

Exploration of the association between serum uric acid and testosterone in adult males: NHANES 2011–2016

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Background: Previous studies have suggested that the possible relationship between serum uric acid (SUA) and testosterone. However, the results of previous studies are controversial and there is limited evidence examining the relationship between SUA and testosterone in a general US population of men. The objective of this study is to explore the correlation of SUA and testosterone among adult males from the US.

Methods: Data from the National Health and Nutrition Examination Survey 2011–2016 were used, including a total of 7,796 male participants aged 18 years or older and excluding those lacking serum testosterone and uric acid data. Clinical characteristics of the participants among different SUA groups and testosterone groups are compared. Univariate and multivariate linear regression analyses were applied to evaluate the association between SUA and testosterone.

Results: We found an inverse association between SUA and testosterone after fully adjusted the potential confounding factors in general US adult males. In the multivariate linear regression analysis, we found that increasing age (estimate testosterone percent difference: -0.20% per year, P<0.01), uric acid (estimate testosterone percent difference: -0.20% per year, P<0.01), uric acid (estimate testosterone percent difference: -2.86% per kg/m2, P<0.01) were associated with declining serum testosterone. This association remained significant in sensitivity analysis, while in the stratified analysis, above association was not significant in men with diabetes or aged 65 and over.

Conclusions: SUA levels might be negatively associated with serum testosterone in adult males.

Keywords: Serum uric acid (SUA); serum testosterone; the National Health and Nutrition Examination Survey (NHANES)

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Introduction

Serum uric acid (SUA) is the end product of purine nucleotide metabolism and hyperuricemia can occur as a result of overproduction or underexcretion of SUA. The prevalence of hyperuricemia has gradually increased in the past 30 years. An epidemiological investigation of the National Health and Nutrition Examination Survey (NHANES) 2007–2008 showed that the overall prevalence of hyperuricemia among US adults was 21.4%, which was significantly higher than that in the NHANES-III [1988– 1994] (1). In addition to joint and kidney involvement, previous studies have suggested that elevated SUA are associated with insulin resistance, elevated blood pressure, triglyceride and the risk of metabolic syndrome (2,3). A significantly higher prevalence of hyperuricemia was observed in participants with metabolic syndrome compared with nonmetabolic syndrome (4), and the converse is also

true, a higher prevalence of metabolic syndrome was also found in participants with higher SUA levels, even in those with normouricemia (5,6). The prevalence of metabolic syndrome was nearly 10-fold higher in those with SUA levels of 10 mg/dL or greater compared with less than 6 mg/dL (7). Hyperuricemia has been believed to be an independent risk factor for cardiovascular events and allcause mortality (8).

Testosterone, the principal male sex hormone mainly secreted by Leydig cells in the testes, is responsible for the maturation of male sexual organs and development of secondary sexual characteristics. Hypogonadism is a clinical and biochemical syndrome that can occur across all ages and the diagnosis of hypogonadism is based on relevant clinical symptoms and low testosterone (9). Testosterone deficiency has become an increasingly concerning and controversial topic around the world, affecting approximately 7% of men in their 50s with an increasing prevalence with age (10). Testosterone is also an important hormone in the pathophysiology of metabolic diseases, and previous studies have shown the association between testosterone and obesity, metabolic syndrome and type 2 diabetes mellitus (T2DM). Hypogonadism is an important comorbidity of obesity (11,12). A nationwide study involves 2,615 participants have found that approximately 52.4% of obese men had low testosterone levels (13). Low testosterone levels are highly prevalent in men with metabolic syndrome and insulin resistance (14,15). Studies have found long-term testosterone replacement therapy can produce significant decrease in body mass index (BMI), improvement in insulin resistance and glycemic control (16,17).

With regard to the relationship between SUA and testosterone levels, the results of previous studies are controversial (Table S1) and lack high-level research evidence. Elevated SUA levels are associated with metabolic syndrome and insulin resistance, both of which increase the risk of low testosterone, so there might be a negative correlation between SUA and testosterone. Some studies have proved SUA is a risk factor for gonadal dysfunction (18), indicating a negative correlation between SUA and testosterone levels (19-23), which is consistent with our results. However, other studies have come to a different conclusion (24-27). Therefore, we analyzed a dataset of male Americans aged 18 years or older from NHANES to explore the relationship between SUA and testosterone and hoped it can provide some information for the treatment of hyperuricemia and low serum testosterone. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tau-20-1114).

Methods

Data source and study population

The National Health and Nutrition Examination Survey (28), which was conducted by the Centers for Disease Control and Prevention of America every 2 years, is a cross-sectional survey that aims to assess the health and nutritional status of the U.S. population. The survey consists of an interview conducted in the home, followed by a standardized health examination in specially equipped mobile examination centers, which includes a physical examination administered by trained medical personnel as well as laboratory tests (29). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) (30). Written informed consent was obtained from all participants prior to completing the NHANES, and all data was de-identified by the National Center for Health Statistics before being made publicly available.

The population for the present analysis consisted of individuals enrolled in three 2-year cycle surveys conducted in 2011–2012, 2013–2014 and 2015–2016. Among the 29,902 participants in the examination, we excluded those who were under the age of 18 years (n=11,933), whose testosterone data (n=1,891) and SUA data (n=17) were missing and who were female (n=8,265). Eventually, 7,796 participants were included in this cross-sectional study (*Figure 1*).

Variables

SUA is measured by the DxC800 synchron using a timed endpoint method (31). Serum testosterone measurement is performed via the isotope dilution liquid chromatography tandem mass spectrometry (ID-LC-MS/MS) method for routine quantitation of serum testosterone based on the National Institute for Standards and Technology's (NIST) reference method (32). Clinically, symptomatic men whose total testosterone lower than 350 ng/dL (12 nmol/L) should be treated with testosterone therapy (33), so we categorized participants into two groups. Participants with testosterone ≤350 ng/dL belonged to the low testosterone level group, and the others were grouped into the normal group. The lower limits of detection of the assays were 0.36 ng/dL for serum testosterone, 0.5 mg/dL for SUA. Concentrations



Figure 1 Flow chart of the screening process for the selection of eligible participants.

below the limit of detection were replaced with limit of detection divided by the square root of 2 (34).

Covariates

Potential confounding factors in this study include age, race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other race), BMI (normal: below 25 kg/m²; overweight: between 25 and <30 kg/m²; obesity: \geq 30 kg/m²) (35), total moderate-to-vigorous minutes of physical activity per week (MVPA, number of days do moderate-to-vigorous physical activities per week × minutes of moderate-to-vigorous physical activities on a typical day) was log-transformed for regression analysis, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), anemia (defined as hemoglobin <13 g/dL) (36), the homeostasis model assessment-insulin resistance index (HOMA-IR) [fasting blood glucose (mmol/L) × fasting insulin (mIU/L)/22.5], a widely used insulin resistance marker (37). C-reactive protein (CRP) (an inflammatory biomarker which was associated with low serum testosterone

and higher prevalence of metabolic syndrome) (38,39), sex hormone binding globulin (SHBG), estradiol. A history of hypertension or diabetes was defined as a self-reported physician diagnosis of hypertension or diabetes. Based on prior studies and theoretical considerations (40-43), above covariates were selected in this study.

Statistical analysis

All statistical analyses were conducted with SPSS 24 and STATA version 14. To account for the complex sampling design and ensure nationally representative estimates, all analyses were adjusted for survey design and weighting variables. The new sample weight (the original 2-year sample weight divided by 3) was constructed according to the analytical guidelines of the NHANES (44). The normality of continuous variables was tested with the Kolmogorov-Smirnov normality test. Normally distributed variables are described as the mean ± standard deviation, and nonnormally distributed continuous variables are described as the median (interquartile range). The median

values among different SUA and testosterone groups were compared with the Mann-Whitney U test and Kruskal-Wallis test. The chi-square test was adopted to compare the percentages of categorical variables among different SUA and testosterone groups. The Bonferroni test was used for the intergroup comparison. We evaluate the correlation between each independent variable and testosterone by using univariate and multivariate linear regression models. Because the distribution of serum testosterone was skewed right, testosterone was log-transformed in the regression analysis. With serum testosterone as the dependent variable, regression coefficients, standard errors and P values were determined. Due to the limitation of data, serum estradiol, SHBG and CRP were only included in the 2015-2016 cycle linear regression analysis (Table S2). Because the concentration of serum testosterone was log-transformed, the percent differences of serum testosterone was calculated by the equation: percent change = $(e^{\beta}-1)\times 100\%$. We performed a sensitivity analysis by excluding participants with serum testosterone <50 or >1,000 ng/dL or outliers (defined as more than 3 standard deviations from the mean). In addition, stratified analyses by age (group 1: 18≤ age <45, group 2: 45≤ age <65, group 3: age \geq 65), BMI (normal, overweight and obesity), history of hypertension and diabetes were performed to examine the association between SUA and log-transformed testosterone. We analyzed the multicollinearity of the multivariate linear regression. The variance inflation factor (VIF) was less than 10, so there was no multicollinearity. A two-sided P<0.05 was considered statistically significant.

Results

A total of 7,796 participants were included in this study and categorized into five racial groups: Mexican American (n=1,112), Other Hispanic (n=761), Non-Hispanic White (n=2,999), Non-Hispanic Black (n=1,673), and the Other race (n=1,251). The mean age was 47.63±18.51 years, the mean serum testosterone level was 417.19±189.59 ng/dL, and mean SUA level was $358.35\pm77.78 \mu$ mol/L. SUA levels were categorized based on SUA quartiles: Q1 (SUA \leq 303.30 µmol/L), Q2 (303.30< SUA \leq 350.90 µmol/L), Q3 (350.90< SUA \leq 404.51 µmol/L) and Q4 (SUA >404.51 µmol/L). Characteristics of the study population among different SUA levels were summarized in *Table 1*. There were significant differences among the four groups with respect to age, race, BMI, serum cholesterol, triglyceride, ALT, AST, testosterone, HOMA-IR, prevalence of anemia, hypertension and diabetes. A Bonferroni test was adopted for intergroup comparison, and we found that with the increasing of SUA quartiles, the proportion of obese participants (P<0.01) and HOMA-IR (P<0.01) increased gradually, while the serum testosterone (P<0.01) decreased gradually.

The clinical characteristics of participants with different testosterone levels were shown in *Table 2*. People with low testosterone levels were older (51 versus 44 years old) (P<0.01) and had higher HOMA-IR (P<0.01), higher triglyceride, ALT and SUA levels (P<0.01), and a higher prevalence of obesity (P<0.01), hypertension (P<0.01), anemia (P<0.01) and diabetes (P<0.01). Participants in the normal testosterone level group performed much more physical activity (P<0.01).

The results of the univariable and multivariate linear regression analysis of the association between each independent variable and log-transformed testosterone were shown in Table 3. In univariable linear regression analysis, we found that age, BMI, HOMA-IR, ALT and uric acid are significantly inversely associated with serum testosterone. In multivariate linear regression, we found that increasing age (estimate testosterone percent difference: -0.20% per year, P<0.01), uric acid (estimate testosterone percent difference: -4.40% per md/dL, P<0.01) and BMI (estimate testosterone percent difference: -2.86% per kg/m², P<0.01) were associated with declining serum testosterone while increasing hemoglobin levels (estimate testosterone percent difference: 6.82% per g/dL, P<0.01) and log(MVPA) [estimate testosterone percent difference: 2.74% per log(MVPA) unit, P<0.01] were associated with elevated testosterone levels. Table 4 showed the results of sensitivity analysis by excluding participants with outlier or extreme value and the negative correlation of age, BMI and SUA with serum testosterone was still significant.

The results of stratified analyses by age, BMI, history of hypertension and diabetes were shown in *Table 5*. In stratified analyses by BMI and history of hypertension, the negative association between SUA and serum testosterone was still significant among different groups, but this negative correlation was not significant in man with diabetes or aged 65 and over. We then tested age and diabetes as an interaction with SUA in the model that adjusted for the same covariates. A significant interaction was noted between age (P<0.05), history of diabetes (P<0.05) and SUA.

Table S2 represented the results of linear regression analysis with CRP, estradiol and SHBG were additionally adjusted. Due to the limitation of data, 2,590 participants

Table 1 Clinical characteristics of the study population disaggregated by quartiles of serum uric acid. NHANES 2011-2016 (N=7,796)

		Uri	c acid quartiles		
Characteristics	Q1	Q2	Q3	Q4	P value
Number of subjects (%)	1,972 (25.3)	1,946 (25.0)	1,983 (25.4)	1,895 (24.3)	
Age (year) [‡]	50 (30.0)	45 (31.0)	45 (31.0)	48 (31.0)	<0.01
Race (%) [†]					<0.01
Mexican American	342 (17.3)	269 (13.8)	297 (15.0)	204 (10.8)	
Other Hispanic	204 (10.3)	199 (10.2)	203 (10.2)	155 (8.2)	
Non-Hispanic White	741 (37.6)	757 (38.9)	744 (37.5)	757 (39.9)	
Non-Hispanic Black	405 (20.5)	390 (20.0)	418 (21.1)	460 (24.3)	
Other race	280 (14.2)	331 (17.0)	321 (16.2)	319 (16.8)	
Body mass index $(\%)^{\dagger}$					<0.01
Normal: <25 (kg/m²)	847 (43.4)	666 (34.5)	483 (24.7)	312 (16.7)	
Overweight: BMI \geq 25 and <30 (kg/m ²)	684 (35.0)	761 (39.5)	754 (38.5)	636 (34.1)	
Obesity: BMI ≥30 (kg/m²)	421 (21.6)	501 (26.0)	722 (36.9)	919 (49.2)	
Cholesterol (mmol/L) [‡]	4.58 (1.42)	4.68 (1.42)	4.81 (1.37)	4.91 (1.52)	<0.01
Triglyceride (mmol/L) [‡]	1.25 (1.26)	1.30 (1.22)	1.49 (1.36)	1.72 (1.55)	<0.01
Alanine aminotransferase (U/L) [‡]	22 (11.0)	23 (13.0)	24 (15.0)	26 (17.0)	<0.01
Aspartate aminotransferase $(U/L)^{\ddagger}$	23 (8.0)	24 (8.0)	25 (8.0)	26 (9.0)	<0.01
Anemia (%) [†]	184 (9.3)	122 (6.3)	125 (6.3)	196 (10.4)	<0.01
Serum uric acid (µmol/L) [‡]	273.6 (41.7)	333.1 (23.8)	380.7 (23.8)	446.1 (65.4)	<0.01
Serum uric acid (mg/dL) [‡]	4.6 (0.7)	5.6 (0.4)	6.4 (0.4)	7.5 (1.1)	<0.01
Testosterone (ng/dL) [‡]	431.00 (267.15)	420.00 (217.00)	378.00 (208.00)	338.26 (193.92)	<0.01
Total moderate-to-vigorous physical activity per week (minutes) [‡]	480 (1,117.5)	480 (1,200)	480 (1,200)	480 (1,050)	0.673
Hypertension (%) †	642 (32.6)	542 (27.9)	662 (33.5)	840 (44.4)	<0.01
Diabetes (%) [†]	352 (17.8)	218 (11.2)	210 (10.6)	276 (14.6)	<0.01
HOMA-IR [‡]	2.02 (2.27)	2.12 (2.13)	2.72 (2.83)	3.38 (3.75)	<0.01

Data are number of subjects (percentage) or medians (inter quartile ranges). [†], Chi-square test was used to compare the percentage among participants in different groups; [‡], Kruskal-Wallis test was used to compare the median values among participants in different groups. Q1 (SUA \leq 303.30 µmol/L), Q2 (303.30< SUA \leq 350.90 µmol/L), Q3 (350.90< SUA \leq 404.51 µmol/L), Q4 (SUA >404.51 µmol/L). HOMA-IR, homeostasis model assessment-insulin resistance index.

from 2015–2016 cycle was involved. Our multiple regression model accounts for 66.2% (Adj. R^2 =0.662) of testosterone variation. In multivariate linear regression, we found that increasing age, SUA, BMI and HOMA-IR were associated with declining serum testosterone while increasing hemoglobin, estradiol and SHBG were associated with elevated testosterone levels.

Discussion

In this study, we combined data from the NHANES 2011–2012, 2013–2014 and 2015–2016, and a total of 7,796 men aged 18 years or older were included. In both univariable and multivariate linear regression analysis, our study indicated that increased SUA might be negatively correlated with serum testosterone. The negative association of

Table 2 Clinical characteristics of the study population in different serum testosterone groups. NHANES 2011-2014 (N=7,796)

Characteristics	Low testosterone level	Normal testosterone level	P value
Number of subjects	3,189	4,607	
Age (year) [‡]	51 (29.0)	44 (32.0)	<0.01
Race $(\%)^{\dagger}$			0.477
Mexican American	453 (14.2)	659 (14.3)	
Other Hispanic	317 (9.9)	444 (9.6)	
Non-Hispanic White	1258 (39.4)	1741 (37.8)	
Non-Hispanic Black	658 (20.6)	1015 (22.0)	
Other race	503 (15.8)	748 (16.2)	
Body mass index (%) [†]			<0.01
Normal: <25 (kg/m²)	506 (16.1)	1802 (39.5)	
Overweight: 25≤ BMI <30 (kg/m²)	1081 (34.4)	1754 (38.4)	
Obesity: BMI ≥30 (kg/m²)	1554 (49.5)	1009 (22.1)	
Cholesterol (mmol/L) [‡]	4.73 (1.45)	4.73 (1.42)	0.811
Triglyceride (mmol/L) [‡]	1.83 (1.69)	1.21 (1.05)	<0.01
Alanine aminotransferase (U/L) [‡]	25 (16.0)	23 (13.0)	<0.01
Aspartate aminotransferase (U/L) [‡]	25 (9.0)	24 (8.0)	0.135
Anemia (%) [†]	354 (11.1)	273 (5.9)	<0.01
Serum uric acid (µmol/L) [‡]	368.8 (107.1)	345.0 (95.2)	<0.01
Serum uric acid (mg/dL)	6.2 (1.8)	5.8 (1.6)	<0.01
Testosterone (ng/dL) [‡]	268.96 (97.53)	487.8 (182.00)	<0.01
Total moderate-to-vigorous physical activity per week (minutes) ‡	420 (960)	540 (1230)	<0.01
Hypertension (%) ^{\dagger}	1366 (42.9)	1320 (28.7)	<0.01
Diabetes (%) [†]	628 (19.7)	428 (9.3)	<0.01
HOMA-IR [‡]	3.88 (4.57)	2.06 (2.07)	<0.01

Data are number of subjects (percentage) or medians (inter quartile ranges). [†], Chi-square test was used to compare the percentage between participants with and without low testosterone level; [‡], Mann-Whitney U test was used to compare the median values between participants with and without low testosterone level. HOMA-IR, homeostasis model assessment-insulin resistance index.

SUA with testosterone was still significant after excluding participants with outlier or extreme value. In stratified analyses, above association was not significant in men with diabetes or aged 65 and over.

The mechanisms of the relationship between SUA and testosterone remain unclear, but several possibilities have been proposed. First, elevated SUA can lead to metabolic syndrome through mitochondrial oxidative stress and inhibition of AMP-activated protein kinase (45,46); in addition, hyperuricemia can cause decreased insulin release and insulin resistance through endothelial dysfunction, reduced nitric oxide bioavailability (6). Metabolic syndrome and insulin resistance have been shown to be associated with increased conversion from testosterone to estradiol and decreased production of testosterone by Leydig cells (47). Moreover, the deposition of urate crystals in the testicular tissue cause oxidative damage and directly affect the secretion of testosterone (18). Low testosterone can also affect the concentration of SUA, for which several mechanisms have been suggested. Low testosterone may lead to insulin resistance, which is inversely correlated with the clearance of UA (14,48,49). In addition, decreased levels

Table 3 Univariable and multivariate linear regression analysis predicting log-transformed serum testosterone, NHANES 2011-2016 (N=7,796)

Variable	Uni	ivariable linear	regression ana	llysis	Multivariable linear regression analys			alysis
Variable	R ²	В	SE	P value	Adj. R ²	В	SE	P value
Age (years)	0.024	-0.005	<0.001	<0.001	0.227	-0.002	0.001	<0.001
Race	<0.001	0.006	0.006	0.365		-0.001	0.009	0.909
BMI (kg/m ²)	0.132	-0.030	0.001	<0.001		-0.029	0.002	<0.001
Uric acid (mg/dL)	0.029	-0.068	0.004	<0.001		-0.045	0.007	<0.001
ALT (U/L)	0.002	-0.001	<0.001	<0.001		-0.001	0.001	0.115
AST (U/L)	<0.001	<0.001	<0.001	0.371		0.001	0.001	0.031
Hypertension	0.021	0.156	0.012	<0.001		-0.021	0.018	0.248
Diabetes	0.017	0.214	0.018	<0.001		0.034	0.031	0.275
Hemoglobin (g/dL)	0.036	0.079	0.005	<0.001		0.066	0.007	<0.001
Log (MVPA)	0.010	0.036	0.005	<0.001		0.027	0.006	<0.001
HOMA-IR	0.039	-0.011	0.001	<0.001		-0.002	0.001	0.135

R², coefficient of determination; B, unstandardized regression coefficient; SE, standard error of the coefficient; Adj. R², adjusted coefficient of determination; BMI, body mass index; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; MVPA, moderate-to-vigorous physical activity per week; HOMA-IR, the homeostasis model assessment-insulin resistance index.

Table 4 Univariable and multivariate linear regression analysis predicting log-transformed serum testosterone (sensitivity analysis by excludin	ıg
participants with outlier or extreme value), NHANES 2011–2016 (N=7,658)	

Variable	Univariable linear regression analysis			Multivariable linear regression analysis				
vanable	R ²	В	SE	P value	Adj. R ²	В	SE	P value
Age (years)	0.019	-0.003	<0.001	<0.001	0.259	-0.002	<0.001	0.001
Race	<0.001	0.007	0.005	0.179		0.002	0.008	0.777
BMI (kg/m²)	0.171	-0.029	0.001	<0.001		-0.027	0.001	<0.001
Uric acid (mg/dL)	0.044	-0.072	0.004	<0.001		-0.051	0.006	<0.001
ALT (U/L)	0.004	-0.001	<0.001	<0.001		-0.001	0.001	0.064
AST (U/L)	<0.001	<0.001	<0.001	0.606		0.001	0.001	0.016
Hypertension	0.024	0.142	0.010	<0.001		-0.009	0.016	0.577
Diabetes	0.016	0.178	0.016	<0.001		0.053	0.028	0.056
Hemoglobin (g/dL)	0.023	0.055	0.004	<0.001		0.055	0.006	<0.001
Log (MVPA)	0.010	0.032	0.004	<0.001		0.026	0.005	<0.001
HOMA-IR	0.046	-0.010	0.001	<0.001		-0.002	0.001	0.040

R², coefficient of determination; B, unstandardized regression coefficient; SE, standard error of the coefficient; Adj. R², adjusted coefficient of determination; BMI, body mass index; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; MVPA, moderate-to-vigorous physical activity per week; HOMA-IR, the homeostasis model assessment-insulin resistance index.

of testosterone can reduce protein synthesis and increase the levels of endogenous purine, which may cause the elevation of SUA (18). In summary, metabolic syndrome, insulin resistance and obesity may play a mediating role in the relationship between low testosterone and SUA and the deposition of urate crystals in the testicular tissue may

 Table 5 Multivariate linear regression analysis predicting log-transformed serum testosterone, stratified analyses by selected characteristic, NHANES 2011–2016 (N=7,796)

Variable	Multivariable linear regression analysis						
vanable	B (serum uric acid)	SE	P value				
Age (years)							
18≤ age <45	-0.059	0.009	<0.001				
45≤ age <65	-0.043	0.013	0.001				
Age ≥65	-0.017	0.015	0.265				
BMI (kg/m ²)							
BMI <25	-0.081	0.014	<0.001				
25≤ BMI <30	-0.029	0.011	0.012				
BMI ≥30	0.062	0.011	<0.001				
Diabetes							
Yes	0.005	0.020	0.788				
No	-0.050	0.007	<0.001				
Hypertension							
Yes	-0.039	0.012	0.001				
No	-0.048	0.008	<0.001				

B, unstandardized regression coefficient; SE, standard error of the coefficient; BMI, body mass index.

directly affects the secretion of testosterone.

Our results were consistent with some previous studies (18-21,23). A cross-sectional study conducted by Chao (18) indicated a significant negative correlation between SUA and testosterone levels in T2DM males. A study conducted by Gambineri, which involved 30 obese male subjects, was designed to investigate the impact of obstructive sleep apnea syndrome on testosterone levels and the main metabolic parameters and found that testosterone values were negatively associated with SUA (20). A prospective cohort study involving 51 men aimed at investigating whether testosterone treatment had an impact on cardiovascular risk factors in patients with T2DM and late-onset hypogonadism (LOH) found that testosterone-metformin combination therapy could help reduce SUA compared with treatment by metformin alone (21). In another prospective cohort of 31 men with LOH, 16 participants received intramuscular testosterone enanthate (100 mg weekly). After 4 months of therapy, increased testosterone levels and decreased UA levels were identified in patients treated with testosterone compared with the control group (23). However, there is also some controversial evidence (24,26,27,50). A prospective study spanning two years including 47 female-to-male transsexuals documented an ensuing significant increase in SUA and a decrease in FEUA (fraction excretion of uric acid) after cross-sex hormone treatment (24). Studies conducted by Marinello and Rosen pointed out that testicular endocrine function was normal in patients with gout, and no significant difference in serum testosterone levels was found between male patients with gout or asymptomatic hyperuricemia men and controls (26,27). Borbélyová found that gonadectomy and longterm hypogonadism in male middle-aged rats had no significant effect on uric acid (50). Possible explanations of the differences in the above research results included the following: (I) previous studies on the relationship between SUA and testosterone included a relatively small sample size; (II) the inclusion criteria of the above research were different, so there were differences in the research objects; (III) there were differences in the research methods, statistical analysis and adjusted covariates.

We used a large national representative sample with participants aged 18 years and older among the general US population, which increased the statistical strength to provide a more reliable result. We also analyzed the relationship between SUA and testosterone with different statistical methods. Furthermore, we fully adjusted for potential confounding factors in the exploration of the association between SUA and testosterone levels. However, our study also has some limitations. Primarily, as a crosssectional study, it was difficult to determine causality between SUA and testosterone. Furthermore, testosterone was measured only once, while the diagnosis of low testosterone needed at least two recorded values measured on different days and serum testosterone was not a static but a dynamic variable, which may cause some bias. Finally, due to the limited data, we only analyzed the relationship between SUA and testosterone but did not further analyze the effects of free testosterone or bioactive testosterone on SUA.

Conclusions

In conclusion, our study suggests that SUA might be negatively associated with serum testosterone levels in the general U.S. adult males. We hope that it can provide some information for the treatment of hyperuricemia and testosterone deficiency. The association we investigated in this study is biologically plausible, and further largescale prospective studies are required to confirm the causal relationship between SUA and testosterone.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from all participants prior to completing the NHANES, and all data was de-identified by the NCHS before being made publicly available.

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Supplementary

Study	Ν	Population	Main results
Chao Liu <i>et al.</i> (18)	205	Male patients with T2DM	SUA was negatively associated with testosterone.
Akishita <i>et al.</i> (19)	172	Male office-workers aged 40-64 years	Linear regression analysis showed a negative association between serum testosterone and SUA
Gambineri <i>et al.</i> (20)	15	Male participants with abdominal obesity and OSAS	A negative correlation between testosterone and SUA and a positive correlation between testosterone and HDL-cholesterol level.
Krysiak <i>et al.</i> (21)	51	Male patients with T2DM and late-onset hypogonadism	Compared with metformin-treated patients, testosterone-metformin combination therapy reduced SUA levels.
Yingli Lu <i>et al.</i> (22)	4,426	Men and postmenopausal women with diabetes	In men patients, serum testosterone was negatively associated with SUA levels and SUA levels decreased with the increased testosterone quartiles.
Krysiak <i>et al.</i> (23)	31	Male late-onset hypogonadism patients	Testosterone therapy are associated with reduced plasma levels of LDL cholesterol and uric acid.
Yahyaoui <i>et al.</i> (24)	69	Healthy transsexual persons, 22 MFTs and 47 FMTs	In FMTs, SUA levels increased significantly after 1 year of testosterone therapy.
Watanabe <i>et al.</i> (25)	160	patients with female to male GID	SUA levels elevated after three months of TRT and there was a tendency toward testosterone dose-dependency.
Marcolongo <i>et al.</i> (26)	132	72 patients with gout and 60 were normal controls	No significant difference in plasma testosterone levels was found between gout patients and controls.
Weinberger <i>et al.</i> (27)	69	38 men with ASH and 31 were healthy controls	The serum testosterone levels were similar in both groups.

Table S1 Previous human studies on the association between serum uric acid and testosterone.

SUA, serum uric acid; T2DM, type 2 diabetes mellitus; OSAS, obstructive sleep apnea syndrome; HDL, high-density lipoprotein; LDL, low density lipoprotein; MFTs, male-to-female transsexuals; FMTs, female-to-male transsexuals; GID, gender identity disorder; TRT, testosterone replacement therapy; ASH, asymptomatic hyperuricemia.

Variable	Univariable linear regression analysis			Mult	Multivariable linear regression analysis			
	R ²	В	SE	P value	Adj. R ²	В	SE	P value
Age (years)	0.019	-0.004	0.001	<0.001	0.662	-0.009	0.001	<0.001
Race	0.001	0.018	0.015	0.214		-0.022	0.010	0.031
BMI (kg/m²)	0.200	-0.032	0.002	<0.001		-0.023	0.002	<0.001
Uric acid (mg/dL)	0.059	-0.091	0.011	<0.001		-0.019	0.008	0.026
ALT (U/L)	0.014	-0.003	0.001	<0.001		-0.001	0.001	0.394
AST (U/L)	<0.001	0.001	0.001	0.831		<0.001	0.001	0.891
Hypertension	0.015	0.124	0.030	<0.001		-0.006	0.022	0.793
Diabetes	0.017	0.191	0.043	<0.001		0.006	0.036	0.861
Hemoglobin (g/dL)	0.033	0.073	0.012	<0.001		0.043	0.009	<0.001
Log (MVPA)	0.002	0.015	0.011	0.180		0.007	0.007	0.327
HOMA-IR	0.065	-0.014	0.002	<0.001		-0.005	0.007	0.014
CRP (mg/L)	0.032	-0.014	0.002	<0.001		-0.003	0.002	0.063
Estradiol (pg/mL)	0.161	0.019	0.001	<0.001		0.016	0.001	<0.001
SHBG (nmol/L)	0.245	0.009	<0.001	<0.001		0.009	< 0.001	<0.001

Table S2 Univariable and multivariate linear regression analysis predicting log-transformed serum testosterone, NHANES 2015–2016 (N=2,590).

R2, coefficient of determination; B, unstandardized regression coefficient; SE, standard error of the coefficient; Adj. R2, adjusted coefficient of determination; BMI, body mass index; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; MVPA, moderate-to-vigorous physical activity per week; HOMA-IR, the homeostasis model assessment-insulin resistance index; CRP, C-reactive protein; SHBG, Sex hormone binding globulin.