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Exploring the Relationship Between Different Obesity Metabolism Indices and Hyperuricemia in Patients with Hypertension and Coronary Heart Disease

Yuanyuan Li[1,*], Shanting Yi[1,*], Wencai Jiang[2,*], Meihui Gong[1]

[1]Cardiovascular Center of the Fifth Affiliated Hospital, Sun Yat-Sen University, Zhuhai, 519000, People's Republic of China; [2]Department of Cardiology, Suining Central Hospital, Suining, 629000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Meihui Gong, Cardiovascular Center of the Fifth Affiliated Hospital, Sun Yat-sen University, Zhuhai, 519000, People's Republic of China, Email yuxy69@mail.sysu.edu.cn

Background: Previous studies have established a strong association between obesity, high metabolism, and the development of hyperuricemia. However, the relationship between obesity metabolism indices and hyperuricemia in high-risk patients with hypertension and coronary heart disease (CHD) remains unclear. The purpose of this study was to investigate this relationship in patients with both hypertension and CHD, and to identify the obesity metabolism index with the best diagnostic value.

Methods: A two-center study encompassed 6344 participants with hypertension and CHD. Multiple logistic regression was utilized to examine the correlation between six obesity metabolism indices and hyperuricemia, with restricted cubic spline (RCS) analysis to identify non-linear relationships. Diagnostic value was assessed via receiver operating characteristic (ROC) curves and decision curve analysis (DCA).

Results: Multivariable logistic regression revealed a significant correlation between increased obesity metabolism indices and hyperuricemia. Furthermore, RCS analysis revealed a nonlinear dose-response relationship (P for nonlinear < 0.001). Moreover, ROC and DCA results showed that METS-VF index, which combined visceral obesity and metabolic parameters, became the most reliable diagnostic tool.

Conclusion: The study underscores a strong association between elevated obesity metabolism indices and hyperuricemia in patients with hypertension and CHD. The METS-VF index, amalgamating visceral obesity and metabolic parameters, emerged as the most reliable diagnostic tool.

Keywords: obesity metabolism indices, hypertension, coronary heart disease, uric acid, hyperuricemia

Introduction

Uric acid (UA), a purine metabolite, accumulates in peripheral blood when its production is upregulated or excretion is diminished, culminating in hyperuricemia.[1,2] The prevalence of this condition has been escalating in tandem with enhancements in living standards and shifts in lifestyle habits. Current estimates indicate that approximately 15% of the adult population in China is affected by hyperuricemia.[3,4] Hyperuricemia has emerged as a pivotal risk factor implicated in a spectrum of disorders, including gout, diabetes, chronic kidney disease, and cardiovascular diseases (CVD).[5–8] It has become a chronic disease that garners more public attention and poses a significant challenge to public health.[9] Thus, early identification and management of hyperuricemia may reduce the disease burden and prevent adverse outcomes associated with it.

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A substantial body of research has established the pertinence of UA to metabolic syndrome.[10–13] However, the specific contributions of various obesity-related metabolic indices to hyperuricemia are less well characterized. Emerging evidence underscores the potential significance of obesity and metabolic abnormalities in UA metabolism dysregulation, leading to hyperuricemia.[14–16] These conditions are also central to the pathophysiology of metabolic syndrome.[17,18] Traditionally, indicators for assessing obesity and metabolism have tended to be homogeneous and lacking in accuracy. Conversely, a suite of more accessible compound markers predicated on obesity and metabolic profiles has been proposed, encompassing the triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C), the triglyceride-glucose (TyG) index, the TyG to body mass index (TyG-BMI) ratio, TyG in conjunction with waist circumference (TyG-WC), the metabolic score for insulin resistance (METS-IR), and the metabolic score for visceral fat (METS-VF).[19–23]

Individuals afflicted with hypertension and concomitant coronary heart disease (CHD) frequently exhibit obesity and a constellation of metabolic irregularities.[24–26] They are at an augmented risk for UA metabolism disturbances that may precipitate hyperuricemia, thereby exacerbating their susceptibility to CVD. While some studies have identified significant correlations between certain indicators, such as the TyG index or TG/HDL-C, and hyperuricemia, the clarity of these relationships within the high-risk group of patients with comorbid hypertension and CHD is yet to be established.[14,27,28] The identification of the most diagnostically valuable indicators for hyperuricemia in this population is an unresolved issue. To address this gap, we have conducted an extensive cross-sectional study to investigate the association between six obesity metabolism indices and hyperuricemia, as well as to evaluate their diagnostic accuracy.

Material and Methods

Study Population

This was a two-center study conducted at the Fifth Affiliated Hospital of Sun Yat-sen University and Suining City Central Hospital. The study population comprised individuals diagnosed with hypertension and CHD, enrolled from the Cardiovascular Center of the Fifth Affiliated Hospital of Sun Yat-sen University between January 2021 to September 2023, and from the Department of Cardiology of the Suining Central Hospital from March 2021 to July 2024. The initial enrollment yielded 7755 participants.

Exclusion criteria were applied to participants with incomplete basic measurement data, including BMI, triglycerides (TG), high-density lipoprotein (HDL), fasting plasma glucose (FPG), and WC, as well as those with severe renal dysfunction, hyperthyroidism, older than 75 years, excessive alcohol intake, or on chronic UA-lowering medication. Following these stringent exclusions, the final analysis included 6364 participants (Figure 1).

Ethical approval for this study was granted by the Ethics Committee of the Fifth Affiliated Hospital of Sun Yat-sen University (Approval No. 2022L047-1) and the Ethics Committee of Suining Central Hospital (Approval No. KYLLKS20240103). The study followed ethical guidelines in the Declaration of Helsinki, and all participants provided informed written consent.

Data Collection and Definitions

Demographic and clinical data were obtained from the electronic medical records and health insurance systems of the respective hospitals. These data included participants' medical history, lifestyle habits, medication profiles, and laboratory results. Detailed methodology for various physical information is provided in the Supplementary Materials. Laboratory assessments included measurements of alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (Cr), urea nitrogen (BUN), total cholesterol (TC), TG, HDL-C, low-density lipoprotein cholesterol (LDL-C), FPG, glycosylated hemoglobin (HbA1c), and UA, all of which were quantified using a fully automated biochemical analyzer. The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula. The Supplementary Materials provide detailed definitions and measurement procedures for the various diseases under investigation.

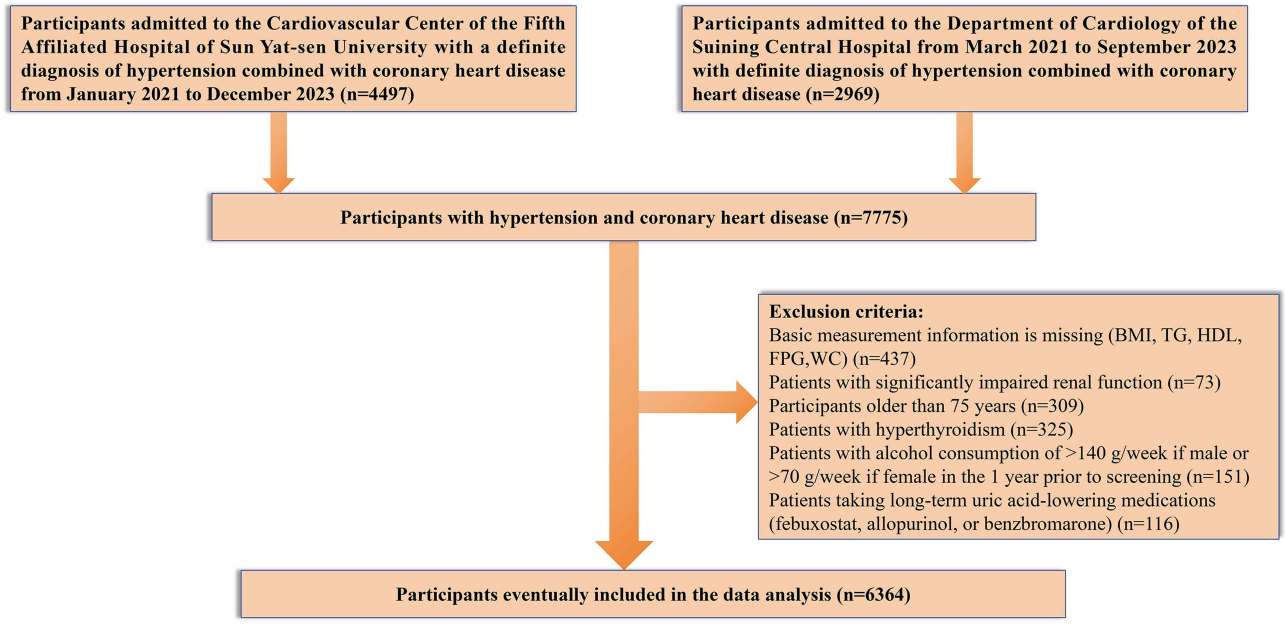

Figure 1 Flowchart for screening of study participants.

Calculation of Obesity Metabolism Indices

The following formulas were used to calculate various obesity metabolism indices, including TG/HDL-C ratio, TyG, TyG-BMI, TYG-WC, METS-IR, METS-VF:

TG/HDL-C = TG (mg/dL)/HDL-C (mg/dL).

TyG = ln[(TG (mg/dL) × FPG (mg/dL)/2)].

TyG-BMI = ln[(TG (mg/dL) × FPG (mg/dL)/2] × BMI.

TyG-WC = ln[(TG (mg/dL) × FPG (mg/dL)/2] × WC.

METS-IR = ln[2×FPG (mg/dL) + TG (mg/dL)] × BMI (kg/m²) / ln[HDL-C (mg/dL)].

METS-VF = 4.466 + 0.011 × (LnMETS-IR)³ + 3.239 × [Ln(WC/height)³ + 0.319 (male sex) + 0.594 × Ln(age)].

Outcome

Hyperuricemia was diagnosed based on the criteria defined by the Chinese Endocrine Association. The condition is identified when serum UA levels surpass 420 μmol/L (equivalent to 7.0 mg/dL) in males and 360 μmol/L (6.0 mg/dL) in females.[29–31]

Statistical Analysis

Participants were categorized into two distinct groups relative to the presence of hyperuricemia. The variance inflation factor (VIF) was used to assess multicollinearity between predictors, and a VIF value less than 5 indicating no multicollinearity (Table S1). To evaluate the correlation between the six obesity metabolism indices and hyperuricemia, these indices were stratified into quartiles. Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were computed using multivariate logistic regression analysis. Furthermore, a restricted cubic spline (RCS) model was applied to scrutinize potential nonlinear dose-response relationships between the indices and hyperuricemia. Ultimately, the diagnostic efficacy of these indices for hyperuricemia was assessed using receiver operating characteristic (ROC) curves and decision curve analysis (DCA). For a detailed exposition of the statistical methods employed, the reader is referred to the Supplementary Material.

Results

Basic Characteristics of Participants

A total of 6364 participants with hypertension combined with CHD were included in the study, with 1488 participants diagnosed with hyperuricemia. Baseline results showed that participants with hyperuricemia tended to be relatively younger, more often

male, and had significantly higher BMI, WC, and diastolic blood pressure (DBP) than those without hyperuricemia. Additionally, the test results indicated that ALT, AST, Cr, TC, TG, LDL-C, FPG, and UA levels were significantly higher in participants with hyperuricemia, whereas LDL-C and eGFR were relatively lower. Furthermore, patients with hyperuricemia had a higher prevalence of diabetes and hyperlipidemia and were more likely to take diuretics. Notably, the six obesity metabolic indices were also significantly higher in hyperuricemia participants compared to non-hyperuricemia participants (Table 1).

Table 1 Characteristics of the Study Population

Characteristic	Total	No-hyperuricemia	Hyperuricemia	P value
N	6364	4876	1488	
Age (years)	62.03±11.21	62.20±11.28	61.46±10.93	0.026
Sex				<0.001
Female	2718 (42.71%)	1992 (40.85%)	726 (48.79%)	
Male	3646 (57.29%)	2884 (59.15%)	762 (51.21%)	
WC (cm)	86.88±10.46	86.42±10.25	88.35±11.00	<0.001
BMI (kg/m^2)	26.98±3.66	26.64±3.68	28.08±3.37	<0.001
SBP (mmHg)	145.89±18.09	145.85±18.35	146.01±17.21	0.761
DBP (mmHg)	88.27±13.56	87.47±13.45	90.89±13.60	<0.001
Current smoking (%)	2180 (34.26%)	1762 (36.14%)	418 (28.09%)	<0.001
Medical history				
Diabetes (%)	2104 (33.06%)	1546 (31.71%)	558 (37.50%)	<0.001
Hyperlipidemia (%)	1708 (26.84%)	1117 (22.91%)	591 (39.72%)	<0.001
Laboratory tests				
ALT (U/L)	27.47±17.54	25.50±16.23	33.93±19.96	<0.001
AST (U/L)	21.04±8.16	20.43±7.73	23.03±9.17	<0.001
Cr (umol/L)	64.88±14.35	62.52±13.65	72.62±13.89	<0.001
eGFR (mL/min/1.73 m^2)	97.99±22.09	98.51±22.27	96.28±21.42	<0.001
TC (mmol/L)	4.55±0.98	4.53±0.99	4.60±0.92	0.012
TG (mmol/L)	1.81±0.93	1.70±0.88	2.15±1.01	<0.001
HDL.C (mg/dL)	1.05±0.25	1.07±0.26	0.98±0.23	<0.001
LDL.C (mg/dL)	2.57±0.90	2.55±0.89	2.63±0.91	0.005
FPG (mmol/L)	5.45±1.32	5.42±1.30	5.55±1.38	<0.001
UA (umol/L)	308.11±110.30	261.72±75.21	460.13±57.75	<0.001
TG/HDL	4.36±2.93	4.03±2.75	5.44±3.21	<0.001
TyG	8.83±0.57	8.75±0.56	9.09±0.55	<0.001
TyG-BMI	245.75±41.65	238.17±38.09	270.59±43.12	<0.001
METS-IR	45.08±9.17	43.08±8.35	51.64±8.66	<0.001
METS-VF	6.65±0.68	6.50±0.62	7.17±0.59	<0.001
TyG-WC	773.09±110.26	754.66±103.16	833.52±111.21	<0.001
Medications				
Statins (%)	6182 (97.14%)	4733 (97.07%)	1449 (97.38%)	0.587
Antiplatelet medication (%)	6283 (98.73%)	4816 (98.77%)	1467 (98.59%)	0.681
Diuretics (%)	1184 (18.60%)	880 (18.05%)	304 (20.43%)	0.039
Beta-blockers (%)	2460 (38.65%)	1874 (38.43%)	586 (39.38%)	0.511
Calcium channel blockers (%)	4396 (69.08%)	3354 (68.79%)	1042 (70.03%)	0.365
ACEIs/ARBs (%)	4128 (64.86%)	3148 (64.56%)	980 (65.86%)	0.358
Antidiabetic agents (%)	1238 (19.45%)	930 (19.07%)	308 (20.70%)	0.165

Note: Data are presented as mean ± standard deviation, or as numbers, and percentages.

Abbreviations: WC, waist circumference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine transaminase; AST, aspartate transaminase; Cr, creatinine; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; UA, Uric acid; TyG, triglyceride-glucose; METS-IR, metabolic score for insulin resistance; METS-VF, metabolic score for visceral fat; ARBs, angiotensin receptor blockers; ACEIs, angiotensin-converting enzyme inhibitors.

Association Between Obesity Metabolic Indices and Hyperuricemia

Participants were stratified into quartiles based on the six obesity metabolic indices. The prevalence of hyperuricemia increased with higher quartiles, and the trend test was statistically significant (P<0.001) (Figure 2). Multivariate logistic regression analysis further showed that the risk of hyperuricemia gradually increased with higher levels of obesity metabolic indices such as TG/HDL-C, TyG, TyG-BMI, TyG-WC, METS-IR, and METS-VF. Specifically, compared to the first quartile (Q1) group, the ORs of the highest quartile (Q4) group were 3.94 (95% CI, 3.29–4.74), 4.37 (95% CI, 3.64–2.27), 7.79 (95% CI, 6.40–9.56), 6.53 (95% CI, 5.40–7.93), 5.06 (95% CI, 6.40–9.56), and 6.31 (95% CI, 5.17–7.74), respectively. Moreover, this relationship remained stable even in the fully adjusted model 4, with the Q4 group showing a 2.44, 3.59, 8.09, 5.13, 2.36, and 6.94-fold increase in disease risk, respectively, compared to the Q1 group (Table 2). Finally, the RCS results also demonstrated the gradually increasing dose-response relationship between the metabolic indexes and hyperuricemia (Figure 3).

Comparative Analysis of Six Obesity Metabolic Indices in Diagnosis of Hyperuricemia

To compare the diagnostic value of these six indicators for hyperuricemia, we first evaluated their diagnostic performance by calculating the area under the curve (AUC) of the ROC. As shown in Figure 4 and Table 3, the AUC of METS-VF (AUC=0.780) was the largest among the six indicators, followed by METS-IR (AUC=0.761), TyG-BMI (AUC=0.712), TyG-WC (AUC=0.700), and TyG (AUC=0.662), while TG/HDL (AUC=0.653) was the smallest among all indicators. This result was consistent across genders (Figure 4B and C).

We then further used DCA to compare the incremental benefits of the six obesity metabolic indices. The results remained consistent, with METS-VF showing the largest overall net benefit compared to the other five measures, while TG/HDL had the smallest benefit. This pattern held true both overall and when analysed independently by gender, further supporting the optimal diagnostic performance of METS-VF for hyperuricaemia (Figure 5A–C).

Subgroup and Sensitivity Analysis

Considering the possible effects of different conditions on UA metabolism, we conducted a stratified analysis based on gender, age, hyperlipidemia, and diabetes. The results showed that even under different stratification conditions, the increase in obesity metabolic index was still independently associated with the occurrence of hyperuricemia (Figure 6). This indicates that the association is not affected by stratification conditions.

Furthermore, we performed a series of sensitivity analyses to assess the robustness of our findings. First, we excluded participants taking diuretics, considering the potential effect of diuretics on UA metabolism, and the results were consistent with the overall trend (Table S2). Next, since the UA metabolism of obese patients might be higher, we excluded obese patients with BMI > 30 kg/m^2, and the results remained stable (Table S3). Moreover, we excluded patients with cancer to account for the potential influence of anti-tumor drugs, and the results remained unchanged (Table S4). Finally, to address the possibility of unmeasured confounders, we conducted an E-value analysis, which showed that unmeasured confounders had little effect on our results (Table S5). Collectively, these analyses reinforce the conclusion that an escalation in obesity metabolism indices is concomitantly associated with an increased risk of hyperuricemia.

Discussion

In this large cross-sectional study, we found that six obesity metabolic indices were associated with hyperuricemia in hypertensive patients with CHD. Our analysis revealed a robust association, indicating that the risk of hyperuricemia escalates in tandem with elevated levels of obesity metabolism indices. Notably, the stratified analysis substantiated these findings, demonstrating that the upsurge in obesity metabolic markers is independently linked to the onset of hyperuricemia, irrespective of various stratified factors In a comparative analysis of the diagnostic efficacy of these metabolic indicators, the METS-VF indice, which integrates both visceral obesity and metabolic dysfunction, emerged as the most efficacious predictor of hyperuricemia. This underscores the potential of METS-VF as a reliable clinical tool for risk assessment in this patient population.

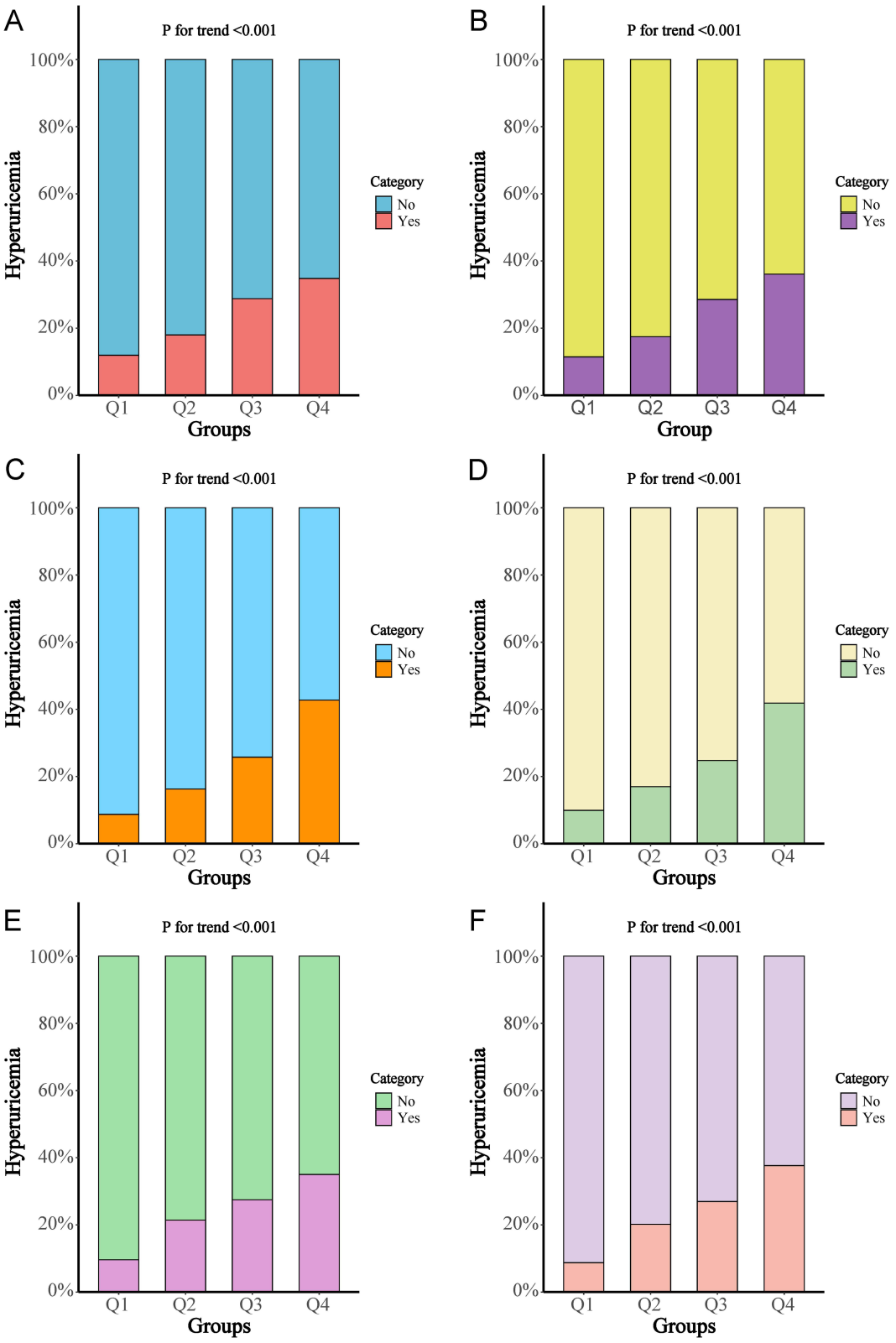

Figure 2 Prevalence of hyperuricaemia according to quartiles of six obesity metabolism indices.
Notes: (**A**) TG/HDL-C; (**B**) TyG; (**C**) TyG-BMI; (**D**)TyG-WC; (**E**) METS-IR; (**F**) METS-VF.

Table 2 Relationship Between Obesity-Related Metabolic Indices and Hyperuricemia

Hyperuricemia	Model 1	Model 2	Model 3	Model 4
	OR (95% CI) P	OR (95% CI) P	OR (95% CI) P	OR (95% CI) P
TG/HDL				
TG/HDL (per - 1SD increase)	1.54 (1.46, 1.63) <0.001	1.46 (1.38, 1.55) <0.001	1.18 (1.03, 1.35) 0.018	1.16 (1.01, 1.33) 0.034
Quartiles of TG/HDL				
Q1	Reference	Reference	Reference	Reference
Q2	1.62 (1.33, 1.97) <0.001	1.50 (1.22, 1.83) <0.001	1.34 (1.09, 1.65) 0.006	1.35 (1.10, 1.67) 0.004
Q3	2.98 (2.48, 3.60) <0.001	2.67 (2.21, 3.24) <0.001	2.25 (1.85, 2.74) <0.001	2.19 (1.80, 2.68) <0.001
Q4	3.94 (3.29, 4.74) <0.001	3.30 (2.73, 4.01) <0.001	2.53 (2.08, 3.10) <0.001	2.44 (2.00, 2.99) <0.001
P for trend	<0.001	<0.001	<0.001	<0.001
TyG				
TyG (per - 1SD increase)	1.85 (1.74, 1.97) <0.001	1.77 (1.66, 1.89) <0.001	1.84 (1.70, 1.99) <0.001	1.81 (1.67, 1.96) <0.001
Quartiles of TyG				
Q1	Reference	Reference	Reference	Reference
Q2	1.64 (1.34, 2.01) <0.001	1.56 (1.28, 1.92) <0.001	1.51 (1.23, 1.87) <0.001	1.52 (1.23, 1.88) <0.001
Q3	3.09 (2.56, 3.74) <0.001	2.85 (2.35, 3.46) <0.001	2.65 (2.17, 3.25) <0.001	2.54 (2.08, 3.13) <0.001
Q4	4.37 (3.64, 5.27) <0.001	3.92 (3.25, 4.75) <0.001	3.69 (2.98, 4.58) <0.001	3.59 (2.96, 4.46) <0.001
P for trend	<0.001	<0.001	<0.001	<0.001
TyG-BMI				
TyG-BMI (per - 1SD increase)	2.28 (2.14, 2.44) <0.001	2.30 (2.15, 2.46) <0.001	2.33 (2.19, 2.51) <0.001	2.36 (2.19, 2.54) <0.001
Quartiles of TyG-BMI				
Q1	Reference	Reference	Reference	Reference
Q2	2.03 (1.63, 2.53) <0.001	2.02 (1.61, 2.52) <0.001	1.93 (1.54, 2.44) <0.001	1.92 (1.53, 2.43) <0.001
Q3	3.63 (2.96, 4.47) <0.001	3.66 (2.98, 4.53) <0.001	3.69 (2.98, 4.60) <0.001	3.73 (3.00, 4.66) <0.001
Q4	7.79 (6.40, 9.56) <0.001	7.84 (6.41, 9.65) <0.001	7.95 (6.46, 9.85) <0.001	8.09 (6.55, 10.03) <0.001
P for trend	<0.001	<0.001	<0.001	<0.001
METS-IR				
METS-IR (per - 1SD increase)	2.77 (2.59, 2.98) <0.001	2.78 (2.59, 2.99) <0.001	3.49 (3.15, 3.87) <0.001	3.39 (3.06, 3.76) <0.001
Quartiles of METS-IR				
Q1	Reference	Reference	Reference	Reference
Q2	2.56 (1.63, 2.53) <0.001	2.65 (2.16, 3.26) <0.001	2.08 (1.67, 2.61) <0.001	2.19 (1.75, 2.74) <0.001
Q3	3.56 (2.96, 4.47) <0.001	3.67 (3.01, 4.51) <0.001	2.25 (1.79, 2.86) <0.001	2.22 (1.75, 2.82) <0.001
Q4	5.06 (6.40, 9.56) <0.001	5.14 (4.22, 6.28) <0.001	2.53 (1.95, 3.31) <0.001	2.36 (1.81, 3.08) <0.001
P for trend	<0.001	<0.001	<0.001	<0.001

(*Continued*)

Table 2 (Continued).

Hyperuricemia	Model 1	Model 2	Model 3	Model 4
	OR (95% CI) P	OR (95% CI) P	OR (95% CI) P	OR (95% CI) P
METS-VF				
METS-VF (per - 1SD increase)	3.31 (3.06, 3.58) <0.001	3.32 (3.07, 3.59) <0.001	4.75 (4.24, 5.33) <0.001	4.62 (4.12, 5.20) <0.001
Quartiles of METS-VF				
Q1	Reference	Reference	Reference	Reference
Q2	2.64 (2.14, 3.27) <0.001	2.68 (2.17, 3.33) <0.001	2.72 (2.20, 3.38) <0.001	2.73 (2.20, 3.39) <0.001
Q3	3.86 (3.15, 4.75) <0.001	3.94 (3.21, 4.86) <0.001	4.04 (3.28, 4.99) <0.001	4.11 (3.34, 5.08) <0.001
Q4	6.31 (5.17, 7.74) <0.001	6.50 (5.32, 7.99) <0.001	6.68 (5.45, 8.23) <0.001	6.94 (5.65, 8.58) <0.001
P for trend	<0.001	<0.001	<0.001	<0.001
TyG-WC				
TyG-WC (per - 1SD increase)	2.14 (2.00, 2.28) <0.001	2.14 (2.00, 2.29) <0.001	1.98 (1.85, 2.15) <0.001	2.01 (1.86, 2.16) <0.001
Quartiles of TyG-WC				
Q1	Reference	Reference	Reference	Reference
Q2	1.85 (1.50, 2.29) <0.001	1.85 (1.50, 2.28) <0.001	1.77 (1.43, 2.21) <0.001	1.77 (1.42, 2.21) <0.001
Q3	2.98 (2.45, 3.65) <0.001	2.99 (2.45, 3.67) <0.001	2.69 (2.18, 3.33) <0.001	2.66 (2.16, 3.30) <0.001
Q4	6.53 (5.40, 7.93) <0.001	6.53 (5.40, 7.95) <0.001	5.09 (4.12, 6.31) <0.001	5.13 (4.15, 6.38) <0.001
P for trend	<0.001	<0.001	<0.001	<0.001

Notes: Model 1: no covariates were adjusted. Model 2: age, sex, BMI, smoking status, Diabetes, and Hyperlipidemia were adjusted. Model 3: Model 2 plus adjustment for ALT, AST, Cr, eGFR, TC, HDL.C, LDL.C, FPG, and UA. Model 4: Model 3 plus adjustment for use of statins, Antiplatelet medication, beta-blockers, calcium channel blockers, ACEIs/ARBs, and Antidiabetic agents.
Abbreviations: WC, waist circumference; BMI, body mass index; TyG, triglyceride-glucose; METS-IR, metabolic score for insulin resistance; METS-VF, metabolic score for visceral fat; OR, odds ratio; CI, confidence interval; Other abbreviations, see Table 1.

The implications of these findings are profound. Hyperuricemia, arising from a metabolic disorder of UA, is not merely a benign condition but is intricately linked to a spectrum of health complications.[5,6,32] Research indicates that hyperuricemia elevates the risk of cardiovascular disease (CVD) and all-cause mortality.[33] In adolescents, it is associated with the onset of early hypertension, and reducing UA levels might prevent the development and progression of hypertension.[34,35] Moreover, prolonged hyperuricemia can lead to phosphate deposition in bones and joints, resulting in bone destruction and promoting gout.[5] Given the multifaceted ramifications of hyperuricemia, the emphasis on early detection and prevention cannot be overstated.

Previous studies have identified obesity as a major risk factor for insulin resistance (IR) and metabolic dysfunction associated with type 2 diabetes.[36] At the same time, one study has identified IR in obesity as a possible pathway to macrovascular disease.[37] Individuals afflicted with hypertension and CHD frequently exhibit comorbidities such as obesity and metabolic dysregulations, which are known to amplify the risk of cardiovascular events.[38–41] When combined with hyperuricemia, this group may face an even higher risk of future cardiovascular events and mortality. However, the relationship between obesity, metabolism, and hyperuricemia has not been thoroughly studied in this population, nor have studies comprehensively compared the predictive performance of various indicators. Therefore, we selected this high-risk population to further explore the relationship between obesity, metabolism, and hyperuricemia and to evaluate the best diagnostic indicators. This aims to provide a more in-depth basis for the future management of hyperuricemia and the prevention of worsening cardiovascular events and mortality.

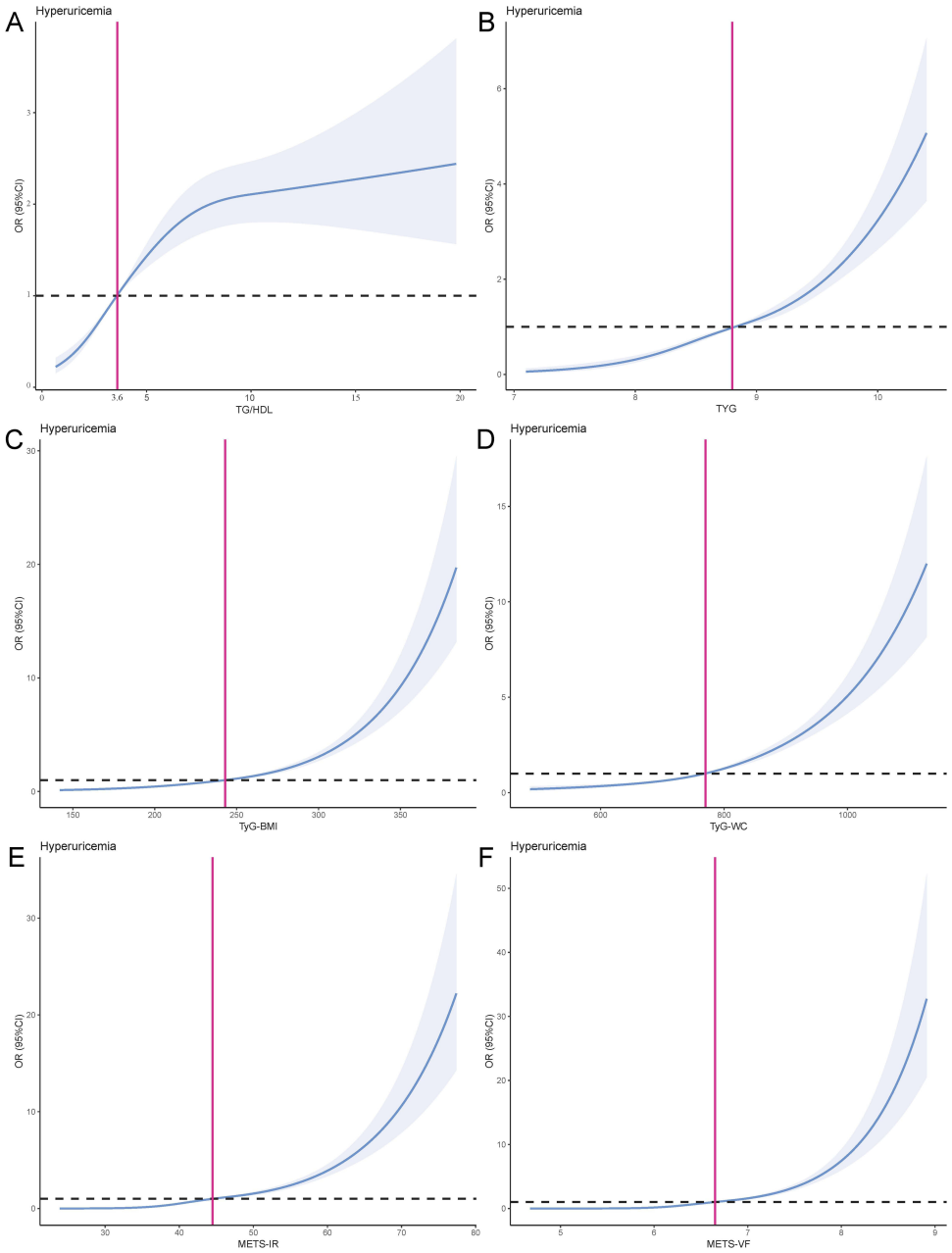

Figure 3 Dose-response association between obesity metabolism indices and risk of hyperuricemia.
Notes: (**A**) TG/HDL-C; (**B**) TyG; (**C**) TyG-BMI; (**D**) TyG-WC; (**E**) METS-IR; (**F**) METS-VF.

High metabolism and obesity are the strongest indicators of metabolic syndrome.[42–44] Previous studies have highlighted that metabolic syndrome increases the risk of several diseases, including hyperuricemia.[45–47] Research on the relationship between dietary patterns, obesity, and hyperuricemia in the United States showed that while the direct effect of diet on hyperuricemia was weak, obesity played a key mediating role in this relationship.[48] Additionally, two national surveys in China identified a high BMI as a major risk factor for hyperuricemia, directly pointing to the role of obesity in its development.[49] At the same time, metabolic factors are also indispensable.[16,50,51] For example, a Mendelian randomized study demonstrated a strong association between hyperuricemia and IR syndrome, where hyperinsulinemia leads to hyperuricemia but not vice versa.[16] Similarly, research on the relationship between hyperuricemia, IR, and the risk of hypertension emphasized that IR is associated with the development of hyperuricemia and may also partially

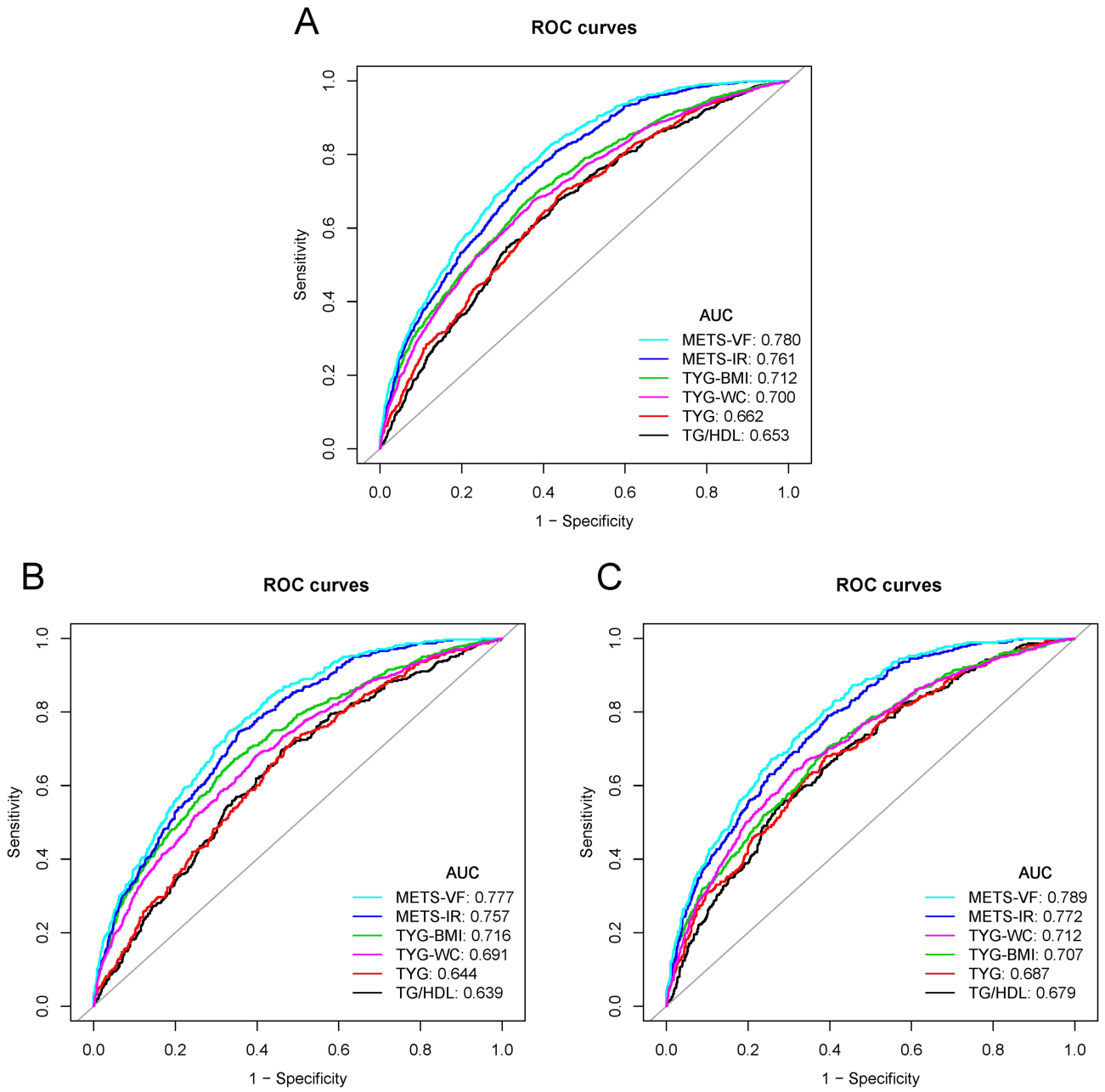

Figure 4 Receiver operating characteristic (ROC) curves assessing the diagnostic utility of six obesity metabolic indices for hyperuricemia.
Notes: (**A**) Total population; (**B**) Male population; (**C**) Female population.

mediate the effects of uric acid on hypertension.[50] Together, these studies support the important role of metabolic functions, represented by obesity and insulin resistance, in the development of hyperuricemia.

In the realm of metabolic health, numerous indices have been developed to evaluate obesity metabolism. The advent of novel surrogates, based on straightforward anthropometric and biochemical indicators such as TG/HDL-C, the TyG index, TyG-BMI, TyG-WC, METS-IR, and METS-VF, has garnered widespread clinical application.[23,52–55] Prior research has consistently demonstrated that these six alternative markers are profoundly correlated with metabolism and obesity, and their utility as reliable indicators of metabolic syndrome has been affirmed.[1–19,20,56,57] Our study corroborates and extends these findings, positing that these metabolic signifiers of obesity are independently correlated with hyperuricemia.[58–61] In a national cohort study of middle-aged and older adults in China, elevated baseline values of several IR alternatives, including TyG, TG/HDL, METS-IR, and TyG-BMI, were significantly associated with an increased risk of hyperuricemia. Compared to individuals with

Table 3 ROC Curve Analysis of Six Obesity-Related Metabolic Indices

Test	ROC area (AUC)	95% CI low	95% CI up	Best threshold	Specificity	Sensitivity
Totality						
TG-HDL	0.653	0.638	0.669	3.625	0.563	0.677
TyG	0.662	0.640	0.677	8.832	0.565	0.687
TyG-BMI	0.712	0.697	0.727	249.788	0.638	0.677
METS-IR	0.761	0.748	0.774	46.279	0.663	0.719
METS-VF	0.780	0.768	0.793	6.731	0.648	0.762
TyG-WC	0.700	0.684	0.715	784.526	0.625	0.675
Male						
TG-HDL	0.639	0.617	0.660	3.731	0.541	0.696
TyG	0.645	0.623	0.666	8.803	0.508	0.730
TyG-BMI	0.716	0.695	0.736	250.967	0.656	0.672
METS-IR	0.757	0.739	0.775	46.247	0.644	0.748
METS-VF	0.777	0.760	0.794	6.792	0.668	0.748
TyG-WC	0.691	0.670	0.713	784.487	0.603	0.681
Female						
TG-HDL	0.679	0.657	0.701	4.311	0.722	0.548
TyG	0.687	0.665	0.709	8.817	0.608	0.680
TyG-BMI	0.707	0.685	0.729	246.831	0.604	0.704
METS-IR	0.772	0.753	0.791	44.062	0.604	0.791
METS-VF	0.789	0.772	0.807	6.617	0.616	0.804
TyG-WC	0.712	0.690	0.734	792.797	0.688	0.642

Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; WC, waist circumference; BMI, body mass index; TyG, triglyceride-glucose; METS-IR, metabolic score for insulin resistance; METS-VF, metabolic score for visceral fat; CI, confidence interval; Other abbreviations, see Table 1.

consistently low IR surrogate levels, those who transitioned from low to high IR levels and those who consistently maintained high IR levels had a significantly higher risk of developing hyperuricemia.[58,59] This relationship has also been demonstrated in other populations. For instance, a study among non-diabetic adults in the United States established a positive correlation between the risk of hyperuricemia and heightened levels of TyG, TyG-BMI, TG/HDL-C, and METS-IR.[60] Similarly, this relationship between obesity metabolism indice and hyperuricemia has been observed in Iranian populations.[61]

The specific relationship between obesity metabolism and hyperuricemia is complex, involving various metabolic pathways and mechanisms that may promote hyperuricemia (Figure S1). First, obesity is frequently comorbid with lipid metabolism disorders, such as hypertriglyceridemia, which can impair the renal excretory capacity for UA, leading to its accumulation within the body.[62–64] Additionally, IR, a condition often observed in obesity, influences UA metabolism by augmenting its renal reabsorption, thus reducing UA excretion and contributing to the development of hyperuricemia.[16,58,65,66] The role of visceral fat accumulation is also significant, as it not only increases the de novo synthesis of UA but also enhances its production through the secretion of free fatty acids and pro-inflammatory cytokines by adipocytes in visceral fat depots.[67–69] Finally, the chronic inflammatory state associated with obesity metabolism is a major etiological factor. This inflammation can stimulate UA synthesis and concurrently attenuate its renal clearance, further propagating the hyperuricemic state.[70–73]

Our study is the first to explore the relationship between six kinds of obesity metabolic indices and hyperuricemia in a high-risk population with hypertension combined with CHD. Notably, our analysis has identified the METS-VF indice, indicative of visceral obesity, as possessing the most robust diagnostic utility. This significant finding is underpinned by rigorously applied inclusion and exclusion criteria, coupled with a comprehensive suite of statistical methodologies. Despite these strengths, it is imperative to acknowledge the limitations inherent to our study. First, the cross-sectional nature of our study can only establish correlations and cannot capture longitudinal effects. Second, our research did not incorporate data pertaining to dietary patterns and levels of physical activity, both of which are recognized to exert influence on UA metabolism, and thus, these factors warrant consideration in forthcoming studies. Third, although our sample was drawn from two distinct centers in southern China, the

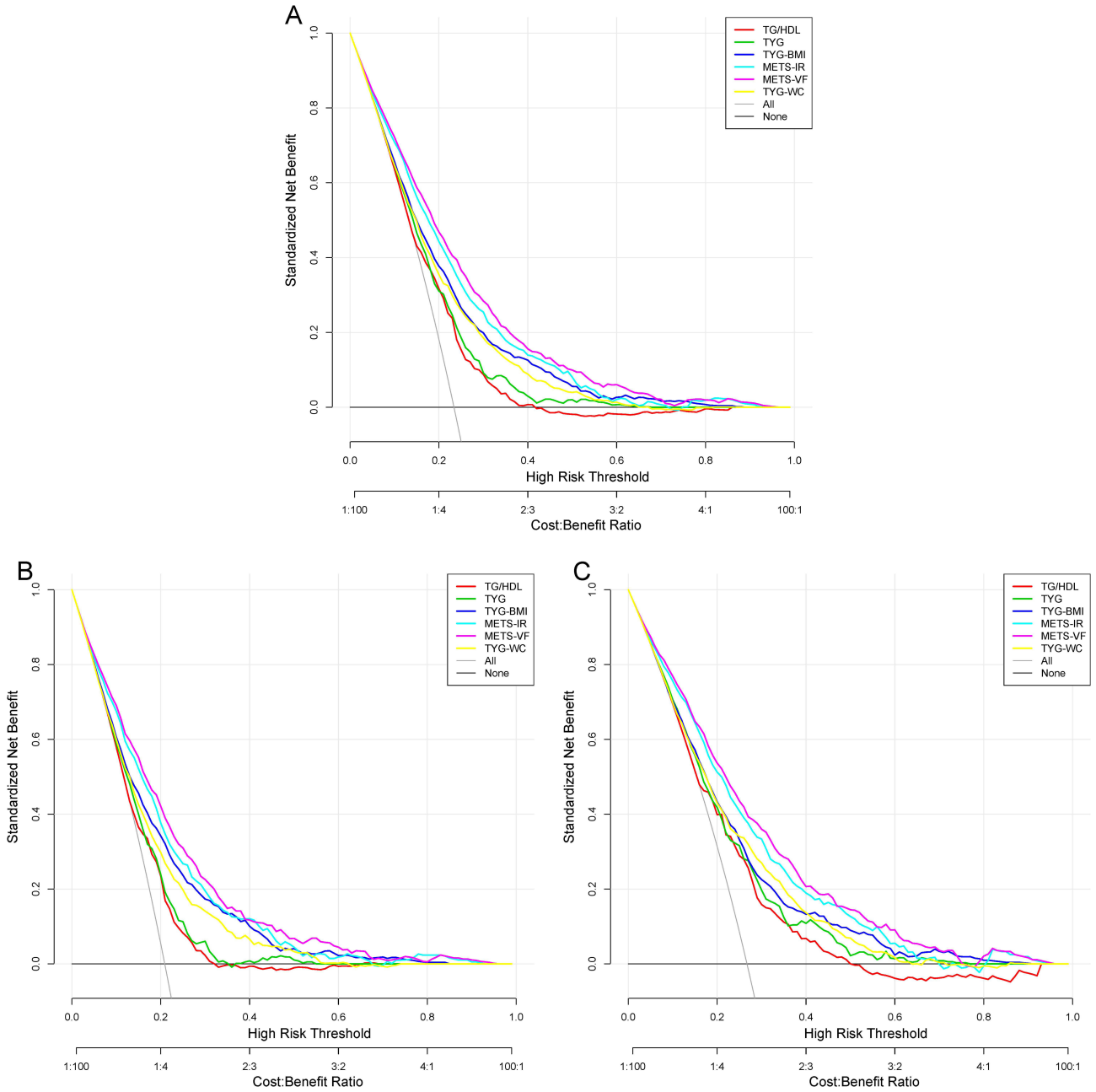

Figure 5 Decision curve analysis (DCA) for the diagnostic evaluation of hyperuricemia using obesity metabolic indices.
Notes: (**A**) Total population; (**B**) Male population; (**C**) Female population.

geographic and demographic homogeneity of our participants may limit the generalizability of our results to other populations. Therefore, caution must be exercised when attempting to extrapolate these findings to different ethnic, geographic, or demographic groups. Lastly, despite our comprehensive approach to adjusting for potential confounding factors, there remains the possibility that unidentified confounders could influence the observed associations. The strength of our study is somewhat mitigated by these limitations; however, the results of our E-value analysis suggest that the likelihood of our conclusions being significantly overturned is minimal. Future research should aim to replicate our findings in more diverse populations and over longer periods to better understand the causal relationships between obesity metabolism and hyperuricemia.

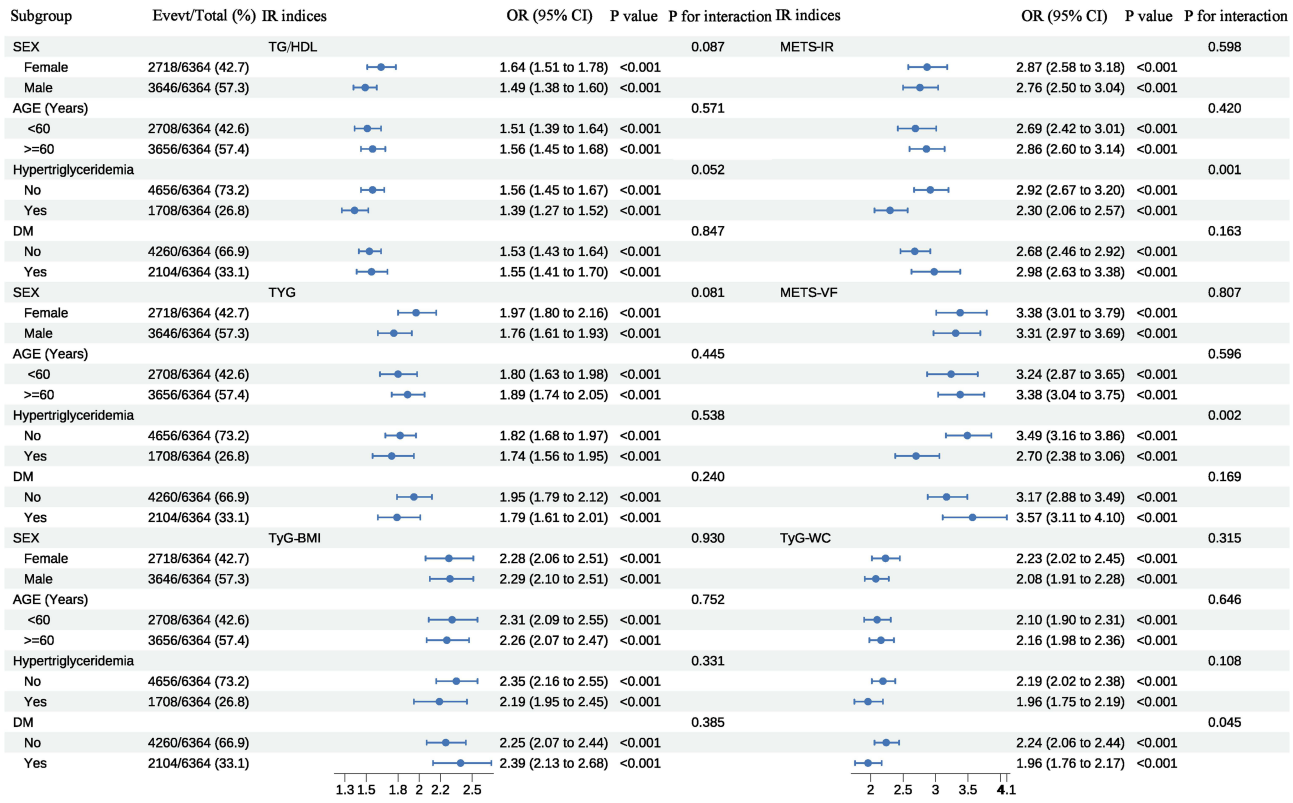

Figure 6 Association between obesity metabolism indices and hyperuricemia in various subgroups.

Conclusion

This study was the first to explore the relationship between various obesity metabolic indices and hyperuricemia in patients with hypertension and CHD. The results showed that the risk of hyperuricemia increased with higher obesity metabolic indices. The METS-VF index, integrating visceral obesity and metabolism, offers optimal diagnostic potential. These findings are instrumental for early clinical intervention, underscoring the need to address abdominal obesity and metabolic health. Further research is essential to confirm these insights.

Data Sharing Statement

The datasets used and/or analysed in this study are available on request from the corresponding author.

Institutional Review Board Statement

This study was approved by the Ethics Committee of the Fifth Affiliated Hospital of Sun Yat-sen University (2022L047-1) and Suining Central Hospital (KYLLKS20240103). All participants signed a written informed consent form.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Wen S, Arakawa H, Tamai I. Uric acid in health and disease: from physiological functions to pathogenic mechanisms. *Pharmacol Ther*. 2024;256:108615. doi:10.1016/j.pharmthera.2024.108615
2. Major TJ, Dalbeth N, Stahl EA, et al. An update on the genetics of hyperuricaemia and gout. *Nat Rev Rheumatol*. 2018;14(6):341–353. doi:10.1038/s41584-018-0004-x
3. Piao W, Zhao L, Yang Y, et al. The prevalence of hyperuricemia and its correlates among adults in China: results from CNHS 2015-2017. *Nutrients*. 2022;14(19):4095. doi:10.3390/nu14194095

4. Wu J, Qiu L, Cheng XQ, et al. Hyperuricemia and clustering of cardiovascular risk factors in the Chinese adult population. *Sci Rep*. 2017;7(1):5456. doi:10.1038/s41598-017-05751-w
5. Dalbeth N, Gosling AL, Gaffo A, et al. Gout. *Lancet*. 2021;397(10287):1843–1855. doi:10.1016/S0140-6736(21)00569-9
6. Song S, Cai X, Hu J, et al. Plasma aldosterone concentrations elevation in hypertensive patients: the dual impact on hyperuricemia and gout. *Front Endocrinol*. 2024;15:1424207. doi:10.3389/fendo.2024.1424207
7. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med*. 2008;359(17):1811–1821. doi:10.1056/NEJMra0800885
8. Lu YH, Chang YP, Li T, et al. Empagliflozin attenuates hyperuricemia by upregulation of ABCG2 via AMPK/AKT/CREB signaling pathway in type 2 diabetic mice. *Int J Biol Sci*. 2020;16(3):529–542. doi:10.7150/ijbs.33007
9. Dehlin M, Jacobsson L, Roddy E. Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors. *Nat Rev Rheumatol*. 2020;16(7):380–390. doi:10.1038/s41584-020-0441-1
10. Cirillo P, Sato W, Reungjui S, et al. Uric acid, the metabolic syndrome, and renal disease. *J Am Soc Nephrol*. 2006;17(12 Suppl 3):S165–8. doi:10.1681/ASN.2006080909
11. Copur S, Demiray A, Kanbay M. Uric acid in metabolic syndrome: does uric acid have a definitive role? *Eur J Intern Med*. 2022;103:4–12. doi:10.1016/j.ejim.2022.04.022
12. Spatola L, Ferraro PM, Gambaro G, et al. Metabolic syndrome and uric acid nephrolithiasis: insulin resistance in focus. *Metabolism*. 2018;83:225–233. doi:10.1016/j.metabol.2018.02.008
13. Kanbay M, Jensen T, Solak Y, et al. Uric acid in metabolic syndrome: from an innocent bystander to a central player. *Eur J Intern Med*. 2016;29:3–8. doi:10.1016/j.ejim.2015.11.026
14. Fritz J, Brozek W, Concin H, et al. The association of excess body weight with risk of ESKD is mediated through insulin resistance, hypertension, and hyperuricemia. *J Am Soc Nephrol*. 2022;33(7):1377–1389. doi:10.1681/ASN.2021091263
15. Dawson J, Wyss A. Chicken or the egg? Hyperuricemia, insulin resistance, and hypertension. *Hypertension*. 2017;70(4):698–699. doi:10.1161/HYPERTENSIONAHA.117.09685
16. McCormick N, O'Connor MJ, Yokose C, et al. Assessing the causal relationships between insulin resistance and hyperuricemia and gout using bidirectional Mendelian randomization. *Arthritis Rheumatol*. 2021;73(11):2096–2104. doi:10.1002/art.41779
17. Koren D, Taveras EM. Association of sleep disturbances with obesity, insulin resistance and the metabolic syndrome. *Metabolism*. 2018;84:67–75. doi:10.1016/j.metabol.2018.04.001
18. Seo YG, Song HJ, Song YR. Fat-to-muscle ratio as a predictor of insulin resistance and metabolic syndrome in Korean adults. *J Cachexia, Sarcopenia Muscle*. 2020;11(3):710–725. doi:10.1002/jcsm.12548
19. Huang R, Cheng Z, Jin X, et al. Usefulness of four surrogate indexes of insulin resistance in middle-aged population in Hefei, China. *Ann Med*. 2022;54(1):622–632. doi:10.1080/07853890.2022.2039956
20. Du T, Yuan G, Zhang M, et al. Clinical usefulness of lipid ratios, visceral adiposity indicators, and the triglycerides and glucose index as risk markers of insulin resistance. *Cardiovasc Diabetol*. 2014;13(1):146. doi:10.1186/s12933-014-0146-3
21. Jia Y, He Z, Liu F, et al. Dietary intake changes the associations between long-term exposure to fine particulate matter and the surrogate indicators of insulin resistance. *Environ Int*. 2024;186:108626. doi:10.1016/j.envint.2024.108626
22. Duan M, Zhao X, Li S, et al. Metabolic score for insulin resistance (METS-IR) predicts all-cause and cardiovascular mortality in the general population: evidence from NHANES 2001-2018. *Cardiovasc Diabetol*. 2024;23(1):243. doi:10.1186/s12933-024-02334-8
23. Bello-Chavolla OY, Antonio-Villa NE, Vargas-Vázquez A, et al. Metabolic Score for Visceral Fat (METS-VF), a novel estimator of intra-abdominal fat content and cardio-metabolic health. *Clin Nutr*. 2020;39(5):1613–1621. doi:10.1016/j.clnu.2019.07.012
24. Cai X, Song S, Hu J, et al. Association of the trajectory of plasma aldosterone concentration with the risk of cardiovascular disease in patients with hypertension: a cohort study. *Sci Rep*. 2024;14(1):4906. doi:10.1038/s41598-024-54971-4
25. Stevenson JE, Wright BR, Boydstun AS. The metabolic syndrome and coronary artery disease: a structural equation modeling approach suggestive of a common underlying pathophysiology. *Metabolism*. 2012;61(11):1582–1588. doi:10.1016/j.metabol.2012.04.010
26. Cai X, Song S, Hu J, et al. Body roundness index improves the predictive value of cardiovascular disease risk in hypertensive patients with obstructive sleep apnea: a cohort study. *Clin Exp Hypertens*. 2023;45(1):2259132. doi:10.1080/10641963.2023.2259132
27. Xu Y, Dong H, Zhang B, et al. Association between dyslipidemia and the risk of hyperuricaemia: a six-year longitudinal cohort study of elderly individuals in China. *Ann Med*. 2022;54(1):2402–2410. doi:10.1080/07853890.2022.2118368
28. Yu Y, Lan T, Wang D, et al. The association of lipid ratios with hyperuricemia in a rural Chinese hypertensive population. *Lipids Health Dis*. 2021;20(1):121. doi:10.1186/s12944-021-01556-z
29. Gou R, Dou D, Tian M, et al. Association between triglyceride glucose index and hyperuricemia: a new evidence from China and the United States. *Front Endocrinol*. 2024;15:1403858. doi:10.3389/fendo.2024.1403858
30. Xiong Y, Wangsheng F, Wang S, et al. Positive association between body fat percentage and hyperuricemia in patients with hypertension: the China H-type hypertension registry study. *Nutr, Metab Cardiovasc Dis*. 2021;31(11):3076–3084. doi:10.1016/j.numecd.2021.07.002
31. Multidisciplinary Expert Task Force on Hyperuricemia and Related Diseases. Chinese multidisciplinary expert consensus on the diagnosis and treatment of hyperuricemia and related diseases. *Chin Med J*. 2017;130(20):2473–2488. doi:10.4103/0366-6999.216416
32. Kleber ME, Delgado G, Grammer TB, et al. Uric acid and cardiovascular events: a Mendelian randomization study. *J Am Soc Nephrol*. 2015;26(11):2831–2838. doi:10.1681/ASN.2014070660
33. Li L, Zhao M, Wang C, et al. Early onset of hyperuricemia is associated with increased cardiovascular disease and mortality risk. *Clin Res Cardiol*. 2021;110(7):1096–1105. doi:10.1007/s00392-021-01849-4
34. Wang Y, Hu JW, Lv YB, et al. The role of uric acid in hypertension of adolescents, prehypertension and salt sensitivity of blood pressure. *Med Sci Monit*. 2017;23:790–795. doi:10.12659/msm.899563
35. Soletsky B, Feig DI. Uric acid reduction rectifies prehypertension in obese adolescents. *Hypertension*. 2012;60(5):1148–1156. doi:10.1161/HYPERTENSIONAHA.112.196980
36. El-Arabey AA, Abdalla M. GATA3 as an immunomodulator in obesity-related metabolic dysfunction associated with fatty liver disease, insulin resistance, and type 2 diabetes. *Chem Biol Interact*. 2022;366:110141. doi:10.1016/j.cbi.2022.110141
37. Abdalla M, El-Arabey AA, Gai Z. PDL-1 and insulin resistance in obesity: a possible pathway for macrovascular disease. *Hum Cell*. 2024;37(2):568–570. doi:10.1007/s13577-024-01029-2

38. Song S, Cai X, Hu J, et al. Effectiveness of spironolactone in reducing osteoporosis and future fracture risk in middle-aged and elderly hypertensive patients. *Drug Des Devel Ther*. 2024;18:2215–2225. doi:10.2147/DDDT.S466904
39. Song S, Cai X, Hu J, et al. Correlation between plasma aldosterone concentration and bone mineral density in middle-aged and elderly hypertensive patients: potential impact on osteoporosis and future fracture risk. *Front Endocrinol (Lausanne)*. 2024;15:1373862. doi:10.3389/fendo.2024.1373862
40. Tillin T, Forouhi N, Johnston DG, McKeigue PM, Chaturvedi N, Godsland IF. Metabolic syndrome and coronary heart disease in South Asians, African-Caribbeans and white Europeans: a UK population-based cross-sectional study. *Diabetologia*. 2005;48(4):649–656. doi:10.1007/s00125-005-1689-3
41. Hu J, Cai X, Li N, et al. Association between triglyceride glucose index-waist circumference and risk of first myocardial infarction in Chinese hypertensive patients with obstructive sleep apnoea: an observational cohort study. *Nat Sci Sleep*. 2022;14:969–980. doi:10.2147/NSS.S362101
42. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature*. 2006;444(7121):881–887. doi:10.1038/nature05488
43. Ruderman NB, Carling D, Prentki M, et al. AMPK, insulin resistance, and the metabolic syndrome. *J Clin Invest*. 2013;123(7):2764–2772. doi:10.1172/JCI67227
44. Zhao J, Cai X, Hu J, et al. J-shaped relationship between weight-adjusted-waist index and cardiovascular disease risk in hypertensive patients with obstructive sleep apnea: a cohort study. *Diabetes Metab Syndr Obes*. 2024;17:2671–2681. doi:10.2147/DMSO.S469376
45. Lee MJ, Khang AR, Kang YH, et al. Synergistic interaction between hyperuricemia and abdominal obesity as a risk factor for metabolic syndrome components in Korean population. *Diabetes Metab J*. 2022;46(5):756–766. doi:10.4093/dmj.2021.0166
46. Battelli MG, Bortolotti M, Polito L, et al. Metabolic syndrome and cancer risk: the role of xanthine oxidoreductase. *Redox Biol*. 2019;21:101070. doi:10.1016/j.redox.2018.101070
47. Cai X, Li N, Hu J, et al. Nonlinear relationship between Chinese visceral adiposity index and new-onset myocardial infarction in patients with hypertension and obstructive sleep apnoea: insights from a cohort study. *J Inflamm Res*. 2022;15:687–700. doi:10.2147/JIR.S351238
48. Wang J, Chen S, Zhao J, et al. Association between nutrient patterns and hyperuricemia: mediation analysis involving obesity indicators in the NHANES. *BMC Public Health*. 2022;22(1):1981. doi:10.1186/s12889-022-14357-5
49. Zhang M, Zhu X, Wu J, et al. Prevalence of hyperuricemia among Chinese adults: findings from two nationally representative cross-sectional surveys in 2015-16 and 2018-19. *Front Immunol*. 2022;12:791983. doi:10.3389/fimmu.2021.791983
50. Han T, Lan L, Qu R, et al. Temporal relationship between hyperuricemia and insulin resistance and its impact on future risk of hypertension. *Hypertension*. 2017;70(4):703–711. doi:10.1161/HYPERTENSIONAHA.117.09508
51. Huang X, Jiang X, Wang L, et al. Visceral adipose accumulation increased the risk of hyperuricemia among middle-aged and elderly adults: a population-based study. *J Transl Med*. 2019;17(1):341. doi:10.1186/s12967-019-2074-1
52. Zhang X, Ye R, Yu C, et al. Correlation between non-insulin-based insulin resistance indices and increased arterial stiffness measured by the cardio-ankle vascular index in non-hypertensive Chinese subjects: a cross-sectional study. *Front Cardiovasc Med*. 2022;9:903307. doi:10.3389/fcvm.2022.903307
53. Paublini H, López González AA, Busquets-Cortés C, et al. Relationship between atherogenic dyslipidemia and lipid triad and scales that assess insulin resistance. *Nutrients*. 2023;15(9):2105. doi:10.3390/nu15092105
54. Fritz J, Brozek W, Concin H, et al. The triglyceride-glucose index and obesity-related risk of end-stage kidney disease in Austrian adults. *JAMA Network Open*. 2021;4(3):e212612. doi:10.1001/jamanetworkopen.2021.2612
55. Cai X, Hu J, Zhu Q, et al. Relationship of the metabolic score for insulin resistance and the risk of stroke in patients with hypertension: a cohort study. *Front Endocrinol*. 2022;13:1049211. doi:10.3389/fendo.2022.1049211
56. Liu Z, Deng B, Huang Q, et al. Comparison of seven surrogate insulin resistance indexes for predicting the prevalence of carotid atherosclerosis in normal-weight individuals. *Front Public Health*. 2023;11:1241523. doi:10.3389/fpubh.2023.1241523
57. Yang W, Cai X, Hu J, et al. The Metabolic Score for Insulin Resistance (METS-IR) predicts cardiovascular disease and its subtypes in patients with hypertension and obstructive sleep apnea. *Clin Epidemiol*. 2023;15:177–189. doi:10.2147/CLEP.S395938
58. Han Y, Zhou Z, Zhang Y, et al. The association of surrogates of insulin resistance with hyperuricemia among middle-aged and older individuals: a population-based nationwide cohort study. *Nutrients*. 2023;15(14):3139. doi:10.3390/nu15143139
59. Liu Z, Zhou Q, Tang Y, et al. Sex-specific differences in the associations between adiposity indices and incident hyperuricemia among middle-aged and older adults: a nationwide longitudinal study. *Front Endocrinol (Lausanne)*. 2024;15:1336471. doi:10.3389/fendo.2024.1336471
60. Wang H, Zhang J, Pu Y, et al. Comparison of different insulin resistance surrogates to predict hyperuricemia among U.S. non-diabetic adults. *Front Endocrinol (Lausanne)*. 2022;13:1028167. doi:10.3389/fendo.2022.1028167
61. Seifi N, Nosrati M, Koochackpoor G, et al. The association between hyperuricemia and insulin resistance surrogates, dietary- and lifestyle insulin resistance indices in an Iranian population: MASHAD cohort study. *Nutr J*. 2024;23(1):5. doi:10.1186/s12937-023-00904-2
62. Zhang H, Chen R, Xu X, et al. Metabolically healthy obesity is associated with higher risk of both hyperfiltration and mildly reduced estimated glomerular filtration rate: the role of serum uric acid in a cross-sectional study. *J Transl Med*. 2023;21(1):216. doi:10.1186/s12967-023-04003-y
63. Tsushima Y, Nishizawa H, Tochino Y, et al. Uric acid secretion from adipose tissue and its increase in obesity. *J Biol Chem*. 2013;288(38):27138–27149. doi:10.1074/jbc.M113.485094
64. Xiang R, Fan LL, Huang H, et al. Increased Reticulon 3 (RTN3) leads to obesity and hypertriglyceridemia by interacting with heat shock protein family A (Hsp70) Member 5 (HSPA5). *Circulation*. 2018;138(17):1828–1838. doi:10.1161/CIRCULATIONAHA.117.030718
65. Yu W, Xie D, Yamamoto T, et al. Mechanistic insights of soluble uric acid-induced insulin resistance: insulin signaling and beyond. *Rev Endocr Metab Disord*. 2023;24(2):327–343. doi:10.1007/s11154-023-09787-4
66. Cai XT, Zhu Q, Liu SS, et al. Associations between the metabolic score for insulin resistance index and the risk of type 2 diabetes mellitus among non-obese adults: insights from a population-based cohort study. *Int J Gen Med*. 2021;14:7729–7740. doi:10.2147/IJGM.S336990
67. Mazidi M, Katsiki N, Mikhailidis DP, et al. The link between insulin resistance parameters and serum uric acid is mediated by adiposity. *Atherosclerosis*. 2018;270:180–186. doi:10.1016/j.atherosclerosis.2017.12.033
68. Matsuura F, Yamashita S, Nakamura T, et al. Effect of visceral fat accumulation on uric acid metabolism in male obese subjects: visceral fat obesity is linked more closely to overproduction of uric acid than subcutaneous fat obesity. *Metabolism*. 1998;47(8):929–933. doi:10.1016/s0026-0495(98)90346-8

69. Li Z, Gao L, Zhong X, et al. Association of visceral fat area and hyperuricemia in non-obese us adults: a cross-sectional study. *Nutrients*. 2022;14(19):3992. doi:10.3390/nu14193992
70. Ouchi N, Parker JL, Lugus JJ, et al. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol*. 2011;11(2):85–97. doi:10.1038/nri2921
71. Suren Garg S, Kushwaha K, Dubey R, et al. Association between obesity, inflammation and insulin resistance: insights into signaling pathways and therapeutic interventions. *Diabet Res Clin Pract*. 2023;200:110691. doi:10.1016/j.diabres.2023.110691
72. Chen R, Yang J, Wu M, et al. M2 macrophage hybrid membrane-camouflaged targeted biomimetic nanosomes to reprogram inflammatory microenvironment for enhanced enzyme-thermo-immunotherapy. *Adv Mater*. 2023;35(39):e2304123. doi:10.1002/adma.202304123
73. Spiga R, Marini MA, Mancuso E, et al. Uric acid is associated with inflammatory biomarkers and induces inflammation via activating the NF-κB signaling pathway in HepG2 cells. *Arterioscler Thromb Vasc Biol*. 2017;37(6):1241–1249. doi:10.1161/ATVBAHA.117.309128