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ORIGINAL PAPER

Relation of BMI and waist circumference with the risk of new-onset hyperuricemia in hypertensive patients

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Summary

Background: We aimed to evaluate the relationship of body mass index (BMI) and waist circumference (WC) with the risk of new-onset hyperuricemia, and examine possible effect modifies in general hypertensive patients.
Methods: A total of 10 611 hypertensive patients with normal uric acid (UA) concentrations (<357 μmol/l) at baseline were included from the UA sub-study of the China Stroke Primary Prevention Trial. The primary outcome was new-onset hyperuricemia, defined as a UA concentration ≥417 μmol/l in men or ≥357 μmol/l in women at the exit visit.
Results: During a median follow-up duration of 4.4 years, 1663 (15.7%) participants developed new-onset hyperuricemia. When analyzed separately, increased BMI (≥25 kg/m^2, quartile 3–4; OR, 1.46; 95% CI: 1.29–1.65), or increased WC (≥85 cm for females, quartile 3–4; OR, 1.24; 95% CI: 1.08–1.42; and ≥84 cm for males, quartile 3–4; OR, 1.30; 95% CI: 1.01–1.67) were each significantly associated with higher risk of new-onset hyperuricemia. When WC was forced into the model with BMI simultaneously, its significant association with new-onset hyperuricemia disappeared in females (<85 vs. ≥85 cm; OR, 0.96, 95% CI: 0.81–1.13) or males (≥84 vs. <84 cm; OR, 1.13; 95% CI: 0.84–1.52); however, BMI was still significantly related with new-onset hyperuricemia (≥25 vs. <25 kg/m^2; OR, 1.48; 95% CI: 1.27–1.73). Moreover, the positive BMI & new-onset hyperuricemia association was more pronounced in participants with higher time-averaged on-treatment systolic blood pressure (median: <138.3 vs. ≥138.3 mmHg; P-interaction = 0.041).
Conclusions: Higher BMI, but not WC, is significantly and independently associated with an increased risk of new-onset hyperuricemia among hypertensive patients.

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Introduction

Over the past few decades, hyperuricemia has become an increased public health concern, and the prevalence of hyperuricemia in China is estimated to be 13.3%.[1] Hyperuricemia is associated with gout, chronic kidney disease (CKD), stroke, cardiovascular diseases (CVD) and mortality.[2–5] Therefore, a better understanding of more modifiable risk factors of hyperuricemia is important to the management of hyperuricemia and its associated disease burden.

Obesity is also a worldwide public health challenge because of its high burden of comorbidity (diabetes, CVD, CKD, etc.).[6–8] To date, some cross-sectional studies[9–14] have assessed the relationship of general obesity, defined by body mass index (BMI), and abdominal obesity, defined by waist circumference (WC), with the prevalence of hyperuricemia, and reported inconsistent results. However, only a few previous studies[15,16] have assessed the prospective association between BMI and risk of hyperuricemia only in males aged 30–59 years, but not in females. Overall, the relationship of BMI and WC with the risk of new-onset hyperuricemia remains uncertain. At the same time, this type of research has not been conducted in hypertensive patients, who have been reported to be at a high risk for developing hyperuricemia.[17] More importantly, the potential modifiers on the relation of BMI and/or WC with new-onset hyperuricemia have not been comprehensively investigated in previous studies.

To address this aforementioned knowledge gap, our current study aimed to evaluate the relationship of BMI and WC with the risk of new-onset hyperuricemia, and examine possible effect modifiers among hypertensive patients, using data from the uric acid (UA) sub-study of the China Stroke Primary Prevention Trial (CSPPT).[18]

Material and methods

Study design and participants

The detailed methods and major findings of CSPPT and the UA sub-study of the CSPPT have been reported previously elsewhere.[18–22] Briefly, the CSPPT was a multi-community, randomized, double-blind, actively controlled trial conducted from 19 May 2008 to 24 August 2013 with 20 702 hypertensive adults in 32 communities in Jiangsu and Anhui provinces of China. Eligible participants were men and women from 45 to 75 years old who had hypertension, defined as seated, resting systolic blood pressure (SBP) of 140 mmHg or higher, or diastolic blood pressure (DBP) of 90 mmHg or higher at both the screening and recruitment visits or, who were taking antihypertensive medication. The major exclusion criteria included a history of physician-diagnosed stroke, myocardial infarction, heart failure, coronary revascularization or congenital heart disease.

The UA sub-study of the CSPPT included 15 364 eligible participants with the UA measurements and without the usage of UA-lowering drugs at baseline from 20 communities in Jiangsu province. This study is a *post hoc* analysis of the UA sub-study. The flow of the participants is presented in Supplementary Figure 1.

The parent study (the CSPPT) and this study were approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China (FWA assurance number: FWA00001263). All participants provided written informed consent.

Intervention and follow-up

In the CSPPT, eligible participants were randomly assigned, in a 1:1 ratio, to one of two treatment groups: a daily oral dose of one tablet containing 10 mg enalapril and 0.8 mg folic acid (the enalapril-folic acid group), or a daily oral dose of one tablet containing 10 mg enalapril only (the enalapril group).

Participants were followed up every 3 months. At each follow-up visit, blood pressure (BP) was measured; study drug compliance, concomitant medication use, adverse events and possible endpoint events were documented by trained research staff and physicians. At the exit visit, final blood samples were collected and assessed.

Anthropometric and BP measurements

Anthropometric measurements, including height, weight and WC were taken using the standard operating procedures. Height was measured without shoes to the nearest 0.1 cm on a portable stadiometer. Weight was measured on a weight scale with subjects wearing light indoor clothing without shoes to the nearest 0.1 kg. BMI was calculated as weight (kg)/height (m^2). WC was measured as the minimum circumference between the inferior margin of the ribcage and the crest of the ileum.[7,8,23]

Seated BP was measured by trained research staff using a mercury manometer after participants had rested for 10 min, following the standard method and with appropriately sized cuffs. Triplicate measurements on the same arm were taken, with at least 2 min between readings. The average of the three independent measures was used in the analyses. BP measurements were taken at baseline, randomization and every 3 months thereafter. Time-averaged on-treatment BP was calculated for each participant using all post baseline results up to the last visit (number of BP measurements during the treatment: median, 16; interquartile range, 12–18).

Laboratory assays

Blood samples of all participants were collected at both the baseline and the exit visits. Serum concentrations of UA, fasting glucose, creatinine, total homocysteine (tHcy) and lipids were measured using automatic analyzers (Beckman Coulter) at the core laboratory of the National Clinical Research Center for Kidney Disease, Nanfang Hospital, Guangzhou, China. The estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation.[24]

Outcomes

The primary outcome was new-onset hyperuricemia in participants with normal UA concentrations [<357 μmol/l (6 mg/dl)] at baseline. Hyperuricemia was defined as a UA concentration ≥417 μmol/l (7 mg/dl) in men or ≥357 μmol/l (6 mg/dl) in women.[18,25,26]

The secondary outcome was change in UA concentrations, defined as UA concentrations at the exit visit minus that at baseline.

Statistical analyses

Baseline characteristics are expressed as mean±standard deviation (SD) for continuous variables or percentages for categorical variables. Differences in population characteristics by baseline BMI quartiles were compared using analysis of variance tests, or chi-square tests, accordingly.

Multivariable logistic regression models and generalized linear regression models were used to examine the relationship of baseline BMI and WC with primary and secondary outcomes, respectively. To evaluate and compare the relation of BMI and WC with study outcomes, BMI and WC were first individually and then simultaneously entered into the multivariable regression models without and with adjustment for treatment group, age, sex, UA, fasting glucose, total cholesterol (TC), triglycerides (TG), tHcy, high-density lipoprotein cholesterol (HDL-C), eGFR, smoking and drinking status, use of antihypertensive drugs, SBP at baseline and time-averaged on-treatment SBP. As additional exploratory analyses, possible modifications on the association between BMI and new-onset hyperuricemia were also evaluated by stratified analyses and interaction testing.

A two-tailed $P < 0.05$ was considered to be statistically significant in all analyses. Statistical analyses were conducted using R software, version 3.6.3 (http://www. R-project.org/).

Results

Characteristics of study participants

As illustrated in the flow chart (Supplementary Figure 1), a total of 10 611 participants with complete data on baseline BMI and WC measurements and exit UA, who were not using UA-lowering drugs during the follow-up period, as well as whose baseline UA levels were <357 μmol/l (6 mg/dl) in the CSPPT UA sub-study, were included in the final analysis.

Baseline characteristics of the participants stratified by baseline BMI quartiles are summarized in Table 1. Participants with higher baseline BMI were less likely to be current smokers and alcohol drinkers; tended to be female; had higher WC, SBP, DBP, TC, TG, fasting glucose, eGFR, UA levels, younger age, and lower HDL-C, tHcy levels; higher frequency usage of antihypertensive drugs, lipid-lowering drugs, glucose-lowering drugs and antiplatelet drugs; higher prevalence of self-reported diabetes and hyperlipidemia at baseline; as well as higher time-averaged on-treatment SBP and DBP.

In addition, during the treatment period, participants with higher baseline BMI levels had a higher frequency in the use of glucose-lowering drugs, calcium channel blockers and diuretics (Supplementary Table 1).

Association between BMI and study outcomes

During a median follow-up of 4.4 years (interquartile range: 4.2–4.6 years), 1663 (15.7%) participants developed new-onset hyperuricemia.

Overall, there was a significantly positive association between baseline BMI and the risk of new-onset hyperuricemia (per SD increment; adjusted OR, 1.22; 95% CI: 1.15–1.30) (Figure 1 and Table 2). Consistently, a significantly higher risk of new-onset hyperuricemia was found in participants with baseline

Table 1. Characteristics of study participants according to quartiles of BMI[a]

	BMI, kg/m^2				P-value
	Q1 (<23) (*n*=2651)	Q2 (23 to <25) (*n*=2653)	Q3 (25 to <28) (*n*=2641)	Q4 (≥28) (*n*=2666)	
Age, year	61.2±7.4	59.8±7.4	58.8±7.3	57.9±7.2	<0.001
Male, *n* (%)	1109 (41.8)	933 (35.2)	754 (28.5)	552 (20.7)	<0.001
BMI, kg/m^2	21.3±1.4	24.2±0.6	26.4±0.7	30.1±2.2	<0.001
Waist circumference, cm	75.6±6.4	82.3±5.8	87.3±5.9	94.4±7.5	<0.001
Current smoking, *n* (%)	798 (30.1)	523 (19.7)	412 (15.6)	308 (11.6)	<0.001
Current alcohol drinking, *n* (%)	663 (25.0)	544 (20.5)	448 (17.0)	319 (12.0)	<0.001
Self-reported hyperlipidemia, *n* (%)	36 (1.4)	59 (2.2)	74 (2.8)	123 (4.6)	<0.001
Self-reported diabetes, *n* (%)	73 (2.8)	94 (3.5)	116 (4.4)	130 (4.9)	<0.001
Enalapril only treatment, *n* (%)	1331 (50.2)	1352 (51.0)	1333 (50.5)	1306 (49.0)	0.521
Blood pressure, mmHg					
Baseline SBP	167.9±20.3	168.7±20.8	169.1±20.8	169.9±21.3	0.006
Baseline DBP	92.4±11.8	94.3±11.6	95.6±11.5	97.5±11.8	<0.001
Time-averaged on-treatment SBP	138.8±11.0	139.1±11.0	139.1±10.5	140.0±10.8	<0.001
Time-averaged on-treatment DBP	81.5±7.1	83.0±7.1	83.5±6.7	84.9±7.1	<0.001
Laboratory results					
Total cholesterol, mmol/l	5.6±1.2	5.7±1.1	5.7±1.2	5.8±1.2	<0.001
Triglycerides, mmol/l	1.3±0.7	1.6±0.8	1.8±1.0	2.0±2.1	<0.001
HDL-C, mmol/l	1.5±0.4	1.4±0.3	1.3±0.3	1.2±0.3	<0.001
Fasting glucose, mmol/l	6.0±1.9	6.0±1.7	6.2±1.9	6.2±1.8	<0.001
Total homocysteine, μmol/l	14.6±8.9	14.2±8.5	13.8±7.8	13.6±8.0	<0.001
eGFR, ml/min/1.73 m^2	93.7±11.7	94.8±11.5	95.9±11.5	96.4±12.1	<0.001
Uric acid, μmol/l	258.0±53.0	262.6±51.6	265.6±52.5	273.6±49.7	<0.001
Medication use, *n* (%)					
Antihypertensive drugs	1058 (39.9)	1222 (46.1)	1310 (49.6)	1477 (55.4)	<0.001
Lipid-lowering drugs	11 (0.4)	21 (0.8)	25 (0.9)	32 (1.2)	0.016
Glucose-lowering drugs	37 (1.4)	48 (1.8)	53 (2.0)	67 (2.5)	0.028
Antiplatelet drugs	68 (2.6)	89 (3.4)	112 (4.2)	121 (4.5)	<0.001

[a]Variables are presented as mean±SD or *n* (%).

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure.

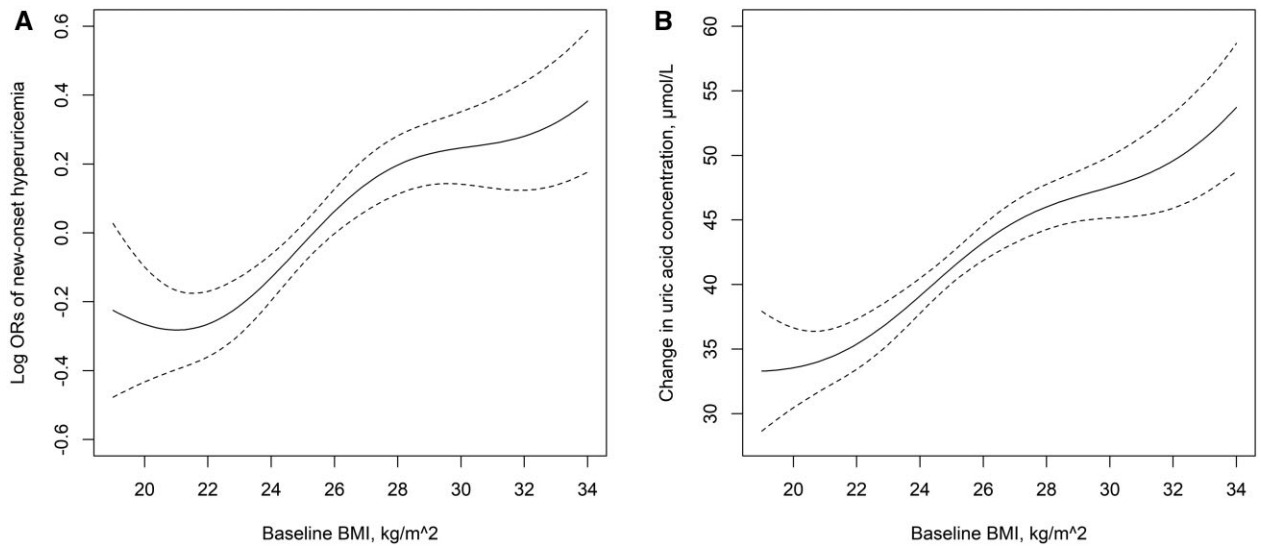

Figure 1. Relationship of BMI with new-onset hyperuricemia (**A**) and change in UA concentrations (**B**)[a]. [a]Adjusted for treatment group, age, sex, uric acid (UA), fasting glucose, total cholesterol, triglycerides (TG), total homocysteine (tHcy), high-density lipoprotein cholesterol (HDL), estimated glomerular filtration rate (eGFR), smoking and drinking status, use of antihypertensive drugs, SBP at baseline and time-averaged on-treatment SBP during treatment period.

Table 2. Association between BMI and new-onset hyperuricemia

BMI, kg/m^2	Events/*N* (%)	Crude model		Model 1		Model 2	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Per SD increment	1663/10 611 (15.7)	1.42 (1.35, 1.49)	<0.001	1.22 (1.15, 1.30)	<0.001	1.36 (1.23, 1.49)	<0.001
Quartiles							
Q1 (<23)	276/2651 (10.4)	ref.		ref.		ref.	
Q2 (23 to <25)	327/2653 (12.3)	1.21 (1.02, 1.43)	0.028	1.01 (0.84, 1.21)	0.907	1.04 (0.86, 1.26)	0.685
Q3 (25 to <28)	472/2641 (17.9)	1.87 (1.60, 2.20)	<0.001	1.41 (1.18, 1.68)	<0.001	1.48 (1.21, 1.82)	<0.001
Q4 (≥28)	588/2666 (22.1)	2.43 (2.09, 2.84)	<0.001	1.52 (1.28, 1.82)	<0.001	1.65 (1.30, 2.11)	<0.001
P for trend		<0.001		<0.001		<0.001	
Medians							
Q1–Q2 (<25)	603/5304 (11.4)	ref.		ref.		ref.	
Q3–Q4 (≥25)	1060/5307 (20.0)	1.95 (1.75, 2.17)	<0.001	1.46 (1.29, 1.65)	<0.001	1.48 (1.27, 1.73)	<0.001

Model 1: Adjusted for treatment group, age, sex, uric acid (UA), fasting glucose, total cholesterol, triglycerides (TG), total homocysteine (tHcy), high-density lipoprotein cholesterol (HDL), estimated glomerular filtration rate (eGFR), smoking and drinking status, use of antihypertensive drugs, SBP at baseline and time-averaged on-treatment SBP during treatment period.
Model 2: Adjusted for the variables in Model 1 plus waist circumference.

BMI≥25 kg/m^2(median) (vs. <25 kg/m^2; OR, 1.46; 95% CI: 1.29–1.65). Of note, further adjustment for baseline WC did not substantially affect the positive association between BMI and new-onset hyperuricemia (≥25 vs. <25 kg/m^2; OR, 1.48; 95% CI: 1.27–1.73) (Table 2). Moreover, further adjustment for concomitant use of glucose-lowering drugs, calcium channel blockers and diuretics during the treatment period also did not significantly change the results (Supplementary Table 2).

Similar results were found for the change in UA concentrations (Supplementary Table 3).

Association between WC and study outcomes

When WC was assessed as quartiles, a significantly higher risk of new-onset hyperuricemia was found in male participants in quartile 3–4 (≥84 cm) compared with those in quartiles 1–2 (<84 cm; OR, 1.30; 95% CI: 1.01–1.67). Among female participants, there was an increased risk of new-onset hyperuricemia in those in quartiles 3–4 (≥85 cm) compared with those in quartile 1–2 (<85 cm; OR, 1.24; 95% CI: 1.08–1.42) (Table 3). Similar results were found for the change in UA concentrations (Supplementary Table 4).

However, after further adjustment for the baseline BMI, the positive association between WC and new-onset hyperuricemia was attenuated and became insignificant both in males (<84 vs. ≥84 cm; OR, 1.13; 95% CI: 0.84–1.52) and in females (<85 vs. ≥85 cm; OR, 0.96, 95% CI: 0.81–1.13) (Table 3). Consistently, in the stratified analysis by the BMI strata (≥25 or <25 kg/m^2), there were no significant association between WC and new-onset hyperuricemia both in males (<84 vs. ≥84 cm; <25 kg/m^2: OR, 1.03; 95% CI: 0.72–1.49; ≥25 kg/m^2: OR, 0.85; 95% CI: 0.51–1.42) and in females (<85 vs. ≥85 cm; <25 kg/m^2: OR, 1.01; 95% CI: 0.77–1.32; ≥25 kg/m^2: OR, 1.06; 95% CI: 0.85–1.31) (Supplementary Table 5). Similar results were also found when separated the patients in the normal-weight (BMI <25 kg/m^2) and overweight (BMI≥25 kg/m^2) group based on the subgroup WC quartiles (Supplementary Table 6).

Accordingly, in the joint effect of BMI and WC on new-onset hyperuricemia, compared with participants with both lower

Table 3. Association between WC and new-onset hyperuricemia

WC, cm	Events/N (%)	Crude model		Model 1		Model 2	
		OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Male							
Quartiles							
Q1 (<78)	60/812 (7.4)	ref.		ref.		ref.	
Q2 (78 to <84)	82/772 (10.6)	1.49 (1.05, 2.11)	0.025	1.38 (0.96, 1.98)	0.084	1.26 (0.87, 1.84)	0.219
Q3 (84 to <91)	120/883 (13.6)	1.97 (1.42, 2.73)	<0.001	1.62 (1.14, 2.30)	0.007	1.38 (0.94, 2.04)	0.101
Q4 (≥91)	121/881 (13.7)	2.00 (1.44, 2.76)	<0.001	1.49 (1.03, 2.16)	0.033	1.11 (0.68, 1.81)	0.670
Categories							
Q1–Q2 (<84)	142/1584 (9.0)	ref.		ref.		ref.	
Q3–Q4 (≥84)	241/1764 (13.7)	1.61 (1.29, 2.00)	<0.001	1.30 (1.01, 1.67)	0.039	1.13 (0.84, 1.52)	0.425
Female							
Quartiles							
Q1 (<79)	216/1756 (12.3)	ref.		ref.		ref.	
Q2 (79 to <85)	263/1731 (15.2)	1.28 (1.05, 1.55)	0.013	1.03 (0.84, 1.27)	0.758	0.87 (0.70, 1.08)	0.217
Q3 (85 to <91)	349/1841 (19.0)	1.67 (1.39, 2.00)	<0.001	1.22 (1.00, 1.50)	0.050	0.92 (0.73, 1.15)	0.451
Q4 (≥91)	452/1935 (23.4)	2.17 (1.82, 2.59)	<0.001	1.29 (1.06, 1.57)	0.012	0.77 (0.59, 1.01)	0.064
Categories							
Q1–Q2 (<85)	479/3487 (13.7)	ref.		ref.		ref.	
Q3–Q4 (≥85)	801/3776 (21.2)	1.69 (1.49, 1.91)	<0.001	1.24 (1.08, 1.42)	0.003	0.96 (0.81, 1.13)	0.611

Model 1: Adjusted for treatment group, age, sex, uric acid (UA), fasting glucose, total cholesterol, triglycerides (TG), total homocysteine (tHcy), high-density lipoprotein cholesterol (HDL), estimated glomerular filtration rate (eGFR), smoking and drinking status, use of antihypertensive drugs, SBP at baseline and time-averaged on-treatment SBP during treatment period.
Model 2: Adjusted for the variables in Model 1 plus BMI.

BMI (<25 kg/m^2) and lower WC (WC<84 cm for males and <85 cm for females), a significantly increased risk of new-onset hyperuricemia was found in those with higher BMI alone (OR, 1.40; 95% CI, 1.14–1.73) or with both higher BMI and higher WC (OR, 1.47; 95% CI, 1.28–1.69), but not in those with higher WC alone (OR, 1.01; 95% CI, 0.82–1.25) (Supplementary Table 7).

Stratified analyses by potential effect modifiers

Stratified analyses were performed to further assess the relationship of baseline BMI as a binary variable (≥25 vs. <25 kg/m^2) with new-onset hyperuricemia. A stronger, positive association was found among participants with higher time-averaged on-treatment SBP (median: <138.3; OR, 1.28; 95% CI: 1.07–1.52; vs. ≥138.3 mmHg; OR, 1.63; 95% CI: 1.38–1.92; *P*-interaction= 0.041) (Figure 2).

None of the other variables, including sex, age, WC, treatment group, current smoking, current drinking, baseline SBP, TC, tHcy, UA, eGFR levels, diabetes at baseline, as well as diuretics usage during the treatment period significantly modified the association between baseline BMI (median, <25 vs. ≥25 kg/m^2) and the risk of new-onset hyperuricemia (*P*-values for all interactions >0.05) (Figure 2).

Discussion

Our study demonstrates that higher BMI is associated with an increased risk of new-onset hyperuricemia among hypertensive patients without hyperuricemia, especially in those with higher time-averaged on-treatment SBP. This association was independent of WC and other major covariates. However, there was no significant association between WC and the new-onset hyperuricemia after further adjustment for BMI.

Few prospective studies[15,16] have assessed the association between BMI and the risk of hyperuricemia. Ryu *et al.*[15] reported that there was a significantly positive association between BMI and hyperuricemia in middle-aged South Korean male workers aged 30–59 years. Consistently, in a cohort of 1312 hyperuricemia-free male office workers aged 30–52 years in Japan, Nakanishi *et al.*[16] found that higher BMI was related to increased risk of hyperuricemia. Of note, previous studies mainly examined the BMI-hyperuricemia relation in males aged 30–59 years. Our study offered a chance to investigate the dose-response relation of BMI or WC with new-onset hyperuricemia in hypertensive patients by leveraging the well-established CSPPT, with high quality baseline and follow-up epidemiological and clinical data, and a comprehensive analysis of many important risk factors or confounders of hyperuricemia.

Our current study has contributed to several new insights. First, BMI was associated with increased risk of hyperuricemia in males and/or females, independent of WC and other important covariates. Our findings seem to be biologically plausible based on the available evidence. Insulin resistance, as a consequence of overweight and obesity, may enhance the reabsorption of UA into the proximal renal tubules and subsequently increase UA levels.[27] Moreover, obese adipose tissue is hypoxic and that hypoxia causes adipose tissue dysfunction; then hypoxic induces an increase in xanthine oxidoreductase activity, leading to increased UA production.[28]

Second, it is worth noting that, in our current study, the significant association between WC and new-onset hyperuricemia in both men and women was attenuated and became insignificant with further adjustment for BMI. Consistently, Ishizaka *et al.*[29] found that change in BMI was, but change in WC was not, significantly and positively associated with the change in serum UA levels in multiple linear regression in postmenopausal women and men in Japan. Generally, BMI is strongly associated with subcutaneous fat area, and WC has a stronger relation with visceral fat area.[30] However, because Asian population are relatively lean, subcutaneous fat has a relatively

Sub-group	Size	<25kg/㎡ Events(%)	≥25kg/㎡ Events(%)	OR (95%CI)	P for interaction
Sex					0.367
Male	3348	178 (8.7)	205 (15.7)	1.59 (1.26, 2.01)	
Female	7263	425 (13.0)	855 (21.4)	1.41 (1.23, 1.62)	
Age, yr					0.363
<60	5758	259 (10.0)	567 (17.9)	1.37 (1.15, 1.62)	
≥60	4853	344 (12.7)	493 (23.1)	1.52 (1.29, 1.80)	
Waist circumference (male), cm					0.370
<84	1584	120 (8.2)	22 (17.1)	2.04 (1.21, 3.44)	
≥84	1764	58 (9.9)	183 (15.5)	1.54 (1.10, 2.15)	
Waist circumference (female), cm					0.633
<85	3487	334 (12.7)	145 (17.0)	1.31 (1.04, 1.66)	
≥85	3776	91 (14.5)	710 (22.6)	1.43 (1.10, 1.85)	
Treatment group					0.987
Enalapril	5322	324 (12.1)	545 (20.7)	1.46 (1.24, 1.72)	
Enalapril-folic acid	5289	279 (10.6)	515 (19.3)	1.46 (1.23, 1.73)	
Current smoking					0.201
No	8569	457 (11.5)	937 (20.4)	1.51 (1.32, 1.72)	
Yes	2041	146 (11.1)	123 (17.1)	1.24 (0.94, 1.64)	
Current drinking					0.674
No	8633	476 (11.6)	919 (20.3)	1.47 (1.29, 1.68)	
Yes	1974	127 (10.5)	141 (18.4)	1.38 (1.04, 1.82)	
Baseline SBP, mmHg					0.420
<166.0	5266	259 (9.6)	404 (15.7)	1.40 (1.17, 1.67)	
≥166.0	5345	344 (13.2)	656 (24.0)	1.54 (1.31, 1.80)	
Time-averaged on-treatment SBP, mmHg					0.041
<138.3	5305	285 (10.5)	436 (16.7)	1.28 (1.07, 1.52)	
≥138.3	5306	318 (12.2)	624 (23.1)	1.63 (1.38, 1.92)	
Total cholesterol, mmol/L					0.959
<5.6	5192	276 (10.2)	443 (17.8)	1.46 (1.22, 1.74)	
≥5.6	5261	321 (12.8)	606 (22.1)	1.45 (1.23, 1.70)	
Total homocysteine, μmol/L					0.841
<15	7919	416 (10.7)	787 (19.4)	1.47 (1.27, 1.69)	
≥15	2613	185 (13.2)	267 (22.0)	1.43 (1.14, 1.79)	
UA at baseline, μmol/L					0.283
<267	5251	163 (5.8)	245 (10.1)	1.70 (1.38, 2.11)	
≥267	5360	440 (17.7)	815 (28.3)	1.49 (1.29, 1.71)	
eGFR, mL/min/1.73㎡					0.240
<90	2798	264 (17.6)	352 (27.2)	1.32 (1.09, 1.61)	
≥90	7655	333 (8.9)	697 (17.7)	1.53 (1.31, 1.78)	
Diabetes					0.978
No	8997	538 (11.6)	897 (20.6)	1.47 (1.29, 1.67)	
Yes	1463	60 (10.3)	154 (17.4)	1.48 (1.05, 2.08)	
Diuretics usage during the treatment period					0.198
No	4218	201 (9.3)	300 (14.7)	1.30 (1.06, 1.59)	
Yes	6393	402 (12.8)	760 (23.3)	1.52 (1.31, 1.77)	

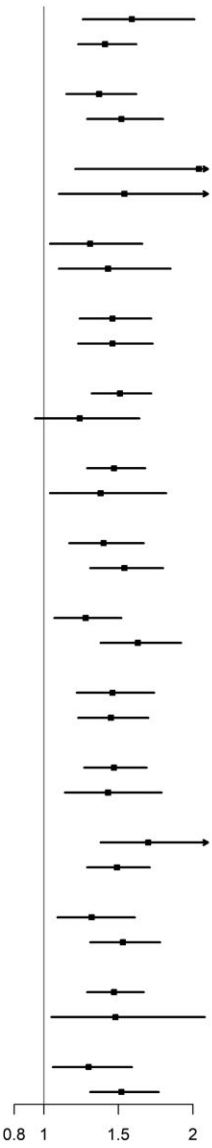

Figure 2. Stratified analyses of the association between BMI (<25 vs. ≥25 kg/m^2) and new-onset hyperuricemia[a]. [a]Adjusted for, if not stratified, treatment group, age, sex, uric acid (UA), fasting glucose, total cholesterol, triglycerides (TG), total homocysteine (tHcy), high-density lipoprotein cholesterol (HDL), estimated glomerular filtration rate (eGFR), smoking and drinking status, use of antihypertensive drugs, SBP at baseline and time-averaged on-treatment SBP during treatment period. Diabetes was defined as self-reported physician-diagnosed diabetes or the use of glucose-lowering drugs or fasting glucose concentrations ≥7.0 mmol/l at baseline.

greater influence on WC. Therefore, BMI may possibly be a more appropriate index of total and abdominal fat in Asian population.[30,31] Accordingly, Retnakaran *et al.*[32] reported that BMI has a much greater effect on insulin resistance in pregnancy in Asian women than in Caucasians. Sakamoto *et al.*[33] further found that the significantly positive BMI & insulin sensitivity association was independent of WC. However, the positive WC & insulin sensitivity relation did not remain significant after controlling BMI. Since insulin resistance has potential to increase the UA levels,[27] we speculate that the different effect between BMI and WC on new-onset hyperuricemia might derive from the difference in insulin resistance between BMI and WC. Nevertheless, the detailed underlying mechanisms still need to be further examined in more studies.

Third, in our study, the stronger positive BMI and new-onset hyperuricemia association is found in those participants with higher time-average on-treatment SBP. Ryu *et al.*[15] demonstrated that high BP was significantly associated with the development of hyperuricemia in middle-aged South Korean men. Consistently, Kuwabara *et al.*[34] also found that hypertension was one of the most important risk factors for hyperuricemia in Japanese adults. The possible explanation is that hypertension may cause renal vascular resistance, along with decreased renal blood flow. When renal blood flow decreases, proximal sodium and UA absorption increase, which may contribute to raising serum UA levels.[35] As such, we speculate that higher BMI and higher time-average on-treatment SBP could jointly increase the risk of hyperuricemia. Therefore, the combination of controlled BP and lower BMI may be a better strategy for the

prevention of new-onset hyperuricemia in hypertensive patients. However, more studies are needed to verify this hypothesis and further investigate the underlying mechanisms.

Inevitably, the study has some limitations. First, serum UA levels of the study participants were only assessed at the baseline and exit visits. More frequent measurements of serum UA levels would allow for a more accurate assessment of the BMI and new-onset hyperuricemia. Second, the CSPPT was conducted in Chinese hypertensive participants, the generality of the results to other populations remains to be determined. Third, our study is a *post hoc* analysis. We cannot exclude any potential residual confounding from unrecorded or unmeasured risk factors.

In conclusion, our study found that higher BMI, but not WC, is significantly and independently associated with a higher risk of new-onset hyperuricemia in Chinese hypertensive population without hyperuricemia at baseline, especially in those with higher SBP during the treatment period. If further confirmed, BMI measurements along with other known risk factors, would further help identify hypertensive patients at high risk of developing hyperuricemia.

Supplementary material

Supplementary material is available at *QJMED* online.

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References

1. Liu R, Han C, Wu D, Xia X, Gu J, Guan H, *et al.* Prevalence of hyperuricemia and gout in Mainland China from 2000 to 2014: a systematic review and meta-analysis. *Biomed Res Int* 2015; **2015**:1–12.
2. Neogi T. Gout. *N Engl J Med* 2011; **364**:443–52.
3. Li M, Hou W, Zhang X, Hu L, Tang Z. Hyperuricemia and risk of stroke: a systematic review and meta-analysis of prospective studies. *Atherosclerosis* 2014; **232**:265–70.
4. Li L, Yang C, Zhao Y, Zeng X, Liu F, Fu P. Is hyperuricemia an independent risk factor for new-onset chronic kidney disease? A systematic review and meta-analysis based on observational cohort studies. *BMC Nephrol* 2014; **15**:122.
5. Kleber ME, Delgado G, Grammer TB, Silbernagel G, Huang J, Kramer BK, *et al.* Uric acid and cardiovascular events: a Mendelian randomization study. *J Am Soc Nephrol* 2015; **26**: 2831–8.
6. Liu M, Zhang Z, Zhou C, He P, Nie J, Liang M, *et al.* Relationship of body mass index and waist circumference with risk of new-onset proteinuria in hypertensive patients. *J Clin Endocrinol Metab* 2020; **105**: dgaa026.
7. He M, Qin X, Cui Y, Cai Y, Sun L, Xu X, *et al.* Prevalence of unrecognized lower extremity peripheral arterial disease and the associated factors in Chinese hypertensive adults. *Am J Cardiol* 2012; **110**:1692–8.
8. Qin X, Li J, Zhang Y, Ma W, Fan F, Wang B, *et al.* Prevalence and associated factors of diabetes and impaired fasting glucose in Chinese hypertensive adults aged 45 to 75 years. *PLoS One* 2012; **7**:e42538.
9. Zhang Y, Gu YA, Wang N, Zhao Q, Ng N, Wang R, *et al.* Association between anthropometric indicators of obesity and cardiovascular risk factors among adults in Shanghai, China. *BMC Public Health* 2019; **19**:1035.
10. Dong J, Ni YQ, Chu X, Liu YQ, Liu GX, Zhao J, *et al.* Association between the abdominal obesity anthropometric indicators and metabolic disorders in a Chinese population. *Public Health* 2016; **131**:3–10.
11. Remedios C, Shah M, Bhasker AG, Lakdawala M. Hyperuricemia: a reality in the Indian obese. *Obes Surg* 2012; **22**:945–8.
12. Choi HK, McCormick N, Lu N, Rai SK, Yokose C, Zhang Y. Population impact attributable to modifiable risk factors for hyperuricemia. *Arthritis Rheumatol* 2020; **72**:157–65.
13. Kim IY, Han K, Kim DH, Eun Y, Cha H, Koh E, *et al.* Women with metabolic syndrome and general obesity are at a higher risk for significant hyperuricemia compared to men. *J Clin Med* 2019; **8**:837.
14. Han QX, Zhang D, Zhao YL, Liu L, Li J, Zhang F, *et al.* Risk factors for hyperuricemia in Chinese centenarians and near-centenarians. *Clin Interv Aging* 2019; **14**:2239–47.
15. Ryu S, Chang Y, Zhang Y, Kim SG, Cho J, Son HJ, *et al.* A cohort study of hyperuricemia in middle-aged South Korean men. *Am J Epidemiol* 2012; **175**:133–43.
16. Nakanishi N, Yoshida H, Nakamura K, Suzuki K, Tatara K. Predictors for development of hyperuricemia: an 8-year longitudinal study in middle-aged Japanese men. *Metabolism* 2001; **50**:621–6.
17. Redon P, Maloberti A, Facchetti R, Redon J, Lurbe E, Bombelli M, *et al.* Gender-related differences in serum uric acid in treated hypertensive patients from central and east European countries: findings from the Blood Pressure control rate and CArdiovascular Risk profilE study. *J Hypertens* 2019; **37**:380–8.
18. Qin X, Li Y, He M, Tang G, Yin D, Liang M, *et al.* Folic acid therapy reduces serum uric acid in hypertensive patients: a substudy of the China Stroke Primary Prevention Trial (CSPPT). *Am J Clin Nutr* 2017; **105**:882–9.
19. Qin X, Spence JD, Li J, Zhang Y, Li Y, Sun N, *et al.* Interaction of serum vitamin B12 and folate with MTHFR genotypes on risk of ischemic stroke. *Neurology* 2020; **94**:e1126–36.
20. Qin X, Shen L, Zhang R, Li Y, Wang X, Wang B, *et al.* Effect of folic acid supplementation on cancer risk among adults with hypertension in China: a randomized clinical trial. *Int J Cancer* 2017; **141**:837–47.

21. Qin X, Li J, Zhang Y, Chen D, Wang B, He M, *et al*. Effect of folic acid supplementation on risk of new-onset diabetes in adults with hypertension in China: findings from the China Stroke Primary Prevention Trial (CSPPT). *J Diabetes* 2016; **8**:286–94.
22. Huo Y, Li J, Qin X, Huang Y, Wang X, Gottesman RF, *et al*. Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. *JAMA* 2015; **313**:1325–35.
23. Qin X, Zhang Y, Cai Y, He M, Sun L, Fu J, *et al*. Prevalence of obesity, abdominal obesity and associated factors in hypertensive adults aged 45-75 years. *Clin Nutr* 2013; **32**:361–7.
24. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AR, Feldman HI, *et al*.; for the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**:604–12.
25. Cao J, Zhang J, Li Q, Jiang C, Song Y, Liu C, *et al*. Serum phosphate and the risk of new-onset hyperuricemia in hypertensive patients. *Hypertension* 2019; **74**:102–10.
26. Cao J, Zhang J, Zhang Y, Li H, Jiang C, Lin T, *et al*. Plasma magnesium and the risk of new-onset hyperuricaemia in hypertensive patients. *Br J Nutr* 2020; 1–8. doi:10.1017/S0007114520001099
27. Facchini F, Chen YD, Hollenbeck CB, Reaven GM. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. *JAMA* 1991; **266**:3008–11.
28. Tsushima Y, Nishizawa H, Tochino Y, Nakatsuji H, Sekimoto R, Nagao H, *et al*. Uric acid secretion from adipose tissue and its increase in obesity. *J Biol Chem* 2013; **288**:27138–49.
29. Ishizaka N, Ishizaka Y, Toda A, Tani M, Koike K, Yamakado M, *et al*. Changes in waist circumference and body mass index in relation to changes in serum uric acid in Japanese individuals. *J Rheumatol* 2010; **37**:410–6.
30. Xie L, Wang B, Jiang C, Zhang X, Song Y, Li Y, *et al*. BMI is associated with the development of chronic kidney diseases in hypertensive patients with normal renal function. *J Hypertens* 2018; **36**:2085–91.
31. Sakurai M, Takamura T, Miura K, Kaneko S, Nakagawa H. BMI may be better than waist circumference for defining metabolic syndrome in Japanese women. *Diabetes Care* 2008; **31**:e12.
32. Retnakaran R, Hanley AJG, Connelly PW, Sermer M, Zinman B. Ethnicity modifies the effect of obesity on insulin resistance in pregnancy: a comparison of Asian, South Asian, and Caucasian women. *J Clin Endocrinol Metab* 2006; **91**:93–7.
33. Sakamoto A, Ishizaka Y, Toda E, Nagai R, Koike K, Yamakado M, *et al*. Impact of changes in obesity parameters on glucose metabolism and insulin resistance over a one-year period. *J Atheroscler Thromb* 2010; **17**:1246–55.
34. Kuwabara M, Borghi C, Cicero AFG, Hisatome I, Niwa K, Ohno M, *et al*. Elevated serum uric acid increases risks for developing high LDL cholesterol and hypertriglyceridemia: a five-year cohort study in Japan. *Int J Cardiol* 2018; **261**:183–8.
35. Messerli FH, Frohlich ED, Dreslinski GR, Suarez DH, Aristimuno GG. Serum uric acid in essential hypertension: an indicator of renal vascular involvement. *Ann Intern Med* 1980; **93**:817–21.