able to identify that the inflection point was located at 4.4 mg/dL (Table 3). On the right side of the inflection point, a negative correlation between serum uric acid levels and testosterone levels was observed (β = − 14.73, 95% CI − 18.51 to − 10.95, $P < 0.0001$). However, on the left side of this inflection point, no statistically significant association was detected (β = 17.93, 95% CI − 3.61 to 39.48, $P = 0.1028$).

Subgroup analysis

The results of the stratified analyses examining the relationship between serum uric acid levels and testosterone levels are shown in Fig. 3. Significant interaction was observed for age, drinking status, CKD, diabetes, hypertension, hyperlipidemia and gout (all P for interaction < 0.05), but not for BMI, ASCVD, or smoking status (all P for interaction > 0.05). Among these strata, participants with higher serum uric acid levels showed a significant decrease in testosterone levels, particularly among those who were younger in age, current alcohol drinkers, and without CKD, diabetes, hypertension, hyperlipidemia and gout.

Discussion

A nonlinear association of serum uric acid levels and testosterone levels was presented in adult males in the present study. The inflection point was identified at 4.4 mg/dL. On the left side of the inflection point, the association did not reach statistical significance. However, a negative correlation between SUA levels and testosterone levels was observed on the right side of the inflection point.

A series of studies have reported a linear association between SUA levels and testosterone levels[18,20,23–25]. However, the conclusions remain controversial, and most of these studies did not consider nonlinearity or

	Q1 (0.40–5.00 mg/dL)	Q2 (5.10–5.80 mg/dL)	Q3 (5.90–6.70 mg/dL)	Q4 (6.80–11.70 mg/dL)	*P*-value
Numbers of participants (100%)	1778	1909	2029	2075	
Testosterone (ng/dL)	464.50 (449.84, 479.17)	443.20 (430.21, 456.20)	409.33 (400.58, 418.08)	365.40 (356.48, 374.33)	< 0.0001
Age (years)	48.03 (46.94, 49.12)	45.03 (43.74, 46.32)	45.48 (44.24, 46.72)	46.26 (45.46, 47.06)	0.0014
Race (%)					< 0.0001
Non-Hispanic Black	11.09 (8.81, 13.87)	9.05 (7.17, 11.35)	9.05 (7.23, 11.28)	10.96 (8.69, 13.74)	
Non-Hispanic White	62.47 (56.46, 68.13)	67.16 (62.55, 71.46)	66.26 (61.46, 70.75)	68.33 (64.00, 72.36)	
Mexican American	11.63 (8.47, 15.76)	8.85 (6.65, 11.70)	10.21 (7.70, 13.42)	7.33 (5.67, 9.43)	
Others	14.81 (12.49, 17.48)	14.94 (12.64, 17.58)	14.48 (12.49, 16.72)	13.38 (11.42, 15.62)	
BMI (%)					< 0.0001
≤ 25 kg/m^2	42.30 (39.22, 45.45)	35.39 (31.73, 39.23)	22.97 (20.37, 25.80)	13.77 (11.99, 15.76)	
25–30 kg/m^2	35.97 (32.95, 39.10)	38.79 (35.74, 41.93)	38.69 (35.59, 41.89)	36.22 (33.29, 39.25)	
> 30 kg/m^2	21.73 (19.02, 24.70)	25.82 (23.03, 28.83)	38.34 (35.85, 40.89)	50.02 (46.74, 53.29)	
Waist circumference (cm)	96.23 (95.24, 97.22)	97.72 (96.64, 98.81)	102.66 (101.70, 103.61)	107.84 (106.65, 109.03)	< 0.0001
Educational level (%)					0.0572
Less than 9th grade	6.96 (5.35, 9.01)	5.12 (3.96, 6.60)	5.13 (4.04, 6.49)	5.53 (4.57, 6.67)	
High school or equivalent	34.29 (29.96, 38.91)	30.14 (27.09, 33.38)	33.86 (30.31, 37.60)	32.56 (29.31, 35.98)	
College or over	58.75 (53.38, 63.91)	64.74 (61.10, 68.21)	61.02 (57.26, 64.64)	61.92 (58.42, 65.29)	
PIR	2.86 (2.68, 3.04)	3.12 (2.94, 3.29)	3.01 (2.90, 3.13)	3.08 (2.95, 3.20)	0.0070
Smoking status (%)					0.0002
Never	46.72 (43.08, 50.39)	54.64 (51.48, 57.75)	49.32 (45.68, 52.98)	48.91 (46.16, 51.66)	
Former	27.11 (23.97, 30.49)	25.39 (22.72, 28.25)	29.16 (26.49, 31.98)	31.70 (28.63, 34.94)	
Current	26.17 (23.35, 29.20)	19.97 (17.39, 22.84)	21.51 (18.85, 24.44)	19.39 (16.82, 22.24)	
Drinking status (%)					< 0.0001
Never	10.47 (8.21, 13.26)	6.38 (5.03, 8.06)	8.65 (6.47, 11.48)	8.44 (6.52, 10.85)	
Former	18.63 (16.39, 21.09)	12.38 (10.85, 14.10)	13.36 (11.37, 15.65)	13.49 (11.71, 15.50)	
Mild	37.04 (32.99, 41.29)	46.00 (42.43, 49.61)	41.16 (37.45, 44.97)	34.91 (30.84, 39.22)	
Moderate	11.72 (9.45, 14.46)	11.73 (9.83, 13.95)	12.10 (10.04, 14.52)	13.79 (11.34, 16.67)	
Heavy	22.14 (18.66, 26.06)	23.50 (20.72, 26.54)	24.73 (21.78, 27.93)	29.37 (26.21, 32.75)	
ALT (U/L)	25.96 (24.74, 27.19)	26.99 (25.93, 28.05)	30.20 (29.05, 31.34)	34.24 (32.48, 35.99)	< 0.0001
AST (U/L)	26.00 (25.15, 26.84)	26.54 (25.64, 27.45)	27.36 (26.67, 28.05)	30.01 (29.00, 31.01)	< 0.0001
Hypersensitive C-reactive protein (mg/L)	2.98 (2.27, 3.68)	2.49 (1.98, 3.00)	3.41 (2.65, 4.17)	3.98 (3.58, 4.38)	0.0008
Blood urea nitrogen (mg/dL)	14.02 (13.70, 14.35)	14.10 (13.82, 14.38)	14.28 (13.99, 14.58)	15.19 (14.84, 15.54)	< 0.0001
Serum creatinine (mg/dL)	0.96 (0.93, 0.98)	0.96 (0.95, 0.98)	0.99 (0.98, 1.01)	1.06 (1.05, 1.08)	< 0.0001
Cholesterol (mmol/L)	4.73 (4.67, 4.79)	4.81 (4.73, 4.89)	4.91 (4.85, 4.97)	5.01 (4.93, 5.08)	< 0.0001
Triglyceride (mmol/L)	1.72 (1.56, 1.88)	1.86 (1.72, 2.00)	1.91 (1.83, 1.99)	2.15 (2.06, 2.24)	< 0.0001
eGFR	97.83 (96.29, 99.37)	96.89 (95.42, 98.36)	94.59 (93.39, 95.78)	89.52 (88.34, 90.70)	< 0.0001
Hypertension (%)					< 0.0001
No	63.79 (60.61, 66.85)	69.41 (67.13, 71.60)	62.40 (59.42, 65.29)	52.16 (49.16, 55.14)	
Yes	36.21 (33.15, 39.39)	30.59 (28.40, 32.87)	37.60 (34.71, 40.58)	47.84 (44.86, 50.84)	
Diabetes (%)					< 0.0001
No	84.04 (80.86, 86.78)	89.86 (87.88, 91.55)	91.72 (89.75, 93.34)	88.31 (86.59, 89.83)	
Yes	15.96 (13.22, 19.14)	10.14 (8.45, 12.12)	8.28 (6.66, 10.25)	11.69 (10.17, 13.41)	
Hyperlipidemia (%)					< 0.0001
No	39.81 (35.76, 44.01)	37.78 (34.42, 41.27)	30.98 (28.22, 33.89)	23.43 (20.89, 26.17)	
Yes	60.19 (55.99, 64.24)	62.22 (58.73, 65.58)	69.02 (66.11, 71.78)	76.57 (73.83, 79.11)	
ASCVD (%)					0.0061
No	88.87 (87.01, 90.50)	92.48 (90.58, 94.02)	91.93 (90.27, 93.33)	90.09 (88.37, 91.59)	
Yes	11.13 (9.50, 12.99)	7.52 (5.98, 9.42)	8.07 (6.67, 9.73)	9.91 (8.41, 11.63)	
Gout (%)					< 0.0001
Continued					

	Q1 (0.40–5.00 mg/dL)	Q2 (5.10–5.80 mg/dL)	Q3 (5.90–6.70 mg/dL)	Q4 (6.80–11.70 mg/dL)	*P*-value
No	95.28 (93.75, 96.45)	96.72 (95.52, 97.61)	96.12 (94.54, 97.26)	90.62 (88.85, 92.13)	
Yes	4.72 (3.55, 6.25)	3.28 (2.39, 4.48)	3.88 (2.74, 5.46)	9.38 (7.87, 11.15)	
CKD (%)					< 0.0001
No	89.21 (87.34, 90.83)	91.95 (90.26, 93.37)	89.22 (87.42, 90.79)	78.89 (76.57, 81.04)	
Yes	10.79 (9.17, 12.66)	8.05 (6.63, 9.74)	10.78 (9.21, 12.58)	21.11 (18.96, 23.43)	

Table 1. Weighted general characteristics of selected participants by serum uric acid levels quartiles from NHANES 2011–2016. Data in the table: For continuous variables: survey-weighted mean (95% confidence interval), *P*-value was by survey-weighted linear regression (svyglm). For categorical variables: survey-weighted percentage (95% confidence interval), *P*-value was by survey-weighted Chi-square test (svytable). BMI, body mass index; PIR, poverty-to-income ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease.

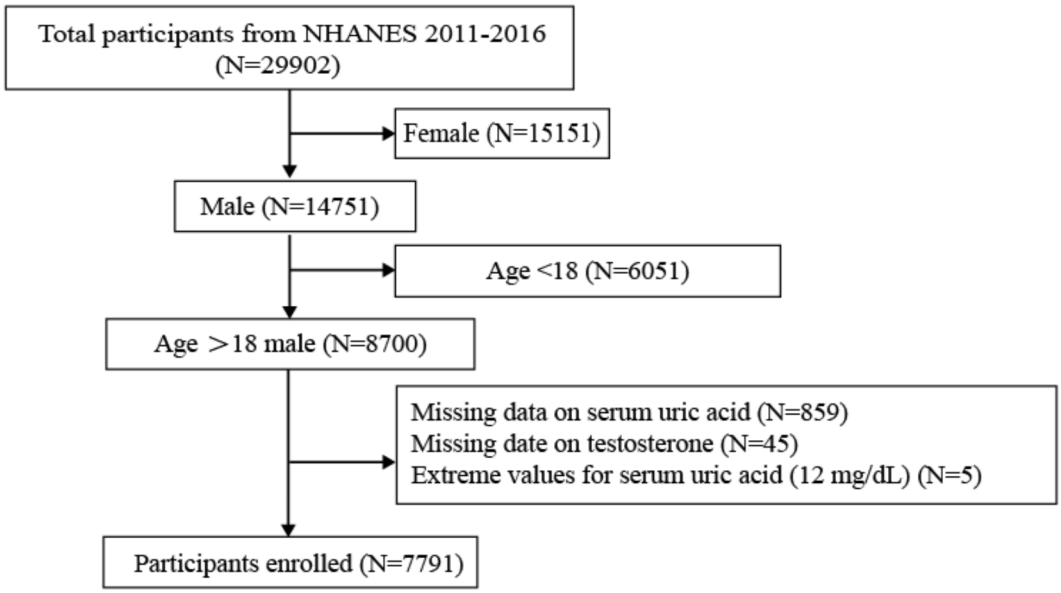

Fig. 1. Flow chart for participant recruitment in this study, NHANES 2011–2016.

	Crude model		Model I		Model II	
Exposure	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
Serum urine acid (mg/dL)						
(continuous)	− 30.22 (− 33.97, − 26.46)	< 0.0001	− 15.56 (− 19.73, − 11.39)	< 0.0001	− 15.66 (− 19.76, − 11.55)	< 0.0001
(quartiles)						
0.40–5.00 mg/dL	Ref		Ref		Ref	
5.10–5.80 mg/dL	− 21.30 (− 41.39, − 1.22)	0.0435	− 15.10 (− 34.10, 3.91)	0.1276	− 12.35 (− 31.47, 6.77)	0.2166
5.90–6.70 mg/dL	− 55.17 (− 71.88, − 38.47)	< 0.0001	− 29.87 (− 46.29, − 13.45)	0.0010	− 33.21 (− 49.79, − 16.63)	0.0006
6.80–11.70 mg/dL	− 99.10 (− 113.53, − 84.67)	< 0.0001	− 52.90 (− 66.89, − 38.92)	< 0.0001	− 51.83 (− 65.27, − 38.39)	< 0.0001
P for trend		< 0.0001		< 0.0001		< 0.0001

Table 2. Relationship between serum uric acid levels and testosterone levels in different models. Model I adjusted for age, race and BMI. Model II further adjusted for ALT, AST, hypertension, diabetes, hyperlipidemia, ASCVD, CKD, smoking status and drinking status. CI, confidence interval; Ref., reference; BMI, body mass index; ASCVD, Atherosclerotic Cardiovascular Disease; CKD, Chronic kidney disease.

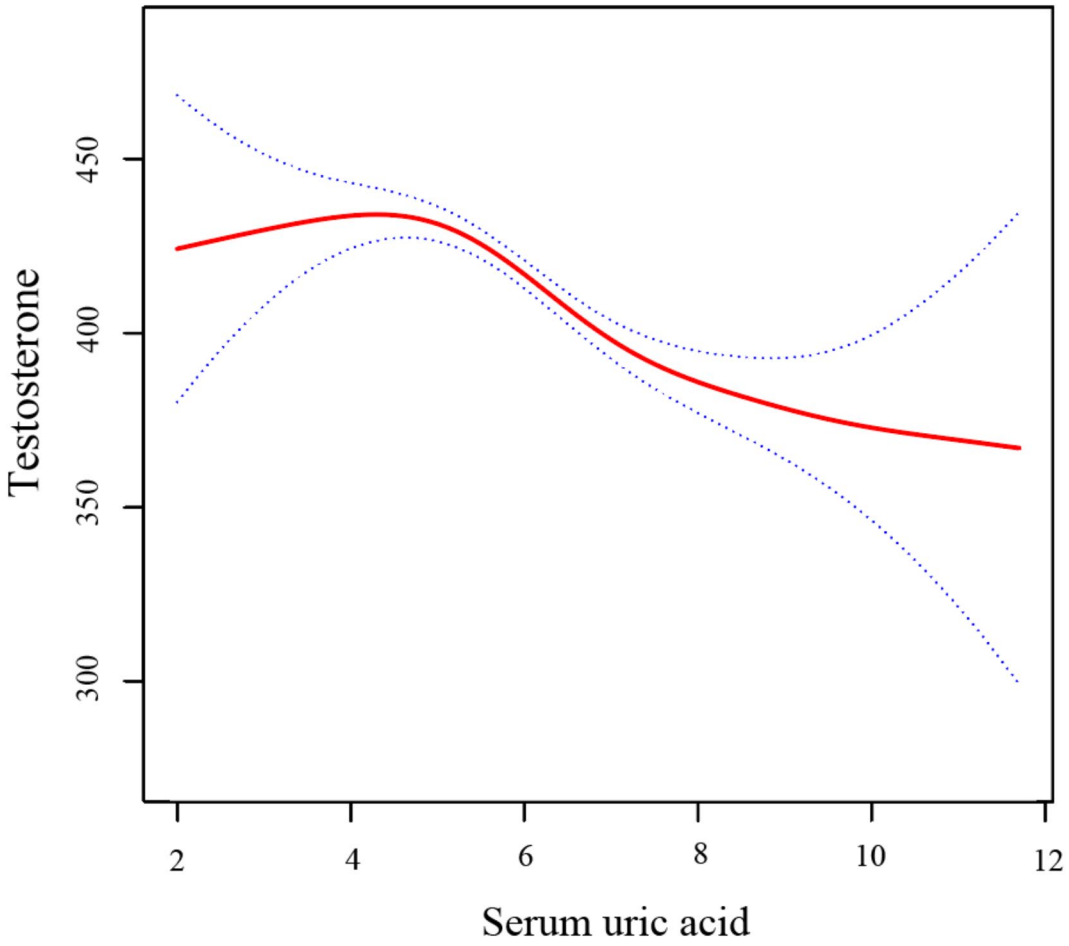

Fig. 2. Adjusted association of serum uric acid levels with testosterone levels in adult males. A non-linear relationship between serum uric acid levels and testosterone levels was found. Red line represents the smooth curve fit between variables. Blue bands represent the 95% of confidence interval from the fit. Adjusted: age, race, BMI, ALT, AST, hypertension, diabetes, hyperlipidemia, ASCVD, CKD, smoking status and drinking status. BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ASCVD, atherosclerotic cardiovascular disease; CKD, Chronic kidney disease.

perform subgroup analysis. A prospective study conducted by Yahyaoui et al.[23] involving 47 female-to-male transsexuals over a 2-year period revealed a significant increase in serum uric acid (SUA) levels and a decrease in the fraction excretion of uric acid (FEUA) following cross-sex hormone treatment, indicating a positive relationship between testosterone levels and SUA levels. Conversely, the study by Marinello and Rosen[20,24], which found normal testicular endocrine function in gout patients, with no significant difference in serum testosterone levels between male patients with gout, asymptomatic hyperuricemia, and controls. Additionally, Borbélyová's research on the effects of gonadectomy and long-term hypogonadism in male middle-aged rats showed no significant impact on serum uric acid levels[25]. In contrast, studies by Han and Wang et al. found that serum uric acid levels might be negatively associated with serum testosterone levels in adult males[18,26]. Furthermore, Lu et al. reported a negative correlation between total testosterone levels and SUA levels in diabetic patients[27]. Possible explanations for the differences include: (I) relatively small sample sizes; (II) variations in inclusion criteria; (III) differences existed in research methods, statistical analysis techniques, and adjusted covariates. In this study, we discovered a nonlinear relationship between SUA levels and testosterone levels with an inflection point of 4.4 mg/dL. The results indicate that the negative linear association between SUA levels and testosterone levels is only observed in participants with a SUA level of 4.4 mg/dL or higher. In individuals with relatively lower SUA levels, this linear relationship cannot be detected. In the present study, we found significant interactions with age, drinking status, CKD, diabetes, hypertension, hyperlipidemia, and gout. Among younger individuals, the negative correlation between SUA and testosterone levels was stronger. This may be attributed to several factors. First, younger individuals typically have a higher metabolic rate, which affects the synthesis and metabolism of testosterone[28]. Additionally, the endocrine system of younger individuals is often more sensitive and active, and higher SUA levels may exert a more pronounced influence on the endocrine system[29].

The mechanisms underlying the relationship between serum uric acid levels and testosterone levels are currently not well understood, but several possibilities have been proposed. Firstly, the deposition of uric acid crystals in testicular tissue can lead to oxidative damage and directly affect testosterone secretion[30]. Second,

Models	Effect size (β)	95% CI	*P* value
Serum uric acid (mg/dL)			
Model 1			
One line effect	− 12.31	− 15.69 to − 8.94	< 0.0001
Model 2			
Inflection point			
< 4.4	17.93	− 3.61 to 39.48	0.1028
≥ 4.4	− 14.73	− 18.51 to − 10.95	< 0.0001
P value for LRT test*			0.005

Table 3. Threshold Effect Analysis of serum uric acid levels and testosterone levels using two-piecewise Linear Regression. Model 1, linear analysis; Model 2, non−linear analysis. Adjusted: age, race, BMI, ALT, AST, hypertension, diabetes, hyperlipidemia, ASCVD, CKD, smoking status and drinking status. CI, confidence interval; LRT, logarithm likelihood radio test; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ASCVD, Atherosclerotic Cardiovascular Disease; CKD, Chronic kidney disease. *$P < 0.05$ indicates Model 2 is significantly different from Model 1.

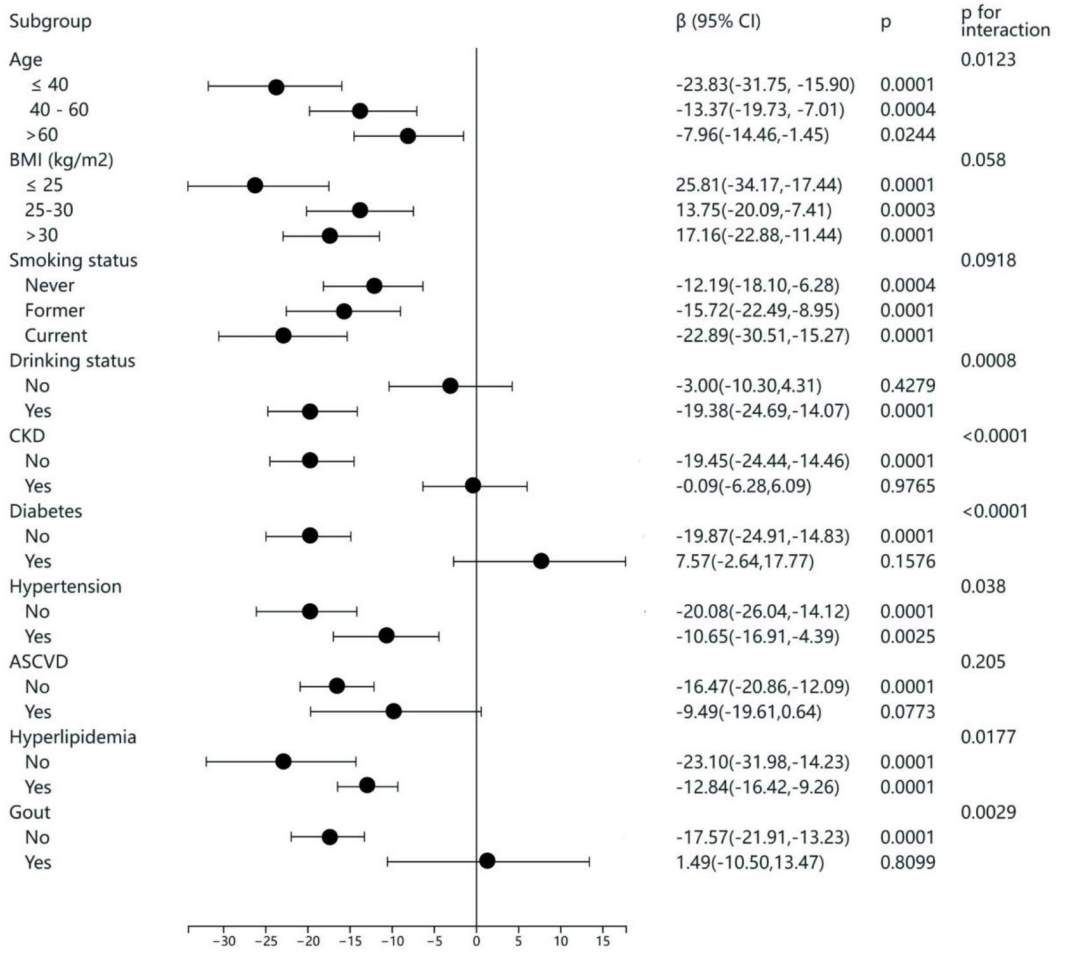

Fig. 3. Effect size of serum uric acid levels on testosterone levels in subgroup analysis. Each stratification adjusted for all the factors (age, race, BMI, ALT, AST, hypertension, diabetes, hyperlipidemia, gout, ASCVD, CKD, smoking status and drinking status) except the stratification factor itself. BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease.

elevated SUA levels can induce metabolic syndrome through mitochondrial oxidative stress and inhibition of AMP-activated protein kinase[31,32]. Hyperuricemia can also cause insulin resistance and decreased insulin secretion by endothelial dysfunction, and reduced nitric oxide bioavailability[33]. Metabolic syndrome and insulin resistance have been shown to be associated with increased conversion of testosterone to estradiol and decreased production of testosterone by Leydig cells[34]. Third, testosterone levels can reciprocally influence uric acid levels, as low testosterone levels may lead to insulin resistance, reducing uric acid clearance and potentially elevating serum uric acid levels[35–37]. Decreased testosterone levels may reduce protein synthesis and increase endogenous purine levels, resulting in elevated uric acid levels[30].

However, there are some limitations to our research. First, we were unable to draw a causal relationship between SUA levels and T levels because of the cross-sectional nature of our study. Second, the dataset used in this study was obtained from a nationwide survey in the United States, so it is uncertain whether the findings can be generalized to populations of other racial backgrounds. Third, testosterone level was measured only once, whereas the diagnosis of low testosterone typically requires at least two recorded values taken on different days. It is important to note that serum testosterone levels are not static but rather dynamic, which may introduce measurement bias in our findings. Fourth, some covariates in our study relied on self-reported data, which introduces potential recall bias. Fifth, cross-sectional studies may fail to fully capture the intricate relationships between variables and are susceptible to selection bias and confounding factors. This could potentially influence our results. Sixth, due to limited data availability, we focused solely on analyzing the relationship between SUA and testosterone without further investigating the effects of SUA on free testosterone or bioactive testosterone. Finally, due to limited research, we have not explored the relationship between serum uric acid levels and hypogonadism. Further investigations are necessary to fully elucidate the complex interplay between serum uric acid and testosterone levels in adult males and to understand the implications of these associations on overall health.

In summary, our study is the first to demonstrate a non-linear correlation between serum uric acid (SUA) levels and testosterone levels in adult males. We found that participants with higher SUA levels exhibited significantly lower testosterone levels, particularly among those with younger age, current alcohol consumption, and the absence of CKD, diabetes, hypertension, and hyperlipidemia.

Methods

Data source and study population

The data for this study were obtained from three consecutive cycles (2011–2012, 2013–2014, and 2015–2016) of NHANES, a national cross-sectional survey designed to assess the health and nutritional status of the United States. NHANES has been approved by National Center for Health Statistics (NCHS) Ethics Review Board, is a major project of the NCHS within the Centers for Disease Control and Prevention (CDC). All research methods of the NHANES were conducted in accordance with the Declaration of Helsinki. The NHANES database is publicly accessible. The data we extracted to validate the study were used to describe the demographic characteristics. An illustration of the participant selection process is depicted in Fig. 1. The study design and data used in this study are available at https://www.cdc.gov/nhcs/nhanes/.

Main variables

Serum uric acid concentration was measured by the timed endpoint method, as detailed in the NHANES Laboratory Procedures Manual[38]. The hydrogen peroxide reacts with 4-aminoantipyrine (4-AAP) and 3,5-dichloro-2-hydroxybenzene sulfonate (DCHBS) under the catalysis of peroxidase to form colored products. The system monitored absorbance changes at 520 nm, which directly indicated SUA levels. Values were reported in mg/dL, but can be converted to μmol/L by multiplying by 59.48. Serum testosterone levels were quantified using the isotope dilution liquid chromatography tandem mass spectrometry (ID-LC–MS/MS) method following the National Institute for Standards and Technology's (NIST) reference guidelines. The detection limits for the assays were established as 0.36 mg/dL for serum testosterone and 0.5 mg/dL for serum uric acid. Concentrations below these limits were handled by replacing them with the respective limit of detection divided by the square root of two, ensuring accurate low-level measurements[18].

Covariates

Covariates were selected according to previous studies. Age, race, BMI, ALT, AST, hypertension, diabetes, hyperlipidemia, ASCVD, CKD, smoking status and drinking status were included as adjustment variables in the adjusted models. Based on the duration of their smoking history, the participants were categorized into three distinct groups: non-smokers, former smokers, and current smokers. Participants who reported consuming alcohol in amounts exceeding 0 g/week were classified as drinkers. As for the drinking status groups: never (had < 12 drinks in lifetime); former (did not drink last year but drink ≥ 12 drinks in lifetime); mild (≥ 2 drinks/day for males); moderate (≥ 3 drinks/day for males), current heavy alcohol use (≥ 4 drinks/day for males)[39,40]. The eGFR was calculated using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation. [41].

Statistical analysis

The statistical analysis process was conducted in four steps. First, we divided the study population into four groups based on serum uric acid quartiles. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were expressed as percentages. Second, following the recommendation of the Strengthening the reporting of observational studies in epidemiology (STROBE) statement[42], linear regression models were applied to estimate the independent correlation between serum uric acid and testosterone before or after the adjustment of confounders. Third, the generalized additive models (GAM) were used to find the non-

linear correlations between serum uric acid and testosterone, and the piecewise linear regression model was used to find the threshold impact of serum uric acid on testosterone. Fourth, subgroup analyses were conducted with stratified linear regression models, and changes and interactions between subgroups were identified through likelihood ratio tests. Data analysis was performed using R (The R Foundation; http://www.r-project.org; version 4.2.0) and EmpowerStats (www.empowerstats.net, X&Y solutions, Inc. Boston, Massachusetts). A two-sided *P* value of less than 0.05 was considered as statistical significance.

Data availability

The datasets generated and/or analyzed during the current study are available in the NHANES database, https://wwwn.cdc.gov/nchs/nhanes/.

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Author contributions
All the authors made a significant contribution to this work. J.C (Jingfei Chen) designed the study. W.C (Wenxiu Chen) and W.S (Wanjuan Song) wrote the manuscript. H.Z (Hanzhi Zhang), W.S (Wanjuan Song) and X.S (Xin Su) collected, analyzed, and interpreted the data. J.C (Jingfei Chen) and J.C (Jianlin Chen) critically reviewed, edited, and approved the manuscript. All authors read and approved the final manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

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