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Association between hyperuricemia and hypertension and the mediatory role of obesity: a large cohort study in China

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SUMMARY

OBJECTIVE: This study aimed to investigate the sex-specific association between hyperuricemia and the risk of hypertension and whether obesity mediates this association.

METHODS: This study included 31,395 (47.0% women) adults without hypertension, cardiovascular disease, or cancer at baseline who completed at least one follow-up annual examination between 2009 and 2016. Cox regression models were performed to calculate hazard ratios and 95% confidence intervals. Mediation analysis was conducted to estimate the effect of body mass index on the association between hyperuricemia and hypertension.

RESULTS: During a median 2.9-year follow-up, hyperuricemia was significantly associated with a higher risk of hypertension (HR 1.15, 95%CI 1.07–1.24 for all participants; HR 1.12, 95%CI 1.03–1.22 for men; and HR 1.23, 95%CI 1.02–1.48 for women) after adjustment for potential confounders. Additional adjustment for body mass index attenuated this association (HR 1.09, 95%CI 1.08–1.10 for all participants; HR 1.07; 95%CI 0.98–1.16 for men; HR 1.18; 95%CI 0.96–1.44 for women). Mediation analysis showed that BMI partially mediated the relationship between hyperuricemia and incident hypertension (indirect effect HR 1.09, 95%CI 1.08–1.10; direct effect: HR 1.08, 95%CI 1.02–1.15). The percentage of the mediation effect was 53.2% (95%CI 37.9–84.5).

CONCLUSION: Hyperuricemia is associated with a risk of hypertension in both sexes, and BMI partially mediates hyperuricemia-related incident hypertension.

KEYWORDS: Uric acid. Hypertension. Obesity. Mediation analysis.

INTRODUCTION

Hypertension is a modifiable risk factor for cardiovascular disease[1]. The China Health and Nutrition Survey of 451,755 adults showed that the prevalence of hypertension was 27.9% in China in 2015[2]. In 2010, the global number of people with hypertension was estimated at 1.4 million, and this number is expected to increase to more than 1.6 million by 2025[3].

Serum uric acid (SUA) is the end product of endogenous and dietary purine metabolism[4]. Experimental evidence has suggested that high SUA levels cause damage to renal microcirculation, tubulointerstitial injury, chronic low-grade inflammation, and endothelial dysfunction and promote the development of hypertension[5,6]. Previous observational studies have shown that an elevated SUA concentration may be associated with an increased risk of hypertension[7-13]. However, studies have reported inconsistent results regarding sex-specific differences in the association between SUA concentration and hypertension[8,11,13,14]. Some of these studies showed a significant association in both sexes[8,11,13], and others showed a significant association in women but not in men[14]. Additionally, limited data are available on the interaction of SUA and sex regarding hypertension. Although changes in obesity have been reported to be independently associated with changes in uric acid concentrations, previous metabolic studies and pathophysiology imply a possible interaction between them[15]. A cross-sectional study showed that body mass index (BMI) increased significantly with elevated SUA in 27,009 Chinese middle-aged and older adults[16]. There is also strong evidence from studies showing a positive association between SUA concentrations and obesity in different populations[17-20]. Obesity is an established

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risk factor for hypertension[21]. Therefore, obesity may play a mediatory role in the relationship between hyperuricemia and hypertension. However, this relation remains unclear. There are also no studies demonstrating that BMI as a mediator affects the relationship between SUA and hypertension.

Therefore, we prospectively investigated the sex-specific difference in the association between hyperuricemia and incident hypertension in a large Chinese cohort study. We also examined the mediation effect of BMI on the association between hyperuricemia and the risk of incident hypertension.

METHODS

Study population

This cohort analysis was based on a large ongoing health examination in China called the Xiaotangshan Health Examination Study. In this study, participants without hypertension at first entry were included in the analysis (n=33,529). We excluded 1,045 adults with missing data on SUA levels at baseline. We also excluded 779 adults with a history of myocardial infarction, stroke, coronary heart disease, or heart failure and 310 adults with cancer at baseline. Finally, data from 31,395 adults were analyzed. The Institutional Review Board of Xiaotangshan Hospital approved this study.

Diagnosis of hypertension and baseline serum uric acid measurement

Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or the use of anti-hypertension medication according to the National High Blood Pressure Education Program[22]. Hyperuricemia was defined as an SUA concentration ≥7.0 mg/dL for men and ≥6.0 mg/dL for women[23].

Measurement of covariates

Data regarding demographic characteristics, medical history, and the use of medications were collected through a face-to-face standardized questionnaire interview. Anthropometry and clinical and biochemical measures were collected by trained staff. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. Overnight fasting blood samples were obtained (at least 8 h of fasting). SUA, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) concentrations were measured by an enzymatic colorimetric assay (Type 7600; Hitachi, Tokyo). Fasting plasma glucose (FPG) and alanine aminotransferase (ALT) concentrations were measured using an automated analyzer. Serum creatinine concentrations were measured using the enzymatic method. The estimated glomerular filtration rate (eGFR) was evaluated using an equation developed by adaptation of the Modification of Diet in Renal Disease equation[24]. This equation was as follows: eGFR (mL/min/1.73 m^2)=175×creatinine$^{-1.234}$×age$^{-0.179}$ (if women, ×0.79), where creatinine is the serum creatinine concentration (denoted in mg/dL) and age is denoted in years.

Statistical analyses

The main characteristics of the study population are described by hyperuricemia at baseline or incident hypertension at follow-up (yes or no). Descriptive data are presented as the mean (standard derivation) for normally distributed continuous variables and the median (interquartile range) for skewed continuous variables. Between-group differences in the main characteristics were evaluated using the Student's t-test for normally distributed variables or the Mann-Whitney U test for skewed variables.

The follow-up time was defined as the period between the visit at first entry and the last confirmed follow-up or the date when an event occurred. The associations of hyperuricemia (yes or no) and the risk of hypertension in the overall population, for men and women, were analyzed using Cox proportional hazards models. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. The following models were used with adjustment for increasing degrees of potential confounders.

Mediation analysis using the natural effect model proposed by Lange et al.[25] was performed to address whether the hyperuricemia–hypertension association could be explained by BMI.

Two sensitivity analyses were performed as follows: exclusion of participants aged ³75 years (n=348) and those with hypertension that occurred in the first 2 years of follow-up (n=2,736). All statistical analyses were performed using R 3.5.2 (R Foundation), and a two-sided P<0.05 was considered statistically significant.

RESULTS

Baseline characteristics

The mean age of the participants was 40.00±11.71 years, and 47.0% were women. During a median follow-up of 2.9 years (total person-years: 100,580), 5,023 (16.0%) participants developed hypertension, of whom 3,729 (22.4%) were men and 1,294 (8.8%) were women. The mean SUA level

was significantly higher in men (6.22±1.24 mg/dL) than in women (4.42±0.95 mg/dL) (P<0.001) who had a higher BMI, age, systolic and diastolic blood pressure, and concentrations of creatinine, TC, TG, and LDL-C and had a lower HDL-C concentration and eGFR compared with those without hyperuricemia (all P<0.05) (Table 1).

Table 1. Baseline characteristics of the study population by hyperuricemia and hypertension.

	Hyperuricemia			Hypertension		
	Yes (n=4,943)	No (n=26,452)		Yes (n=5,023)	No (n=26,372)	
Men						
n	4,043	12,587		3,729	12,901	
Age (years)	40.76 (12.48)	41.63 (12.04)	<0.001	45.78 (13.27)	40.16 (11.51)	<0.001
Heart rate (beats/min)	75.44 (9.83)	74.69 (9.53)	<0.001	76.17 (9.57)	74.50 (9.59)	<0.001
BMI (kg/m^2)	26.53 (3.03)	25.07 (3.05)	<0.001	26.69 (3.09)	25.06 (3.02)	<0.001
Weight (kg)	79.24 (10.65)	74.35 (10.16)	<0.001	78.93 (10.83)	74.56 (10.18)	<0.001
Blood pressure (mmHg)						
Systolic	118.07 (10.11)	116.64 (10.53)	<0.001	122.42 (8.87)	115.43 (10.34)	<0.001
Diastolic	75.00 (7.21)	73.37 (7.48)	<0.001	78.52 (6.12)	72.41 (7.23)	<0.001
SUA (mg/dL)	7.88 (0.78)	5.69 (0.82)	<0.001	6.40 (1.32)	6.17 (1.22)	<0.001
FPG (mmol/L)	5.42 (0.92)	5.47 (1.21)	0.002	5.76 (6.12)	5.38 (7.23)	<0.001
TC (mmol/L)	5.04 (0.94)	4.78 (0.89)	<0.001	5.06 (1.41)	4.78 (1.04)	<0.001
TG (mmol/L)	2.22 (1.76)	1.63 (1.26)	<0.001	2.10 (0.93)	1.68 (0.89)	<0.001
HDL-C (mmol/L)	1.21 (0.26)	1.28 (0.28)	<0.001	1.25 (1.73)	1.27 (1.31)	<0.001
LDL-C (mmol/L)	3.13 (0.75)	2.97 (0.73)	<0.001	3.13 (0.27)	2.97 (0.28)	<0.001
Albumin (g/L)	45.69 (3.02)	45.35 (3.06)	<0.001	45.24 (3.01)	45.49 (3.06)	<0.001
ALT (IU/L)	26.6 (19.0–39.1)	21.2 (16.0–30.0)	<0.001	25.0 (18.4–35.8)	22.0 (16.0–31.0)	<0.001
Women						
n	900	13,865		1,294	13,471	
Age (years)	42.83 (14.75)	38.01 (10.6)	<0.001	48.34 (13.27)	37.34 (11.51)	<0.001
Heart rate (beats/min)	76.12 (9.9)	76.33 (9.74)	0.522	76.67 (9.57)	76.29 (9.59)	<0.001
BMI (kg/m^2)	25.48 (3.66)	22.83 (3.11)	<0.001	25.28 (3.09)	22.78 (3.02)	<0.001
Weight (kg)	65.61 (10.01)	59.02 (8.39)	<0.001	64.38 (10.83)	58.95 (10.18)	<0.001
Blood pressure (mmHg)			<0.001			<0.001
Systolic	113.79 (11.64)	108.79 (11.48)	<0.001	120.6 (8.87)	108 (10.34)	<0.001
Diastolic	72.08 (7.93)	68.24 (7.85)	<0.001	76.67 (6.12)	67.69 (7.23)	<0.001
SUA (mg/L)	6.62 (0.62)	4.28 (0.78)	<0.001	4.84 (1.32)	4.38 (1.22)	<0.001
FPG (mmol/L)	5.36 (0.91)	5.08 (0.65)	<0.001	5.43 (1.41)	5.06 (1.04)	<0.001
TC (mmol/L)	5.18 (1.05)	4.63 (0.88)	<0.001	5.12 (0.93)	4.62 (0.89)	<0.001
TG (mmol/L)	1.65 (1.15)	1.05 (0.68)	<0.001	1.42 (1.73)	1.06 (1.31)	<0.001
HDL-C (mmol/L)	1.4 (0.3)	1.54 (0.34)	<0.001	1.47 (0.27)	1.54 (0.28)	<0.001
LDL-C (mmol/L)	3.2 (0.86)	2.73 (0.72)	<0.001	3.11 (0.74)	2.72 (0.73)	<0.001
eGFR (mL/min/1.73 m^2)	95.66 (23.63)	106.97 (24.18)	<0.001	95.49 (17.25)	107.32 (17.92)	<0.001
Albumin (g/L)	44.51 (3.04)	44.37 (3.18)	0.245	43.9 (3.01)	44.43 (3.06)	<0.001
ALT (IU/L)	18.0 (13.0–26.0)	13.7 (11.0–18.0)	<0.001	16.7 (13.0–22.58)	13.5 (11.0–18.0)	<0.001

Data are mean (SD) or median (IQR). BMI: body mass index; SUA: serum uric acid; FPG: fast plasma glucose; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate; ALT: alanine aminotransferase.

Association between hyperuricemia and hypertension

In the age- and sex-adjusted Cox model, hyperuricemia was significantly associated with an increased risk of hypertension (HR 1.43, 95%CI 1.34–1.52; P<0.001). After adjusting for age, sex, heart rate, systolic blood pressure, eGFR, and concentrations of FPG, TC, TG, HDL-C, albumin, and ALT at baseline, this association was weakened but remained significant (HR 1.15, 95%CI 1.07–1.24; P<0.001). Further adjustment for BMI attenuated this association (Table 2).

In the sex-specific analysis, we used the Cox proportional hazards model to assess men and women separately. The age-adjusted Cox regression model showed a significant association in men (HR 1.34, 95%CI 1.25–1.44; P<0.001) and women (HR 1.60, 95%CI 1.36–1.88; P<0.001). After adjusting for mixed factors at baseline, this association was weakened but remained significant for both sexes (HR 1.12, 95%CI 1.03–1.22; P=0.007 for men; HR 1.23, 95%CI 1.02–1.48; P=0.034 for women). (Table 1).

Mediation analysis

In mediation analysis (Figure 1), the total effect of hyperuricemia on hypertension was significant (HR 1.18, 95%CI 1.11–1.26). BMI partially mediated the relationship between hyperuricemia and hypertension, which indicated a significant indirect effect (HR 1.09; 95%CI 1.08–1.10) and a significant

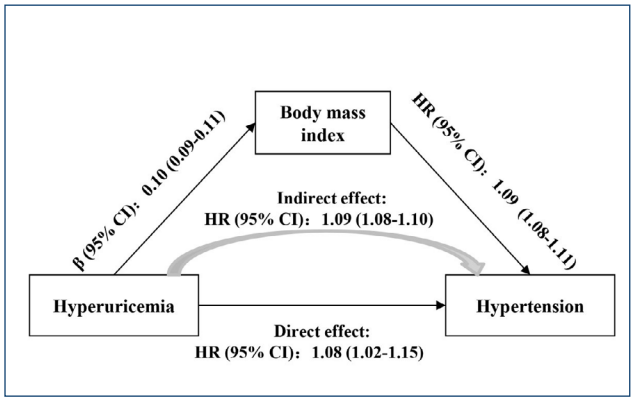

Figure 1. Mediation analysis to determine the relationship between hyperuricemia and hypertension through body mass index (kg/m²).

Table 2. Association between hyperuricemia and risk of incident hypertension.

	Whole cohort		Sensitivity analysis[d]		Sensitivity analysis[e]	
	Hazard ratio (95%CI)	P-value	Hazard ratio (95%CI)	P-value	Hazard ratio (95%CI)	P-value
Overall						
Model 1[a]	1.43 (1.34–1.52)	<0.001	1.44 (1.35–1.54)	<0.001	1.44 (1.31–1.59)	<0.001
Model 2[b]	1.15 (1.07–1.24)	<0.001	1.17 (1.09–1.27)	<0.001	1.19 (1.06–1.33)	0.003
Model 3[c]	1.10 (1.02–1.19)	0.018	1.11 (1.03–1.20)	0.007	1.14 (1.01–1.28)	0.032
Men						
Model 1[a]	1.34 (1.25–1.44)	<0.001	1.36 (1.27–1.46)	<0.001	1.40 (1.26–1.56)	<0.001
Model 2[b]	1.12 (1.03–1.22)	0.007	1.14 (1.05–1.24)	0.002	1.20 (1.06–1.36)	0.004
Model 3[c]	1.07 (0.98–1.16)	0.131	1.08 (0.99–1.18)	0.066	1.15 (1.01–1.31)	0.034
Women						
<50 years						
Model 1[a]	1.37 (1.27–1.47)	<0.001	1.37 (1.27–1.47)	<0.001	1.20 (1.10–1.31)	<0.001
Model 2[b]	1.26 (1.16–1.37)	<0.001	1.26 (1.16–1.37)	<0.001	1.29 (1.16–1.43)	<0.001
Model 3[c]	1.18 (1.07–1.29)	<0.001	1.18 (1.07–1.29)	<0.001	1.25 (1.11–1.40)	<0.001
≥50 years						
Model 1[a]	1.17 (1.09–1.27)	<0.001	1.19 (1.10–1.30)	<0.001	1.42 (1.27–1.59)	<0.001
Model 2[b]	1.12 (1.02–1.24)	0.017	1.13 (1.02–1.25)	0.018	1.23 (1.07–1.41)	0.003
Model 3[c]	1.12 (1.01–1.24)	0.031	1.13 (1.02–1.26)	0.023	1.16 (1.00–1.34)	0.052

CI: confidence interval; HR: hazard ratio. HR (95%CI) was presented in the Cox proportional model. [a]Model 1: adjusted for age at baseline. [b]Model 2: adjusted for age, heart rate, systolic blood pressure, fast plasma glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, estimated glomerular filtration rate, serum albumin, and alanine aminotransferase at baseline. [c]Model 3: adjusted for BMI plus all the variables in model 2. [d]Sensitivity analysis 1: excluding participants aged >75 years at baseline (n=348). [e]Sensitivity analysis 2: excluding participants without hypertension that occurred in the first 2 years of follow-up (n=2,736).

direct effect (HR 1.08, 95%CI 1.02–1.15). The percentage of the mediation effect was 53.2% (95%CI 37.9–84.5).

Sensitivity analysis

Participants aged >75 years were then excluded due to a substantial potential risk of other comorbidities, but this sensitivity analysis did not obviously affect any of the associations (Table 2). In mediation analysis, the total effect of hyperuricemia on hypertension was significant (HR 1.20; 95%CI 1.13–1.27). BMI partially mediated the relationship between hyperuricemia and hypertension (indirect effect: HR 1.09; 95%CI 1.08–1.10; direct effect: HR 1.10; 95%CI 1.03–1.17). The percentage of the mediation effect was 49.1% (95%CI 36.1–75.6).

We conducted a sensitivity analysis by excluding participants who developed hypertension in the first 2 years of follow-up. This analysis showed a slightly attenuated effect of hyperuricemia on hypertension (Table 2). In mediation analysis, the total effect of hyperuricemia on hypertension was significant (HR 1.27; 95%CI 1.16–1.38). BMI partially mediated the relationship between hyperuricemia and hypertension (indirect effect: HR 1.08; 95%CI 1.07–1.10; direct effect: HR 1.17; 95%CI 1.07–1.29).

In general, the mean of menopause is 50 years[26]. In addition, we performed a subgroup analysis of women's age with a cutoff of 50 years. In a mediation analysis of a population of women <50 years of age, the total effect of hyperuricemia on hypertension was significant (HR 1.30; 95%CI 1.19–1.43). BMI partially mediated the association between hyperuricemia and hypertension (indirect effect: HR 1.18; 95%CI 1.07–1.30; direct effect: HR 1.10; 95%CI 1.07–1.13). The total effect of hyperuricemia on hypertension was significant when women were ³50 years of age (HR 1.16; 95%CI 1.04–1.32). BMI partially mediated the association between hyperuricemia and hypertension (indirect effect: HR 1.13; 95%CI 1.02–1.27; direct effect: HR 1.03; 95%CI 1.00–1.08).

DISCUSSION

This study showed that hyperuricemia was associated with an increased risk of incident hypertension in men and women. BMI partially mediated the association between hyperuricemia and incident hypertension.

SUA levels are different between men and women, but inconsistent findings were found regarding the sex-specific difference in this association. Our study showed a significant association between hyperuricemia and the risk of hypertension in both sexes, which is consistent with previous studies[9,11,13]. We also observed that sex did not modify the association between hyperuricemia and the risk of hypertension. This finding is inconsistent with a cohort study in the USA[14].

This study is the first to examine the mediation effect of BMI on the association between hyperuricemia and the development of hypertension. This finding is critically important to prevent or alleviate hyperuricemia-related hypertension.

The strengths of this study include a large sample size and adequate adjustment for a broad range of potential well-measured confounders. However, the limitations of our study should also be considered. Some confounders were not collected, such as smoking, alcohol drinking, physical activity, and a family history of hypertension, although we controlled for a series of well-measured cardiovascular risk factors. However, an experimental study[27] showed that the ingestion of fructose increased SUA concentrations and caused mitochondrial oxidative stress, thereby stimulating fat accumulation. A population-based study[20] used cross-lagged panel analysis to examine the temporal relationship between hyperuricemia and obesity. Future research is required using multiple time points to investigate the temporal relationship between hyperuricemia and obesity.

In conclusion, hyperuricemia is significantly associated with an increased risk of hypertension for both sexes, and obesity partially mediates the association between hyperuricemia and hypertension. However, the generalizability of our findings is limited because we studied a highly educated Chinese population. Future cohort studies in other ethnic populations are required to further confirm our findings.

DATA AVAILABILITY STATEMENT

Derived data supporting the findings of this study are available from the corresponding author [YLo] on request.

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AUTHORS' CONTRIBUTIONS

CW: Conceptualization, Methodology, Writing – review & editing. **PQ:** Conceptualization, Methodology, Writing – original draft. **YLi:** Formal Analysis, Visualization. **LW:** Formal Analysis, Software. **SX:** Supervision. **HC:** Methodology, Supervision. **SD:** Methodology, Project administration. **PZ:** Data curation. **FH:** Resources, Validation. **YLo:** Funding acquisition, Investigation, Resources.

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