

Triglycerides and HDL Cholesterol Mediate the Association Between Waist Circumference and Hyperuricemia in Normal-Weight Men

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Purpose: Hyperuricemia has traditionally been associated with obesity and dyslipidemia. However, the relationship between waist circumference (WC) and hyperuricemia in normal-weight men is still unclear, particularly regarding the roles of triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C). The aim of this research was to explore the mediating roles of TG and HDL-C in the association between WC and hyperuricemia in normal-weight men.

Methods: A retrospective observational study was conducted among normal-weight men ($18.5 \leq \text{BMI} < 24 \text{ kg/m}^2$) aged ≥ 18 years who underwent health checkups in Nanjing from 2021–2023. Relationships between WC, blood lipids, and hyperuricemia were investigated by multivariable regression models and mediation analysis.

Results: We enrolled 35,984 participants, with an overall hyperuricemia prevalence of 24.2%. The research found a significant positive association between WC and hyperuricemia in normal-weight men ($P < 0.001$). For hyperuricemia across rising WC quartiles, with WC divided as follows: Q1 ($59 \leq \text{WC} < 77 \text{ cm}$), Q2 ($77 \leq \text{WC} < 81 \text{ cm}$), Q3 ($81 \leq \text{WC} < 85 \text{ cm}$), and Q4 ($85 \leq \text{WC} \leq 107 \text{ cm}$), the multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were 1.00 (reference), 1.09 (1.01, 1.18), 1.26 (1.15, 1.37), and 1.34 (1.22, 1.46), respectively (all $P < 0.001$). The mediation analysis indicated that WC had a significant total effect on hyperuricemia (Coefficient = 0.0046, 95% CI: 0.0028, 0.0070, $P < 0.001$), with significant indirect effects mediated through TG and HDL-C, contributing mediation proportions of 22.3% and 18.3%, respectively (both $P < 0.05$).

Conclusion: Elevated WC is associated with an increased likelihood of hyperuricemia in normal-weight men. TG and HDL-C play substantial mediating roles in this association. These findings suggest that monitoring WC and lipid profiles in normal-weight men could help identify those at higher risk of hyperuricemia, even in the absence of general obesity.

Keywords: waist circumference, triglycerides, high-density lipoprotein cholesterol, central obesity, hyperuricemia, mediation analysis

Introduction

Hyperuricemia, characterized by increased serum uric acid concentrations, is a prevalent metabolic disorder linked to gout, cardiovascular disease, and renal dysfunction.^{1,2} Genetic variations, environmental exposures, and their interactions contribute to hyperuricemia. Certain dietary exposures, such as alcohol, red meat, seafood, and sugary drinks, are known to raise blood uric acid levels.^{3,4} Additionally, hyperuricemia is closely associated with obesity and metabolic syndrome.⁵ Although traditionally associated with obesity, hyperuricemia also occurs in normal-weight individuals, especially among

Asian populations.⁶ Notably, the prevalence of hyperuricemia in normal-weight individuals is significantly higher in males than in females. A cross-sectional study in 2019 reported that 16.3% of normal-weight men and 4.6% of normal-weight women in China were affected by hyperuricemia.⁷ Although Asians generally have a lower body mass index (BMI) than other ethnic groups, they appear more susceptible to visceral fat accumulation.⁸ A nationwide survey in China showed that 10.5% of individuals with a BMI < 24 kg/m² also presented with central obesity.⁹ CT scan measurements indicated that men had twice the amount of visceral fat as premenopausal women.¹⁰ Even with identical waist circumference (WC), men accumulated more visceral fat than women.¹¹ This gender disparity emphasizes the importance of gender-specific research to effectively address hyperuricemia. These normal-weight individuals with hyperuricemia may have an excess accumulation of visceral adipose tissue that BMI does not reflect. Currently, most published studies on hyperuricemia primarily focus on individuals with excess weight, often overlooking those who may not have overall obesity but do exhibit central obesity.

Central obesity has a stronger correlation with metabolic disturbances than total body obesity, and WC is a critical indicator of abdominal obesity.^{12,13} A population-based longitudinal study in Japan discovered that individuals with larger WC had a higher risk for the development of hyperuricemia.¹⁴ Kim et al assessed fat distribution via abdominal CT scans and identified visceral fat as an independent predictor of hyperuricemia, while subcutaneous fat showed no association with serum uric acid levels.¹⁵ Abdominal obesity is also closely related to elevated plasma triglycerides (TG) and reduced high-density lipoprotein cholesterol (HDL-C).¹⁶ Moreover, previous studies have reported a positive association between serum TG levels and hyperuricemia and a negative association between HDL-C levels and hyperuricemia.^{17–19} However, few studies have investigated the relationships among blood lipids, WC, and hyperuricemia.

High TG and low HDL-C are central components of metabolic syndrome.²⁰ Metabolic syndrome includes a variety of cardiovascular risk factors, such as central obesity, dyslipidemia, hypertension, and hyperglycemia. Previous clinical studies have established a strong association between hyperuricemia and metabolic syndrome.^{21,22} Insulin resistance is a key characteristic of metabolic syndrome.²³ Insulin resistance, often related to elevated TG and lowered HDL-C levels, can decrease renal uric acid excretion, leading to hyperuricemia.²⁴ In addition, some studies suggested that fat distribution affected insulin action, highlighting a close relationship between visceral fat and insulin resistance, whereas overall obesity did not correlate with insulin resistance.²⁵ A study from Mexico showed that even after adjusting for age and BMI, the correlation between serum uric acid concentration and the insulin resistance index remained significant. This suggests that serum uric acid is associated with insulin resistance, even in normal-weight populations.²⁶ Based on the close relationship between WC, TG, HDL-C, and insulin resistance, as well as hyperuricemia, we hypothesize that the impact of WC on hyperuricemia may be mediated by TG and HDL-C. Moriwaki et al found that gout patients with the APO E4/3 phenotype had higher TG and cholesterol levels, indicating that dyslipidemia and hyperuricemia might share common susceptibility genes.²⁷ These mechanisms suggest that TG and HDL-C may have a mediation function in the relationship between WC and hyperuricemia. However, it is still unclear how TG and HDL-C contribute to the relationship between WC and hyperuricemia among normal-weight men.

This study aims to investigate how TG and HDL-C mediate the association between WC and hyperuricemia in normal-weight men. By focusing on this specific population, we seek to elucidate the mechanisms linking central obesity to hyperuricemia, thereby providing insights for early intervention and prevention of related comorbidities.

Methods

Subjects and Research Design

This study used data from male participants who underwent health checkups at the Drum Tower Hospital in Nanjing, China, between January 2021 and January 2023. The inclusion criteria specified men aged ≥ 18 years who consented to participate. Since BMI is an indirect measure of adiposity and may overlook central obesity, this study focuses on the impact of central obesity on hyperuricemia. Consequently, we excluded individuals with a BMI beyond the normal range and included only normal-weight men in the analysis. Out of 108,332 men with complete data, we excluded 66,634 individuals with excess weight (BMI ≥ 24 kg/m²), along with 562 who were underweight (BMI < 18.5 kg/m²).

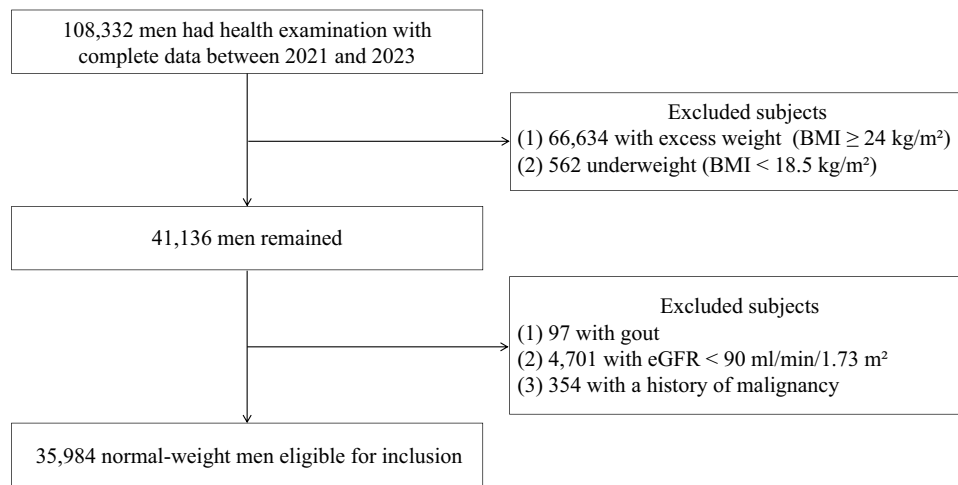


Figure 1 Flowchart of this study.

Additionally, we excluded 97 participants with gout, 4701 with renal insufficiency [estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73 m²], and 354 with a history of malignancy. Consequently, we analyzed data from 35,984 normal-weight men (Figure 1).

This research was conducted in adherence to the ethical standards outlined in the Helsinki Declaration. Consent had been obtained from each subject after a full explanation of the purpose and nature of all procedures used. The research protocol received approval from the Ethics Committee of Nanjing Drum Tower Hospital (Ethical Approval Number: 2022–698-01).

Definitions

The weight (kg) divided by the square of the height (m²) was used to compute BMI. $18.5 \leq \text{BMI} < 24 \text{ kg/m}^2$ was used to identify normal-weight.²⁸ Serum uric acid levels of more than 420 $\mu\text{mol/L}$ were used to define hyperuricemia.² Dyslipidemia criteria were based on Chinese guidelines:²⁹ elevated TG levels (TG $\geq 1.7 \text{ mmol/L}$), elevated total cholesterol (TC) levels (TC $\geq 5.2 \text{ mmol/L}$), lowered HDL-C levels (HDL-C < 1.0 mmol/L), and elevated low-density lipoprotein cholesterol (LDL-C) levels (LDL-C $\geq 3.4 \text{ mmol/L}$).

Anthropometric and Biochemical Measurements

Trained staff conducted physical examinations. Participants' body weight and height were measured while they were barefoot and wearing light clothing. WC was measured with participants standing, using a tape placed horizontally at the midpoint between the lower margin of the last rib and the iliac crest. After resting for 30 minutes, the blood pressure was reported using the mean of two separate measurements. By inquiring about medical history, record the chronic disease conditions of the participants.

Blood samples from each participant were collected after a 12-hour fasting period to analyze serum uric acid, TG, HDL-C, TC, LDL-C, fasting blood glucose (FBG), blood urea nitrogen (BUN), serum creatinine (Cr), as well as alanine aminotransferase (ALT) and aspartate aminotransferase (AST). These parameters were analyzed with the aid of a Beckman AU5400 automatic biochemistry analyzer (Beckman Coulter Corp., Brea, California, United States). The eGFR was calculated according to the MDRD formula.

Mediation Model

The mediation model depicted in Figure 2 shows WC as the independent variable (X), hyperuricemia as the dependent variable (Y), and blood lipids (eg, TG, HDL-C) as the mediators (M). The total effect (c) of WC on hyperuricemia consists of two parts: the direct effect (c') and the indirect effect (ab). The direct effect (c') represents the effect of WC on hyperuricemia after controlling for the mediators. The indirect effect (ab) is the combined impact of WC on the

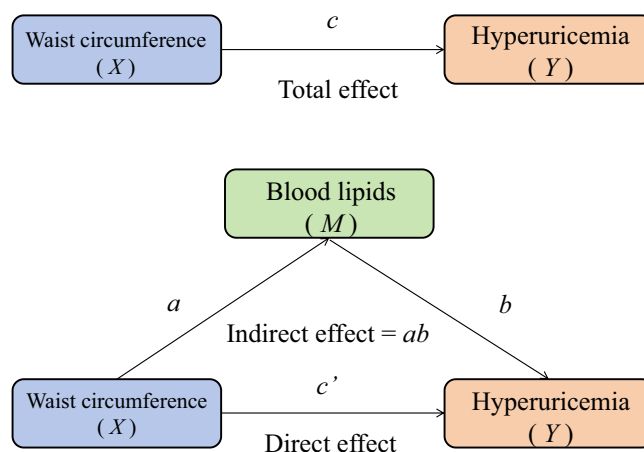


Figure 2 Mediation effect model diagram of waist circumference, blood lipids, and hyperuricemia.

mediators (a) and the mediators on hyperuricemia (b). The mediation proportion is the ratio of the indirect effect (ab) to the total effect (c), which indicates the proportion of the total effect explained by the mediators.

Statistical Analyses

For continuous variables normally distributed, the mean \pm standard deviation (SD) was utilized, whereas for variables with a non-normal distribution, the median (interquartile range) was employed. Categorical variables were presented as frequency (percentage). Trend tests across WC groups were assessed using linear regression models or the Cochran-Armitage trend test for categorical data.

To explore the potential nonlinear relationships between WC and hyperuricemia, restricted cubic splines (RCS) were used. The RCS with 3 knots at the 10th, 50th, and 90th percentiles of WC was chosen. Multivariable logistic regression analyzed associations between WC and hyperuricemia, with results shown as odds ratios (OR) with 95% confidence intervals (CI). WC was categorized into four quartiles for the analysis, with the first quartile (Q1) serving as the reference group. In addition to the quartile-based analysis, we conducted sensitivity analyses with WC as a continuous variable to further assess its association with hyperuricemia. Absolute risk differences (ARD) were also calculated to provide clinically interpretable insights into the impact of WC on hyperuricemia. The correlation between WC and blood lipids was assessed by Spearman correlation coefficient. Furthermore, the association between blood lipids and hyperuricemia was analyzed using multivariable logistic regression.

To ensure the robustness of our logistic regression model, we conducted diagnostics for multicollinearity (variance inflation factor, VIF), influential observations (Cook's distance), and goodness of fit (Hosmer-Lemeshow test). We used a stepwise regression approach to select confounders, identifying the model with the lowest Akaike Information Criterion (AIC). The final confounders included age, BMI, SBP, DBP, FBG, BUN, eGFR, ALT, AST, diabetes, hypertension, fatty liver, CVD, and dyslipidemia. Due to both eGFR and Cr having a VIF greater than 10, we chose eGFR, more commonly used in clinical practice, as our adjustment factor.

Stratified and interaction analyses were conducted to assess how chronic disease statuses (diabetes, hypertension, fatty liver, CVD, dyslipidemia) and age (18–39, 40–59, ≥ 60 years) modified the association between WC and hyperuricemia. Interaction terms between WC (categorized as ≥ 85 cm and < 85 cm) and these variables were included in the multivariable logistic regression models. To control for multiple comparisons, a Bonferroni correction was applied, setting the significance threshold at 0.017 for age groups and 0.025 for chronic disease subgroups. Significant interaction terms ($P < 0.05$) indicated effect modification, suggesting variations in the WC-hyperuricemia relationship across different subgroups.

Causal mediation analysis was conducted employing the “mediation” package with 1000 bootstrap simulations. We also conducted sensitivity analyses to assess the robustness of our mediation results. Specifically, we employed E-values to evaluate the potential impact of unmeasured confounding on our findings.

All statistical analyses were conducted using R software, specifically version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). A threshold of $P < 0.05$ was set to indicate statistical significance.

Results

Characteristics of Participants

The study comprised 35,984 participants, with a mean BMI of 22.2 ± 1.3 kg/m² and an age range of 18 to 97 years. Among the normal-weight men, the overall prevalence of hyperuricemia was 24.2%. WC was divided into four quartiles: Q1 ($59 \leq WC < 77$ cm), Q2 ($77 \leq WC < 81$ cm), Q3 ($81 \leq WC < 85$ cm), and Q4 ($85 \leq WC \leq 107$ cm) (Table 1). The prevalence of hyperuricemia and serum uric acid levels significantly increased with higher WC (all P for trend < 0.001). Similarly, levels of TG, TC, and LDL-C demonstrated an increasing trend with increasing WC, while HDL-C exhibited a lowering tendency (all P for trend < 0.001).

Participants in the Q4 group had higher levels of age, ALT, AST, FBG, systolic blood pressure (SBP), and diastolic blood pressure (DBP) in comparison with other groups (all P for trend < 0.001). Likewise, higher WC was related to an increasing trend in the prevalence rates of diabetes, hypertension, fatty liver, CVD, and hyperlipidemia (all P for trend < 0.001). However, BUN and eGFR did not differ statistically significantly among the four groups (all P for trend > 0.05).

Associations Between WC, Hyperuricemia and Blood Lipids

After controlling for age, SBP, DBP, TG, HDL-C, LDL-C, FBG, eGFR, ALT, and AST, the RCS analysis suggested a linear association between WC and hyperuricemia (P for nonlinearity > 0.05) (Figure 3). Multivariable logistic regression analysis further examined the relationship between WC and hyperuricemia. Table 2 shows that a larger WC was significantly associated with hyperuricemia. In Model 1, controlled for age and BMI, individuals with the largest WC (Q4) exhibited notably elevated odds of hyperuricemia compared to individuals with the smallest WC (Q1), with an OR of 1.57 (95% CI:

Table 1 35,984 Men's Baseline Characteristics Based on WC Quartiles

Characteristics	Overall (n = 35,984)	Q1 (n = 8996)	Q2 (n = 8996)	Q3 (n = 8996)	Q4 (n = 8996)	P for trend
Age (years)	45.0 ± 14.19	42.0 ± 14.32	43.6 ± 13.81	45.8 ± 13.95	48.5 ± 13.83	<0.001
WC (cm)	80.4 ± 5.54	73.2 ± 2.83	78.7 ± 1.13	82.4 ± 1.05	87.2 ± 2.52	<0.001
Hyperuricemia (n, %)	8,691 (24.2%)	1,715 (19.1%)	2,076 (23.1%)	2,379 (26.4%)	2,521 (28.0%)	<0.001
SBP (mmHg)	127.4 ± 16.59	124.6 ± 15.94	126.5 ± 16.12	128.4 ± 16.61	130.2 ± 17.14	<0.001
DBP (mmHg)	78.7 ± 10.77	76.6 ± 10.41	78.2 ± 10.55	79.4 ± 10.82	80.6 ± 10.91	<0.001
ALT (U/L)	18.8 (14.4, 25.7)	16.6 (12.9, 22.0)	18.3 (14.2, 24.7)	19.6 (15.1, 26.8)	21.1 (16.0, 29.5)	<0.001
AST (U/L)	19.2 (16.6, 22.7)	18.8 (16.2, 22.0)	19.1 (16.6, 22.3)	19.4 (16.7, 22.9)	19.6 (16.8, 23.4)	<0.001
Uric Acid (umol/L)	374.0 ± 72.75	361.5 ± 70.59	372.0 ± 71.28	379.4 ± 73.63	382.9 ± 73.57	<0.001
TG (mmol/L)	1.1 (0.8, 1.5)	0.8 (0.6, 1.1)	1.0 (0.7, 1.4)	1.1 (0.8, 1.6)	1.3 (0.9, 1.8)	<0.001
HDL-C (mmol/L)	1.4 ± 0.34	1.5 ± 0.36	1.4 ± 0.33	1.3 ± 0.32	1.3 ± 0.30	<0.001
TC (mmol/L)	4.8 ± 0.89	4.6 ± 0.85	4.8 ± 0.88	4.8 ± 0.89	4.8 ± 0.91	<0.001
LDL-C (mmol/L)	2.8 ± 0.75	2.7 ± 0.72	2.8 ± 0.73	2.9 ± 0.74	2.9 ± 0.77	<0.001
FBG (mmol/L)	5.2 ± 1.18	5.0 ± 0.96	5.1 ± 1.05	5.2 ± 1.21	5.4 ± 1.42	<0.001
BUN (mmol/L)	5.2 ± 1.15	5.2 ± 1.15	5.2 ± 1.14	5.2 ± 1.15	5.3 ± 1.17	0.059
eGFR (mL/min/1.73 m ²)	114.9 (104.3, 127.8)	115.3 (104.6, 128.4)	114.6 (104.2, 127.1)	114.8 (104.6, 127.7)	114.9 (104.0, 128.1)	0.191
History of chronic diseases						
Diabetes (n, %)	2,655 (7.4%)	363 (4.0%)	551 (6.1%)	729 (8.1%)	1,012 (11.2%)	<0.001
Hypertension (n, %)	10,416 (28.9%)	1,921 (21.4%)	2,282 (25.4%)	2,783 (30.9%)	3,430 (38.1%)	<0.001
Fatty Liver (n, %)	2,184 (6.1%)	90 (1.0%)	331 (3.7%)	699 (7.8%)	1,064 (11.8%)	<0.001
CVD (n, %)	489 (1.4%)	80 (0.9%)	98 (1.1%)	151 (1.7%)	160 (1.8%)	<0.001
Dyslipidemia (n, %)	16,194 (45.0%)	2,821 (31.4%)	3,867 (43.0%)	4,443 (49.4%)	5,063 (56.3%)	<0.001

Notes: Data are presented as mean ± SD, median (interquartile range), or frequency (percentage).

Abbreviations: WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease.

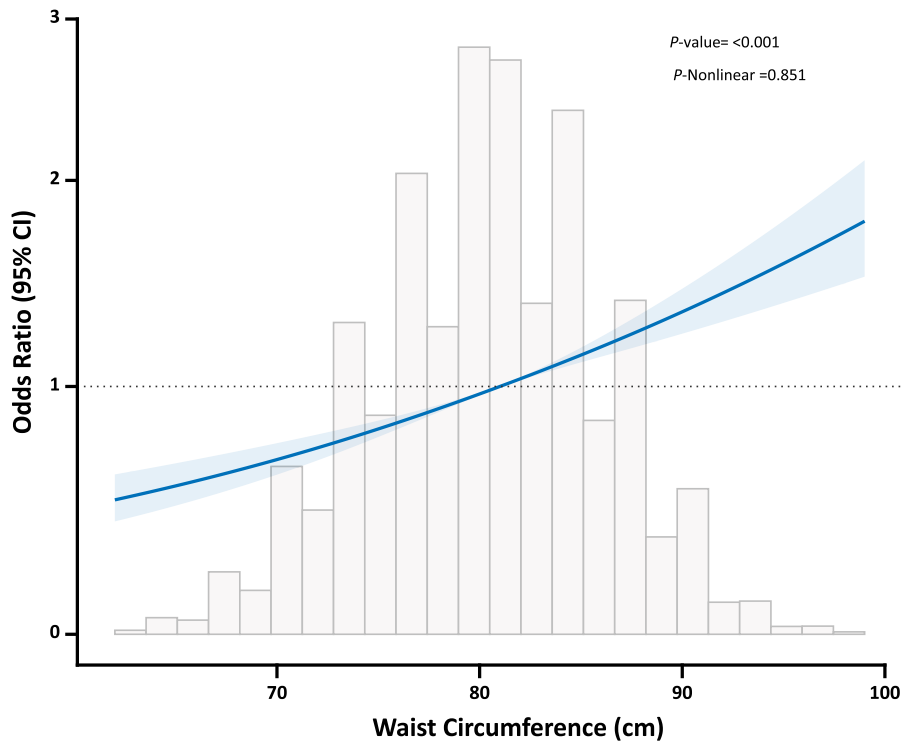


Figure 3 A linear relationship between waist circumference and hyperuricemia using restricted cubic spline (RCS).

Notes: P -value < 0.05 indicates a positive association between waist circumference and hyperuricemia. The P -Nonlinear value > 0.05 suggests a linear relationship between waist circumference and hyperuricemia.

1.44, 1.71) ($P < 0.001$). This association remained significant even after adjusting for additional factors, including SBP, DBP, FBG, BUN, eGFR, ALT, AST, diabetes, hypertension, fatty liver, CVD, and dyslipidemia in Model 2. The adjusted ORs with 95% CIs for hyperuricemia across increasing quartiles of WC were 1.09 (1.01, 1.18), 1.26 (1.15, 1.37), and 1.34 (1.22, 1.46), respectively, compared to Q1 (all $P < 0.05$). Notably, the ARD for hyperuricemia relative to Q1 were 4.0% in Q2, 7.3% in Q3, and 8.9% in Q4, highlighting the progressive in the likelihood of hyperuricemia with higher WC categories. Additionally, after multivariable adjustment (Model 2), each 1 cm increase in WC was significantly associated with a higher likelihood of hyperuricemia, with an OR of 1.02 (95% CI: 1.02, 1.03) ($P < 0.001$).

Table 2 Adjusted ORs with 95% CIs for Hyperuricemia Based on Both Categorical and Continuous Measures of WC

	Crude Model		Model 1		Model 2		ARD (%)
	Crude OR (95% CI)	Crude P	Adjusted OR (95% CI)	Adjusted P	Adjusted OR (95% CI)	Adjusted P	
WC category							
Q1	1.00 (Reference)	–	1.00 (Reference)	–	1.00 (Reference)	–	–
Q2	1.27 (1.19, 1.37)	<0.001	1.17 (1.08, 1.26)	<0.001	1.09 (1.01, 1.18)	0.031	4.0
Q3	1.53 (1.42, 1.64)	<0.001	1.40 (1.29, 1.52)	<0.001	1.26 (1.15, 1.37)	<0.001	7.3
Q4	1.65 (1.54, 1.77)	<0.001	1.57 (1.44, 1.71)	<0.001	1.34 (1.22, 1.46)	<0.001	8.9
WC per 1 cm increase	1.04 (1.03, 1.04)	<0.001	1.03 (1.01, 1.04)	<0.001	1.02 (1.02, 1.03)	<0.001	

Notes: Model 1: adjusted for age and BMI. Model 2: adjusted for age, BMI, SBP, DBP, FBG, BUN, eGFR, ALT, AST, diabetes, hypertension, fatty liver, CVD, and dyslipidemia.

Abbreviations: OR, odds ratios; CI, confidence intervals; WC, waist circumference; ARD, absolute risk differences; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CVD, cardiovascular disease.

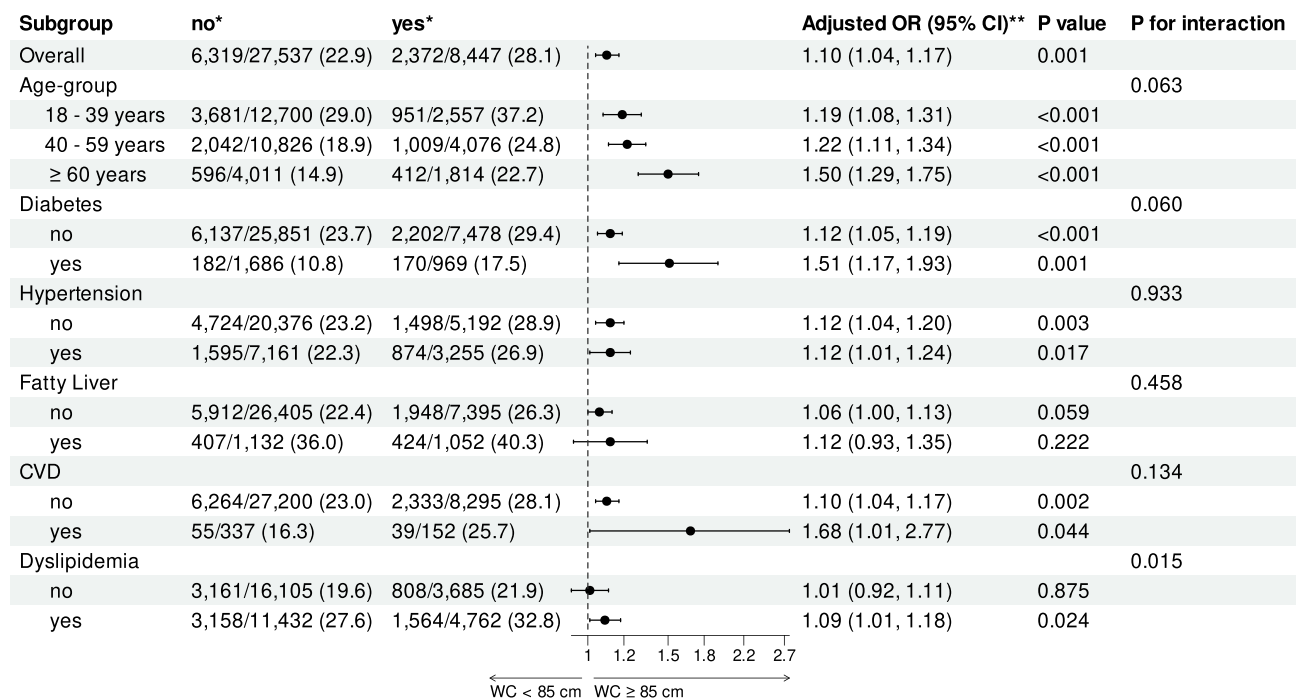


Figure 4 The stratified associations between waist circumference and hyperuricemia according to baseline characteristics.

Notes: *no. of hyperuricemia / total no. (%) **adjusted for BMI, ALT, AST and eGFR.

Model diagnostics indicated no significant multicollinearity among predictors ($VIF < 5$) and revealed no influential observations (Cook's distance < 0.001). The goodness-of-fit test showed a satisfactory fit for the logistic regression models ($P > 0.05$), confirming that the models appropriately described the data.

The stratified analysis revealed that the dyslipidemia status affected the impact of WC ($WC \geq 85\text{cm}$) on hyperuricemia (P for interaction < 0.05). A positive association between WC and hyperuricemia was observed exclusively among individuals with hyperlipidemia ($P < 0.025$). However, the association between WC and hyperuricemia remained consistent across various subgroups, including age, diabetes status, hypertension status, fatty liver presence, and CVD status (all P for interaction > 0.05) (Figure 4).

Spearman correlation analysis indicated that WC showed a positive correlation with TG levels ($r = 0.309$, $P < 0.001$), TC levels ($r = 0.081$, $P < 0.001$), and LDL-C levels ($r = 0.171$, $P < 0.001$), whereas it exhibited a negative correlation with HDL-C levels ($r = -0.250$, $P < 0.001$).

Associations Between Blood Lipids and Hyperuricemia

Multivariable logistic regression analyses indicated that TG, TC, and LDL-C were linked to elevated odds of hyperuricemia (Table 3). In Model 2, after adjusting for age, BMI, SBP, DBP, FBG, BUN, eGFR, ALT, AST, diabetes, hypertension, fatty liver, and CVD, an increase of 1-SD in TG, TC, and LDL-C corresponded to increases in the OR for hyperuricemia by 34%, 17%, and 15%, respectively. The adjusted ORs with 95% CIs were 1.34 (1.30, 1.38) for TG, 1.17 (1.13, 1.20) for TC, and 1.15 (1.11, 1.19) for LDL-C (all $P < 0.001$). Conversely, HDL-C showed an inverse relationship with the OR for hyperuricemia. For every 1-SD rise in HDL-C, there was a 40% decrease in the odds of hyperuricemia (adjusted OR = 0.60, 95% CI: 0.55, 0.65) ($P < 0.001$).

Mediation Analysis of TG and HDL-C in the Association Between WC and Hyperuricemia

Table 4 shows WC had a significant total effect on hyperuricemia ($P < 0.001$). After adjusting for age, BMI, SBP, DBP, FBG, BUN, eGFR, ALT, and AST, the influence of blood lipids as mediators in the association between WC and

Table 3 Association Between Blood Lipids and Hyperuricemia

Crude Model			Model 1		Model 2	
Blood lipids	Crude OR (95% CI)	Crude P	Adjusted OR (95% CI)	Adjusted P	Adjusted OR (95% CI)	Adjusted P
TG	1.38 (1.34, 1.42)	<0.001	1.35 (1.32, 1.39)	<0.001	1.34 (1.30, 1.38)	<0.001
HDL-C	0.46 (0.43, 0.50)	<0.001	0.60 (0.55, 0.65)	<0.001	0.60 (0.55, 0.65)	<0.001
TC	1.18 (1.15, 1.22)	<0.001	1.20 (1.17, 1.23)	<0.001	1.17 (1.13, 1.20)	<0.001
LDL-C	1.22 (1.18, 1.26)	<0.001	1.19 (1.16, 1.23)	<0.001	1.15 (1.11, 1.19)	<0.001

Notes: Lipid parameters are expressed as per 1 standard deviation (SD) increase. Model 1: adjusted for age, BMI. Model 2: adjusted for age, BMI, SBP, DBP, FBG, BUN, eGFR, ALT, AST, diabetes, hypertension, fatty liver, and CVD.

Abbreviations: OR, odds ratios; CI, confidence intervals; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CVD, cardiovascular disease.

Table 4 Mediation of Blood Lipids in the Associations Between WC and Hyperuricemia

Mediator	Total Effect		Indirect Effect		Direct Effect		Proportion Mediated (% 95% CI)
	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P	
TG	0.0046 (0.0028, 0.0070)	<0.001	0.0010 (0.0005, 0.0018)	<0.001	0.0036 (0.0022, 0.0052)	<0.001	22.3 (18.1, 27.7)
HDL-C	0.0043 (0.0026, 0.0067)	<0.001	0.0008 (0.0004, 0.0014)	<0.001	0.0035 (0.0021, 0.0053)	<0.001	18.3 (14.7, 22.6)
TC	0.0045 (0.0027, 0.0069)	<0.001	0.0001 (0.0001, 0.0002)	<0.001	0.0044 (0.0026, 0.0067)	<0.001	2.7 (1.7, 3.8)
LDL-C	0.0045 (0.0027, 0.0068)	<0.001	0.0002 (0.0001, 0.0003)	<0.001	0.0043 (0.0026, 0.0065)	<0.001	3.7 (2.7, 4.9)

Notes: The total effect coefficient represents the overall impact of WC on hyperuricemia, encompassing both direct and indirect effects. The indirect effect quantifies the portion of this impact mediated through factors like TG and HDL-C. The direct effect measures the impact of WC on hyperuricemia independent of the mediator. The proportion mediated indicates the fraction of the total effect explained by the mediator. WC was considered as a continuous variable (per 10 cm increase) in the mediation analysis. The mediation analyses were adjusted for age, BMI, SBP, DBP, FBG, BUN, eGFR, ALT, and AST.

Abbreviations: WC, waist circumference; CI, confidence intervals; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

hyperuricemia was assessed. The results showed that all lipid mediators, particularly TG and HDL-C, significantly mediated the association between WC and hyperuricemia. Specifically, 22.3% of the total effect of WC on hyperuricemia was mediated by TG, and 18.3% was mediated by HDL-C (both $P < 0.001$). Additionally, the mediated effects through TC and LDL-C respectively constituted 2.7% and 3.7% of the total effect (both $P < 0.001$). The E-value estimation indicated that the results for TG and HDL-C were robust to unmeasured confounders.

Discussion

This study provides evidence of a positive association between WC and hyperuricemia in normal-weight men. Additionally, TG and HDL-C significantly mediate the impact of WC on hyperuricemia. The results highlight the importance of considering central adiposity and lipid profiles when assessing hyperuricemia risk in normal-weight men.

Our findings align with previous studies identifying central obesity, as indicated by WC, as a strong predictor of hyperuricemia.^{30,31} The study revealed that in normal-weight men, as WC increased, the prevalence of hyperuricemia also rose. Clinical studies also found that WC, visceral adiposity index, and lipid accumulation product were more strongly associated with hyperuricemia than BMI alone.^{32,33} The RCS analysis indicated a linear positive association between WC and hyperuricemia prevalence. In a meta-analysis, the pooled hyperuricemia prevalence in mainland China was estimated at 16.7%.³⁴ Although the diagnostic threshold for abdominal obesity in Chinese men is ≥ 90 cm, we found

that when WC is ≥ 85 cm, the prevalence of hyperuricemia in normal-weight men reaches 28% and is significantly higher than the average prevalence rate.

The baseline characteristics revealed significant associations between WC and various metabolic parameters. Studies suggest that conditions such as diabetes, hypertension, and fatty liver are associated with hyperuricemia, potentially confounding the link between WC and hyperuricemia.^{35–37} However, our stratified analysis showed that the relationship between WC and hyperuricemia remains robust, regardless of these comorbid conditions. It is worth noting that, only individuals with hyperlipidemia showed a positive relationship between WC and hyperuricemia. A cross-sectional study conducted in China found that the lipid accumulation product, which includes WC, TG, and HDL-C, had the strongest association with hyperuricemia in both men and women compared to other anthropometric indices. Therefore, WC, TG, and HDL-C may be important contributors to hyperuricemia.³⁸ According to a genome-wide association research, central obesity may strengthen the impact of the APOA5 signal's TG-increasing allele.³⁹ Our further analysis of lipid profiles confirmed a close association between central obesity and dyslipidemia. Higher WC was correlated with increased TG, TC, and LDL-C, as well as reduced HDL-C, emphasizing the adverse metabolic effects of visceral fat accumulation, even in the absence of general obesity.

Dyslipidemia has been identified as a potential contributor to hyperuricemia.² Previous study reported that individuals with increased TG levels had elevated serum uric acid levels.⁴⁰ A cross-sectional study revealed an inverse correlation between HDL-C and serum uric acid levels in young people.⁴¹ Our analysis, consistent with these findings, indicated significant positive associations between TG, TC, and LDL-C with the likelihood of hyperuricemia, while HDL-C was inversely related. These associations persisted after adjusting for multiple confounders, suggesting that dyslipidemia plays an important role in hyperuricemia development.

Given the significant associations between WC, blood lipids, and hyperuricemia, we further investigated the potential mediating role of blood lipids. Mediation analysis revealed that TG and HDL-C significantly mediated the relationship between WC and hyperuricemia, with TG mediating 22.3% and HDL-C mediating 18.3% of the total effect of WC on hyperuricemia. A previous study reported lower mediating proportions of TG and HDL-C between BMI and uric acid in the general population, with mediation proportions of 10.2% and 8.9%, respectively.⁴² Our study, focusing on normal-weight men, revealed higher mediating proportions, suggesting that central obesity's impact on hyperuricemia is significantly mediated through these lipid parameters.

The mechanisms by which TG and HDL-C influence hyperuricemia are not fully understood. Hypertriglyceridemia might increase the generation and utilization of free fatty acids, with fatty acid synthesis in the liver linked to purine de novo synthesis, promoting uric acid production.⁴³ Additionally, reduced HDL-C impaired cholesterol transport, promoting endogenous processing and reducing reverse transport, leading to kidney cholesterol accumulation. Ectopic cholesterol deposition caused lipotoxicity, triggering mitochondrial dysfunction and oxidative stress in renal tubular cells, thereby affecting kidney function.⁴⁴ A decline in HDL-C could lead to a lower eGFR, contributing to uric acid excretion disorders.⁴⁵ Insulin resistance, associated with central obesity and dyslipidemia, may also play a role. Lipids related to TG synthesis, such as diacylglycerol (DAG) and ceramide, may exacerbate insulin resistance, while low HDL-C may affect insulin sensitivity through its anti-inflammatory and antioxidant properties.³ Insulin resistance has been associated with elevated uric acid synthesis and reduced uric acid excretion by the renal system.⁴⁶

These findings have significant clinical implications. First, TG and HDL-C could serve as markers for identifying individuals at higher risk of hyperuricemia due to central obesity. Regular screening of TG and HDL-C levels in clinical practice may help pinpoint individuals likely to gain benefit from early intervention to prevent hyperuricemia. Second, interventions aimed at reducing WC and improving lipid profiles could be effective strategies for preventing hyperuricemia, even among normal-weight individuals. Lifestyle modifications, including diet and exercise targeting central obesity and dyslipidemia, may be essential in managing uric acid levels and reducing hyperuricemia-related diseases.

This study has several advantages. Firstly, the substantial sample size reinforces the reliability of our conclusions, enabling a detailed examination of various subgroups. Secondly, to our knowledge, it is the first study that focuses on how blood lipids mediate the association between WC and hyperuricemia in men without obesity, providing new insights. Despite these strengths, it is essential to identify certain limitations of the study. First, its cross-sectional design prevents us from establishing causal relationships between WC and hyperuricemia; longitudinal studies are needed to

confirm these findings and to assess whether reducing WC can lower serum uric acid levels in normal-weight populations. Second, while we identified TG and HDL-C as mediators between WC and hyperuricemia, further research is necessary to understand the biological mechanisms behind these relationships. Additionally, although we applied standard cut-offs for hyperuricemia and lipid levels, evaluating the suitability of these thresholds for risk identification in normal-weight populations may offer further insights. Third, our study population comprised normal-weight men, which may limit the generalizability of our findings to other groups, such as women and individuals with excess body weight. Fourth, the use of health check-up data may introduce selection bias, as participants tend to be more health-conscious. Moreover, since our study was conducted in a single city in China, the findings may not be fully generalizable to broader populations. Expanding future research to include more varied and representative samples could enhance the external validity of our findings. Finally, due to the lack of baseline data on dietary habits, physical activity, smoking, alcohol consumption, and medication use, these factors were not included in the analysis, which may influence the relationships studied.

Conclusion

In conclusion, this study highlights that TG and HDL-C act as significant mediators in the relationship between WC and hyperuricemia among normal-weight men. Our findings emphasize the importance of managing dyslipidemia to alleviate the risk of hyperuricemia associated with central obesity. Monitoring TG and HDL-C levels in clinical practice may aid in identifying individuals at higher risk and guiding early intervention strategies. Subsequent studies should concentrate on clarifying the underlying mechanisms and exploring effective interventions to prevent hyperuricemia in individuals with central obesity.

Data Sharing Statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

Ethics Statement

This research adhered to the principles outlined in the Declaration of Helsinki. Approval for the study protocol was granted by the Ethics Committee of Nanjing Drum Tower Hospital, with the ethical approval reference number being 2022-698-01.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no potential conflicts of interest relevant to this article.

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