Association between Serum Uric Acid and Hypertension in Han and Yugur of Gansu Province: The China National Health Survey

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Keywords

Serum uric acid · Blood pressure · Hypertension · Yugur people · China National Health Survey

Abstract

Introduction: Serum uric acid (SUA) has been found correlated with an increased risk of hypertension, but evidence is sparse regarding the association in Gansu Province, especially in Yugur people. This study aimed to explore the non-linear relationship between SUA levels and hypertension in Han and Yugur people in China. **Methods:** The cross-sectional study samples ($n = 5,327$) were from the China National Health Survey (CNHS) in Gansu Province. Participants were selected using a multistage stratified cluster sampling method. SUA was measured by enzymatic methods. The restricted cubic spline regression was performed to evaluate the shape of the association. **Results:** The overall prevalence of hypertension and hyperuricemia was 28.4% and 17.0%, respectively, in this study. Comparing the highest ($>416.4 \mu\text{mol/L}$) to the lowest ($<254.1 \mu\text{mol/L}$) SUA level groups, the multivariable adjusted differences and 95% confidence intervals (CIs) in blood pressure (BP) were 6.15 (4.22, 8.08) mm Hg and 4.87 (3.51, 6.23) mm Hg for SBP and DBP in Han, and 2.22 (–0.73, 5.18) mm Hg and 2.56 (0.38, 4.75) mm Hg for SBP

and DBP in Yugur people, respectively. The corresponding odds ratios (95% CIs) for hypertension were 3.16 (2.26, 4.43) and 2.37 (1.46, 3.89) in Han and Yugur people, respectively. The restricted cubic spline regression models illustrated that both BP level and the risk of hypertension increased with elevated SUA levels in Han and Yugur people. **Conclusions:** SUA was significantly and independently associated with an increased risk of hypertension in Han and Yugur people. Prospective studies are needed to confirm these findings.

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Introduction

Hypertension is an important global public-health challenge due to its high prevalence and concomitant risks of other cardiovascular and chronic kidney diseases [1]. In China, the prevalence of hypertension was 29.6% among adults in 2012 [2]. Deaths caused by high blood pressure (BP) accounted for 24.6% of all the deaths in China in 2010 [3]. It is extremely important to identify individuals who are at high risk of hypertension.

Serum uric acid (SUA) has been found correlated with increased risk of hypertension, diabetes, renal failure, obesity, and metabolic syndrome [4–10]. Recent experi-

mental studies also suggested that SUA could have a contributory role in the pathogenesis of hypertension [11, 12]. The potential mechanisms included inhibition of nitric oxide, activation of the renin-angiotensin system, induction of oxidative stress, vascular smooth muscle cell proliferation, endothelial cell dysfunction, and inflammation [13, 14]. Although an elevated SUA level is known to be correlated with cardiovascular events in hypertensive patients, it is still unclear whether hyperuricemia is the causal factor in hypertension or whether it is only a marker of a cardiovascular disease [15, 16].

Yugur is a minority of Gansu Province located in northwest China. Compared with Han, the dietary pattern of Yugur people tends to be traditionally rich in beef, mutton, and alcohol, which might increase the risk of hyperuricemia and hypertension. The prevalence of hyperuricemia and hypertension in Yugur was higher than that in Han [17, 18]. However, evidence is sparse regarding the association between SUA and hypertension in Gansu Province, China [19], especially in Yugur people. Therefore, the present study aimed to examine the ethnic-specific associations between SUA and hypertension in Han and Yugur people.

Materials and Methods

Study Design and Population

The data of this cross-sectional study were derived from the China National Health Survey (CNHS) in the Gansu province in 2016, which was conducted by the Institute of Basic Medical Sciences (IBMS), Chinese Academy of Medical Sciences (CAMS), and School of Basic Medicine, Peking Union Medical College (PUMC). Details of the sampling procedure have been described elsewhere [20]. In brief, a multistage stratified cluster sampling method was used. Four districts of Gansu Province were selected including Chengguan district of Lanzhou, Ganzhou district of Zhangye, Yugur Autonomous County of Sunan, and Gaotai County. We recruited a total of 5,884 eligible Han and Yugur participants aged 20–80 years who had been living in Gansu Province for at least one year. The research was approved by the Institutional Review Board of the IBMS, CAMS, and conducted in accordance with the ethical principles of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

The inclusion criteria for participant recruitment were (1) aged 20–80 and (2) local residency for at least one year. Participants who had no history of hypertension and BP measurements ($n = 7$), or had urinary diseases ($n = 506$) or gout ($n = 33$) that may affect the level of SUA, or had missing values on SUA ($n = 11$) were excluded. Participants who took medication for hypertension were also excluded when we examined the relationship between SUA and BP.

Measures and Procedures

Blood Pressure

BP was measured three times using the Omron digital BP measuring device (HEM907, Kyoto, Japan) on the right upper arm af-

ter participants had been seated and resting quietly for at least five minutes with feet on the ground and back supported. The average of three measurements was used as mean BP for analysis. Hypertension was defined as mean systolic BP (SBP) ≥ 140 mm Hg and/or mean diastolic BP (DBP) ≥ 90 mm Hg or self-report hypertension diagnosis [21, 22].

Serum Uric Acid

A fasting blood sample was collected from each participant after at least eight hours fasting overnight. SUA was measured by enzymatic methods (Chemistry Analyzer ROCHE Cobas 8000 C701, USA) and categorized into four groups by quartiles as follows: 1st, <254.1 $\mu\text{mol/L}$; 2nd, 254.1 – 303.7 $\mu\text{mol/L}$; 3rd, 303.8 – 365.7 $\mu\text{mol/L}$; and 4th, >365.7 $\mu\text{mol/L}$. To capture individuals who meet the criteria for hyperuricemia, the 4th group was further split into two groups (365.8 – 416.4 $\mu\text{mol/L}$ and >416.4 $\mu\text{mol/L}$). Hyperuricemia was defined as SUA levels >416.4 $\mu\text{mol/L}$ (7.0 mg/dL) in men and >356.9 $\mu\text{mol/L}$ (6.0 mg/dL) in women [23].

Covariates

Using the unified questionnaire, data on demographic information, hypertension history, medication history of hypertension, family history of hypertension, smoking status, alcohol consumption, and occupational and leisure-time physical activity were collected by face-to-face interview. Ethnicity was verified by identity certification and categorized as Han and Yugur people. A person was considered Han or Yugur only if he/she had the same ethnicity with both his/her parents. Height and weight were measured with light clothing and without shoes. Height was measured to the nearest 0.1 cm using a fixed stadiometer, and weight was measured to the nearest 0.1 kg with a body composition analyzer (BC-420; TANITA, Tokyo, Japan). According to the World Health Organization [24], body mass index (BMI) was defined as weight in kilograms divided by the square of height in meters (kg/m^2). Overweight and obesity were defined as a participant with 25.0 $\text{kg/m}^2 \leq \text{BMI} < 30.0$ kg/m^2 and $\text{BMI} \geq 30.0$ kg/m^2 , respectively. As described in detail before [20], a current smoker was defined as smoking at least one cigarette per day and lasting for at least six months, and a former smoker was defined as having quit smoking for more than six months preceding the survey. A current drinker was defined as those who drank at least twice per month (>640 mL of beer or 100 mL of Chinese liquor, about 57 g of alcohol) and had lasted for at least six months. A former drinker was defined as a person who had stopped drinking more than six months before the study [25]. Based on the average daily alcohol consumption levels, a current drinker was further grouped into low risk (1 – 40 g in males and 1 – 20 g in females) and medium/high risk (>40 g in males and >20 g in females) [26]. The level of physical activity, considered both occupational and leisure-time physical activity, was classified as low (light levels of both occupational and leisure-time physical activity), moderate (moderate or high levels of either occupational or leisure-time physical activity), or high (moderate or high level of both occupational and leisure-time physical) [27].

Statistical Analysis

Considering possible ethnic differences, all analyses were stratified by Han and Yugur people. Results were presented as mean and standard deviation for continuous variables and number (percentage) for categorical variables. Differences in means and proportions of covariates between normotensive and hypertensive

Table 1. Characteristics of participants by hypertension status in Han and Yugur people, CNHS (2013–2018)

Parameter	Han (N = 3,828)			Yugur (N = 1,499)		
	normotension (N = 2,813)	hypertension (N = 1,015)	p value	normotension (N = 1,004)	hypertension (N = 495)	p value
Age, years	47.51 (11.96)	56.30 (10.16)	<0.001	44.47 (11.36)	54.34 (10.51)	<0.001
Gender, n (%)						
Male	1,035 (36.8)	452 (44.5)	<0.001	422 (42.0)	247 (49.9)	0.004
Female	1,778 (63.2)	563 (55.5)		582 (58.0)	248 (50.1)	
BMI, kg/m ²	23.25 (3.02)	25.20 (2.95)	<0.001	24.13 (3.63)	26.57 (4.03)	<0.001
BMI categories, ^a n (%)						
Normal weight	2,066 (74.0)	474 (47.7)	<0.001	612 (61.5)	168 (35.5)	<0.001
Overweight	670 (24.0)	461 (46.4)		326 (32.8)	222 (46.9)	
Obesity	55 (2.0)	59 (5.9)		57 (5.7)	83 (17.5)	
Current residence, n (%)						
Urban	1,894 (67.3)	643 (63.3)	0.021	369 (36.8)	165 (33.3)	0.194
Rural	919 (32.7)	372 (36.7)		635 (63.2)	330 (66.7)	
Educational level, ^b n (%)						
Low	741 (26.4)	425 (42.1)	<0.001	504 (50.3)	330 (66.9)	<0.001
Medium	1,204 (42.9)	372 (36.8)		330 (32.9)	114 (23.1)	
High	862 (30.7)	213 (21.1)		168 (16.8)	49 (9.9)	
Smoking status, ^c n (%)						
Nonsmoker	2,059 (73.2)	681 (67.1)	<0.001	647 (64.4)	280 (56.6)	<0.001
Former smoker	184 (6.5)	128 (12.6)		75 (7.5)	65 (13.1)	
Current smoker	569 (20.2)	206 (20.3)		282 (28.1)	150 (30.3)	
Alcohol consumption, ^d n (%)						
Nondrinker	1,244 (44.3)	457 (45.0)	<0.001	318 (31.7)	149 (30.1)	<0.001
Former drinker	228 (8.1)	150 (14.8)		128 (12.7)	111 (22.4)	
Current drinker	1,339 (47.6)	408 (40.2)		558 (55.6)	235 (47.5)	
Physical activity, ^e n (%)						
Low	440 (15.7)	113 (11.1)	0.001	104 (10.4)	59 (11.9)	0.647
Moderate	1,970 (70.1)	761 (75.0)		644 (64.1)	310 (62.8)	
High	400 (14.2)	141 (13.9)		256 (25.5)	125 (25.3)	
Hypertension family history, n (%)						
No	435 (15.5)	74 (7.3)	<0.001	143 (14.2)	42 (8.5)	<0.001
Yes	1,449 (51.5)	686 (67.6)		631 (62.8)	362 (73.1)	
Unknown	929 (33.0)	255 (25.1)		230 (22.9)	91 (18.4)	
SBP,* mm Hg	113.89 (11.33)	140.54 (13.62)	<0.001	115.91 (10.10)	140.18 (12.65)	<0.001
DBP,* mm Hg	70.48 (8.06)	86.49 (9.93)	<0.001	72.36 (7.79)	89.40 (8.02)	<0.001
Hyperuricemia, n (%)						
No	2,461 (87.5)	745 (73.4)	<0.001	848 (84.5)	366 (73.9)	<0.001
Yes	352 (12.5)	270 (26.6)		156 (15.5)	129 (26.1)	
SUA, μmol/L	303.65 (79.90)	339.92 (89.57)	<0.001	305.09 (85.35)	338.60 (87.61)	<0.001
In male	357.89 (80.57)	382.19 (87.96)	<0.001	352.15 (83.70)	371.97 (84.06)	0.003
In female	272.08 (60.13)	305.99 (75.33)	<0.001	270.96 (68.73)	305.35 (78.04)	<0.001

Values are presented as mean (SD) or number (percentage) for continuous or categorical variables, respectively. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CNHS, China National Health Survey; SD, standard deviation; SUA, serum uric acid. The number of missing data: ^a BMI: 74. ^b Educational level: 15. ^c Smoking status: 1. ^d Alcohol consumption: 2. ^e Physical activity: 4. * The means (SDs) of SBP and DBP were calculated in participants who were not taking antihypertensive agents. Counts may not add up to the total due to missing values, and percentages may not sum to 100% due to rounding.

groups were analyzed using Student's *t* test and the χ^2 test, respectively. The trend associations between covariates and SUA were estimated using linear regression analysis and the Cochran-Mantel-Haenszel χ^2 test for continuous and categorical variables, respectively. Adjusted means for BP differences and odds ratios for

hypertension comparing the four groups (2nd to 5th) to the reference group (first group) were calculated using multivariable linear and logistic regression models, respectively. Model 1 was adjusted for age (continuous), gender (male and female), current residence (rural and urban), educational level (low, medium, and high), and

family history of hypertension (no, yes, and unknown). Model 2 was further adjusted for smoking status (nonsmoker, former smoker, and current smoker), alcohol consumption (nondrinker, former drinker, and current drinker), and physical activity (low, moderate, and high). Model 3 was further adjusted for BMI (continuous). Tests for linear trends were calculated by including SUA as a continuous variable in the models. Generalized additive models were used to estimate the nonlinearity of association between SUA and BP and hypertension. To further evaluate the shape of the association, we performed restricted cubic spline regressions with knots at the 10th, 50th, and 90th percentiles of the SUA distribution [28]. Continuous covariates were included as linear terms, and categorical variables were transformed into dummy variables designating the first level as the reference in all models. Two-sided p values <0.05 were regarded as statistically significant. Statistical analyses were performed by using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Table 1 presents the characteristics of participants by hypertension in Han and Yugur people. Following the exclusion criteria, 5,327 participants with 2,156 males (40.5%) and 3,171 females (59.5%) were included in final analyses. The mean (standard deviation) of SUA was 314.08 (85.07) $\mu\text{mol/L}$. The overall prevalence of hypertension was 28.4% (95% confidence interval [CI], 27.1–29.6%), and Han people had a lower hypertension prevalence than that in Yugur people (26.5% vs. 33.0%, $p < 0.001$). The overall prevalence of hyperuricemia was 17.0% (95% CI, 16.0–18.1%), and Han people had a lower prevalence than that in Yugur people (16.3% vs. 19.0%, $p = 0.0158$). Compared with normotensive participants, the hypertensive ones had a higher BMI and SUA, but a lower educational level and were more likely to be older, overweight, or obese in both ethnic groups (all $p < 0.001$).

The characteristics of participants by SUA groups are shown in Table 2. The levels of BMI, SBP, and DBP, the proportion of male, current smoker, current drinker, medium/high-risk daily alcohol consumption, and the prevalence of hypertension significantly increased with elevated levels of SUA (all $p < 0.001$).

Participants with hypertension had a higher SUA level than normotensive ones (339.5 $\mu\text{mol/L}$ vs. 304.0 $\mu\text{mol/L}$, $p < 0.001$). Table 3 presents the differences in BP in participants taking no hypertension medication stratified by ethnicity and SUA groups. Progressive and significant increases in SBP and DBP across SUA groups were observed in both Han and Yugur people after adjusting for age, gender, current residence, educational level, family history of hypertension, smoking status, alcohol con-

sumption, and physical activity (all p for trend <0.001). When further adjusted for BMI (model 3), the differences were evidently attenuated in SBP and DBP in Han people, but the increases were still significant (p for trend <0.001). Different from Han people, the increase in SBP among Yugur was no longer significant after additional adjustment for BMI (p for trend = 0.147). In model 3, the differences comparing the 5th group ($>416.4 \mu\text{mol/L}$) to the reference group ($<254.1 \mu\text{mol/L}$) for SBP and DBP were 6.15 (95% CI, 4.22–8.08) mm Hg and 4.87 (95% CI, 3.51–6.23) mm Hg in Han people and 2.22 (95% CI, –0.73 to 5.18) mm Hg and 2.56 (95% CI, 0.38–4.75) mm Hg in Yugur people, respectively. Han people had greater increases in SBP and DBP than those in Yugur with increasing SUA levels.

Results of generalized additive models showed that the associations between SUA and SBP (p for nonlinearity = 0.161 and 0.244 for Han and Yugur) and DBP (p for nonlinearity = 0.659 and 0.257 for Han and Yugur) in participants taking no hypertension medication appeared to be linear. Figure 1 shows the shape of the associations using restricted cubic spline regression analyses. SBP and DBP levels increased with elevated SUA levels in both populations, but the increases of SBP levels in Yugur were not statistically significant.

After adjusting for the covariates in model 2, the ORs for hypertension comparing the 5th group to the reference group were 5.61 (95% CI, 4.08–7.73) and 4.64 (95% CI, 2.94–7.40) for Han and Yugur people, respectively (Table 4). Interestingly, when BMI was additionally adjusted in model 3, the ORs were evidently attenuated, as were 3.16 (95% CI, 2.26–4.43) in Han and 2.37 (95% CI, 1.46–3.89) in Yugur.

The association between SUA and hypertension was found as a nonlinear relationship in Han (p for nonlinearity <0.001) but a linear one in Yugur (p for nonlinearity = 0.315). In restricted cubic spline regression models, the risk of hypertension increased with increasing SUA (Fig. 2). Comparing the 90th (425.7 $\mu\text{mol/L}$) percentile to the 10th (214.2 $\mu\text{mol/L}$) percentile of SUA distribution, the ORs of hypertension were 2.12 (95% CI, 1.62–2.76) and 2.02 (95% CI, 1.36–2.99) for Han and Yugur people, respectively.

Discussion

In this representative cross-sectional study, high SUA levels were found independently associated with hypertension both in Han and Yugur people. The association

Table 2. Characteristics of participants by SUA groups in Han and Yugur people, CNHS (2013–2018)

	Han (SUA groups), $\mu\text{mol/L}$					Yugur (SUA groups), $\mu\text{mol/L}$					P_{trend} value [#]	5th >416.4	P_{trend} value [#]
	1st <254.1	2nd 254.1–303.7	3rd 303.8–365.7	4th 365.8–416.4	5th >416.4	1st <254.1	2nd 254.1–303.7	3rd 303.8–365.7	4th 365.8–416.4	5th >416.4			
N	941	1,005	955	491	436	387	329	378	204	201			
Age, years	48.35 (11.42)	49.81 (12.34)	51.64 (11.58)	49.93 (12.87)	49.10 (13.10)	47.60 (10.96)	48.44 (11.94)	47.45 (11.75)	48.46 (13.25)	46.58 (13.20)			0.475
Male, n (%)	116 (12.3)	231 (23.0)	443 (46.4)	341 (69.5)	356 (81.7)	65 (16.8)	104 (31.6)	201 (53.2)	133 (65.2)	166 (82.6)			<0.001
BMI, ^a kg/m ²	22.44 (2.79)	23.15 (2.90)	24.13 (2.92)	25.00 (3.04)	25.81 (3.08)	23.53 (3.68)	24.48 (3.53)	25.06 (3.77)	25.91 (4.25)	26.94 (3.83)			<0.001
Urban, n (%)	528 (56.1)	666 (66.3)	654 (68.5)	359 (73.1)	330 (75.7)	108 (27.9)	119 (36.2)	137 (36.2)	83 (40.7)	87 (43.3)			<0.001
High educational level, ^b n (%)	209 (22.2)	263 (26.3)	268 (28.2)	164 (33.5)	171 (39.4)	39 (10.1)	44 (13.4)	49 (13.0)	35 (17.2)	50 (24.9)			<0.001
Current smoker, ^c n (%)	60 (6.4)	129 (12.8)	241 (25.2)	178 (36.3)	167 (38.3)	52 (13.4)	66 (20.1)	137 (36.2)	80 (39.2)	97 (48.3)			<0.001
Current drinker, ^d n (%)	296 (31.5)	387 (38.5)	475 (49.7)	297 (60.5)	292 (67.0)	167 (43.2)	155 (47.1)	207 (54.8)	124 (60.8)	140 (69.7)			<0.001
Daily alcohol consumption (medium/high risk), ^e n (%)	15 (5.1)	25 (6.5)	64 (13.5)	30 (10.1)	46 (15.8)	14 (8.4)	12 (7.7)	37 (17.9)	25 (20.2)	47 (33.6)			<0.001
Physical activity (high), ^f n (%)	144 (15.3)	128 (12.7)	139 (14.6)	71 (14.5)	59 (13.5)	103 (26.7)	75 (22.8)	107 (28.3)	51 (25.0)	45 (22.4)			0.614
Hypertension family history, n (%)	495 (52.6)	568 (56.5)	528 (55.3)	287 (58.5)	257 (58.9)	253 (65.4)	209 (63.5)	248 (65.6)	140 (68.6)	143 (71.1)			0.228
Hypertension, n (%)	146 (15.5)	239 (23.8)	264 (27.6)	173 (35.2)	193 (44.3)	82 (21.2)	98 (29.8)	131 (34.7)	90 (44.1)	94 (46.8)			<0.001
SBP,* mm Hg	112.27 (12.66)	114.45 (14.70)	118.06 (13.29)	120.85 (12.87)	124.15 (13.43)	115.32 (12.70)	118.98 (13.70)	120.39 (13.41)	121.20 (12.42)	123.87 (12.38)			<0.001
DBP,* mm Hg	68.87 (8.38)	70.73 (9.36)	73.02 (9.15)	75.29 (9.30)	77.84 (9.89)	71.53 (9.74)	74.18 (9.53)	75.47 (9.27)	77.54 (9.28)	78.18 (9.21)			<0.001
SUA, $\mu\text{mol/L}$	216.79 (28.22)	278.51 (14.14)	332.57 (17.82)	388.82 (14.18)	474.29 (54.29)	213.89 (32.54)	278.80 (14.54)	332.97 (17.66)	388.63 (14.28)	469.00 (47.61)			–

Values are presented as mean (SD) and number (percentage) for continuous and categorical variables, respectively. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CNHS, China National Health Survey; SD, standard deviation; SUA, serum uric acid. The number of missing data: ^a BMI: 74; ^b Educational level: 15; ^c Smoking status: 1; ^d Alcohol consumption: 2; ^e Daily alcohol consumption in current drinkers: 3; ^f Physical activity: 4. * According to the daily alcohol consumption levels, current drinkers were further divided into low or medium/high risk. * The means (SDs) of SBP and DBP were calculated in participants who were not taking antihypertensive agents. # The P values were assessed using linear regression analysis and the Cochran-Mantel-Haenszel χ^2 test for continuous and categorical variables, respectively.

Table 3. Adjusted differences (95% CIs) in BP comparing the four groups of higher levels to the first group of SUA in Han and Yugur people, CNHS (2013–2018)

	Han (SUA groups), μmol/L						Yugur (SUA groups), μmol/L					
	1st <254.1	2nd 254.1–303.7	3rd 303.8–365.7	4th 365.8–416.4	5th >416.4	<i>P</i> _{trend} value [#]	1st <254.1	2nd 254.1–303.7	3rd 303.8–365.7	4th 365.8–416.4	5th >416.4	<i>P</i> _{trend} value [#]
SBP, ^a mm Hg	112.27 (12.66)	114.45 (14.70)	118.06 (13.29)	120.85 (12.87)	124.15 (13.43)		115.32 (12.70)	118.98 (13.70)	120.39 (13.41)	121.20 (12.42)	123.87 (12.38)	
Model 1	Ref	1.73 (0.48, 2.98)	3.84 (2.50, 5.19)	6.60 (4.87, 8.34)	9.93 (8.02, 11.85)	<0.001	Ref	2.77 (0.70, 4.84)	3.14 (1.04, 5.24)	3.73 (1.07, 6.39)	5.79 (2.89, 8.68)	<0.001
Model 2	Ref	1.77 (0.52, 3.02)	3.88 (2.54, 5.22)	6.58 (4.84, 8.31)	9.78 (7.87, 11.70)	<0.001	Ref	2.78 (0.71, 4.85)	3.22 (1.12, 5.32)	3.61 (0.95, 6.28)	5.86 (2.96, 8.75)	<0.001
Model 3	Ref	0.94 (−0.28, 2.17)	2.12 (0.79, 3.45)	3.78 (2.05, 5.51)	6.15 (4.22, 8.08)	<0.001	Ref	1.67 (−0.37, 3.71)	1.56 (−0.53, 3.66)	1.02 (−1.67, 3.70)	2.22 (−0.73, 5.18)	0.147
DBP, ^a mm Hg	68.87 (8.38)	70.73 (9.36)	73.02 (9.15)	75.29 (9.30)	77.84 (9.89)		71.53 (9.74)	74.18 (9.53)	75.47 (9.27)	77.54 (9.28)	78.18 (9.21)	
Model 1	Ref	1.55 (0.67, 2.42)	3.23 (2.29, 4.17)	5.17 (3.95, 6.38)	7.53 (6.19, 8.88)	<0.001	Ref	2.29 (0.76, 3.82)	2.99 (1.43, 4.54)	4.99 (3.02, 6.96)	5.33 (3.19, 7.47)	<0.001
Model 2	Ref	1.53 (0.65, 2.41)	3.21 (2.27, 4.15)	5.10 (3.89, 6.32)	7.43 (6.09, 8.78)	<0.001	Ref	2.27 (0.74, 3.80)	3.05 (1.51, 4.60)	4.89 (2.93, 6.86)	5.34 (3.21, 7.48)	<0.001
Model 3	Ref	0.95 (0.09, 1.81)	1.91 (0.98, 2.85)	3.06 (1.84, 4.28)	4.87 (3.51, 6.23)	<0.001	Ref	1.45 (−0.06, 2.95)	1.74 (0.20, 3.29)	2.93 (0.94, 4.92)	2.56 (0.38, 4.75)	0.013

The results were calculated in participants taking no antihypertensive agents. ^a Unadjusted means (SDs). Models 1–3 used multiple linear regression models. Continuous covariables were included as linear terms in the models. Categorical variables were transformed into dummy variables by designating the first level as the reference level. Model 1: adjusted for age (continuous), gender (male and female), current residence (rural and urban), educational level (low, medium, and high), and family history of hypertension (no, yes, and unknown). Model 2: further adjusted for smoking status (nonsmoker, former smoker, and current smoker), alcohol consumption (nondrinker, former drinker, and current drinker), and physical activity (low, moderate, and high). Model 3: further adjusted for BMI (continuous). BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; SUA, serum uric acid; CNHS, China National Health Survey; SD, standard deviation; BMI, body mass index. [#] Tests for linear trend were calculated by including SUA as a continuous variable in the models.

Fig. 1. Adjusted differences (95% CIs) for SBP (**A**) and DBP (**B**) by SUA in Han and Yugur people. SUA was modeled as restricted cubic splines with three knots located at the 10th, 50th, and 90th percentiles (214.2, 303.7, 425.7 $\mu\text{mol/L}$) of the distribution of SUA. Multivariable linear regression models were adjusted for age (continuous), gender (male and female), current residence (rural and urban), educational level (low, medium, and high), family history of hypertension (no, yes, and unknown), BMI (continuous), smoking status (nonsmoker, former smoker, and current smoker), alcohol consumption (nondrinker, former drinker, and current drink-

er), and physical activity (low, moderate, and high). Categorical variables were transformed into dummy variables designating the first level as reference. BP levels at the 10th percentile (214.2 $\mu\text{mol/L}$) of SUA distribution was used as reference. Dashed lines represented the 95% CIs surrounding the estimates (solid lines), and the density plots showed the distribution of SUA in Han and Yugur people. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; CI, confidence interval; SUA, serum uric acid; BP, blood pressure.

between SUA and DBP was consistent in both populations, but there was an ethnic difference in the association between SUA and SBP. Furthermore, we revealed a non-linear relationship between SUA and hypertension in Han and a linear relationship in Yugur people.

To our best knowledge, this is the first study to explore the nonlinear relationship between SUA and BP in Yugur people. Zhou et al. [29] found that SUA levels at midpregnancy had a nonlinear association with maternal DBP/mean arterial pressure and a linear association with SBP in pregnant women. A rural, community-based prospective cohort in South Korea showed that there was a significant linear association between SUA and incident hypertension in people younger than 55 years, but the association was not significant in people older than 55 years [30].

The result of the association between SUA and hypertension is consistent with previous studies [8, 31–37]. After further adjustment for BMI, the associations between SUA and BP and hypertension were obviously attenuated, suggesting that BMI may influence these associations. A cross-sectional study found that BMI, SUA, and the interaction between them were significantly and inde-

pendently associated with hypertension. It indicated that BMI may modify the association between SUA and BP progression [38]. Hwang et al. [39] explored the relationship between changing the BMI and SUA alteration among clinically apparently healthy Korean men and found that BMI change could have a significant association with the alteration of SUA levels. Other studies observed that participants with abdominal obesity had a higher risk of hypertension than those without, and adjusted HR of hypertension was higher in overweight or obese ones than those with normal weight, but these differences were not significant (all p for interaction >0.05) [40, 41].

In participants taking no hypertension medication, SUA was found independently associated with elevated BP. Feig et al. [42] had demonstrated that lowering SUA could result in the reduction of BP in adolescents [42, 43]. However, their study included hypertensive patients who were treated with antihypertensive agents that could have an effect on the SUA level. For example, calcium channel blockers and losartan can decrease the levels of SUA and result in a lower risk of incident gout, and diuretics, β blockers, angiotensin-converting enzyme inhibitors, and

Table 4. Adjusted ORs (95% CI) for hypertension comparing the four groups of higher levels to the first group of SUA in Han and Yugur people, CNHS (2013–2018)

	Han (SUA groups), $\mu\text{mol/L}$					Yugur (SUA groups), $\mu\text{mol/L}$					P_{trend} value [#]	P_{trend} value [#]
	1st <254.1	2nd 254.1–303.7	3rd 303.8–365.7	4th 365.8–416.4	5th >416.4	1st <254.1	2nd 254.1–303.7	3rd 303.8–365.7	4th 365.8–416.4	5th >416.4		
Hypertension, %	15.5	23.8	27.6	35.2	44.3	21.2	29.8	34.7	44.1	46.8		
Model 1	1.00	1.63 (1.28, 2.10)	1.90 (1.47, 2.45)	3.26 (2.42, 4.41)	5.62 (4.09, 7.75)	1.00	1.58 (1.09, 2.30)	2.24 (1.55, 3.25)	3.37 (2.18, 5.22)	4.52 (2.87, 7.17)		<0.001
Model 2	1.00	1.63 (1.27, 2.09)	1.91 (1.48, 2.46)	3.27 (2.42, 4.43)	5.61 (4.08, 7.73)	1.00	1.61 (1.11, 2.34)	2.28 (1.57, 3.31)	3.42 (2.21, 5.32)	4.64 (2.94, 7.40)		<0.001
Model 3	1.00	1.46 (1.13, 1.90)	1.42 (1.09, 1.86)	2.12 (1.55, 2.90)	3.16 (2.26, 4.43)	1.00	1.30 (0.88, 1.93)	1.60 (1.08, 2.38)	2.06 (1.29, 3.30)	2.37 (1.46, 3.89)		<0.001

Models 1–3 used multiple logistic regression models. Continuous covariables were included as linear terms in the models. Categorical variables were transformed into dummy variables by designating the first level as the reference level. Model 1: adjusted for age (continuous), gender (male and female), current residence (rural and urban), educational level (low, medium, and high), and family history of hypertension (no, yes, and unknown). Model 2: further adjusted for smoking status (nonsmoker, former smoker, and current smoker), alcohol consumption (nondrinker, former drinker, and current drinker), and physical activity (low, moderate, and high). Model 3: further adjusted for BMI (continuous). OR, odds ratio; CI, confidence interval; SUA, serum uric acid; CNHS, China National Health Survey; BMI, body mass index. # Tests for linear trend were calculated by including SUA as a continuous variable in the models.

nonlosartan angiotensin II receptor blockers can increase SUA and lead an increased risk of gout [44]. In this study, we explored the association between SUA and BP in an untreated, healthy general population.

Several pathogenic mechanisms, which were based on evidence from animal models, have been implicated in the association between uric acid and hypertension [45–47]. Although uric acid is an antioxidant in the extracellular environment, it causes oxidative stress within cells with inhibition of the endothelial nitric oxide pathway and the activation of the renin-angiotensin system. These effects result in systemic and renal vasoconstriction and the development of salt-resistant hypertension. Over time, uric acid induces vascular smooth muscle cell proliferation, and inflammation and may lead to irreversible damage to small renal vessels, leading to renal microvascular lesions and subsequent elevated BP [48, 49]. The mechanism whereby BMI may modify the association between uric acid and BP is not completely understood. A possible one is that the hyperinsulinemia and insulin resistance that accompanies obesity can induce the specific activation of the tubular sodium-hydrogen exchanger, facilitating the active reabsorption of uric acid and decreasing its renal clearance [50, 51].

Our study has some strengths. First, this is the first one to explore the nonlinear relationship between SUA and BP and hypertension in Han and Yugur people in China. Second, participants who were taking antihypertensive agents or had diseases of urinary system or gout that may affect SUA were excluded to prevent bias on the association between SUA and BP. Third, by restricted cubic spline regression models, we increased the statistical power and reduced the loss of information when SUA was analyzed as categories.

The present study also has limitations. First, the nature of cross-sectional does not allow us to make inferences about the causality for the effects. Second, the lack of data on taking medication for hyperuricemia or gout may underestimate SUA levels in the study population and result in a bias of the association between SUA and hypertension. Third, due to a lack of information on serum biochemical markers (i.e., fasting glucose and creatinine), we cannot adjust models using these factors, thus effects may be overestimated.

Conclusion

Our study demonstrated that SUA was significantly and independently associated with an increased risk of hypertension. BMI may influence this association, and

Fig. 2. Adjusted ORs (95% CIs) for hypertension by SUA in Han and Yugur people. SUA was modeled as restricted cubic splines with three knots located at the 10th, 50th, and 90th percentiles (214.2, 303.7, and 425.7 $\mu\text{mol/L}$) of the distribution of SUA. Multivariable logistic regression models were adjusted for age (continuous), gender (male and female), current residence (rural and urban), educational level (low, medium, and high), family history of hypertension (no, yes, and unknown), BMI (continuous), smoking status (nonsmoker, former smoker, and current smoker), alco-

hol consumption (nondrinker, former drinker, and current drinker), and physical activity (low, moderate, and high). Categorical variables were transformed into dummy variables designating the first level as reference. The ORs for hypertension at the 10th percentile (214.2 $\mu\text{mol/L}$) of SUA distribution was used as reference. Dashed lines represented the 95% CIs surrounding the estimates (solid lines), and the density plots showed the distribution of SUA in Han and Yugur people. OR, odds ratio; BMI, body mass index; CI, confidence interval; SUA, serum uric acid.

there were over twofold risks comparing the 5th group ($>416.4 \mu\text{mol/L}$) to the reference group ($<254.1 \mu\text{mol/L}$) both in Han and Yugur people. Particularly, our study indicated a nonlinear relationship between SUA and hypertension in Han and a linear relationship in Yugur people, with a significantly increased trend of odds ratio per unit increase in SUA. Prospective studies are needed to confirm these findings.

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Statement of Ethics

The research was approved by Institutional Review Board of the IBMS and CAMS (approval reference number: 029-2013) and conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all individual participants included in the study.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

Dr. C.Y. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The conception and design of the study: C.Y.

and G.S.; acquisition, analysis, or interpretation of data: all the authors; drafting of the manuscript: C.Y. and H.H.; critical revision of the manuscript for important intellectual content: all the authors; statistical analysis: C.Y.; supervision: G.S. and H.H.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

- 1 Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005;365:217–23.
- 2 Wang J, Zhang L, Wang F, Liu L, Wang H. Prevalence, awareness, treatment, and control of hypertension in China: results from a national survey. *Am J Hypertens*. 2014;27:1355–61.
- 3 Liu M, Li Y, Liu S, Wang W, Zhou M. Burden on blood-pressure-related diseases among the Chinese population, in 2010. *Chin J Epidemiol*. 2014;35:680–3.
- 4 Haque T, Rahman S, Islam S, Molla NH, Ali N. Assessment of the relationship between serum uric acid and glucose levels in healthy, prediabetic and diabetic individuals. *Diabetol Metab Syndr*. 2019;11:49.
- 5 Ali N, Miah R, Hasan M, Barman Z, Mou AD, Hafsa JM, et al. Association between serum uric acid and metabolic syndrome: a cross-sectional study in Bangladeshi adults. *Sci Rep*. 2020;10:7841.
- 6 Liu C, Qiu D, Zhang M, Hou J, Lin J, Liao H. Association of hyperuricemia and hypertension phenotypes in hypertensive patients without uric acid lowering treatment. *Clin Exp Hypertens*. 1993;2021:1–6.
- 7 Ali N, Perveen R, Rahman S, Mahmood S, Rahman S, Islam S, et al. Prevalence of hyperuricemia and the relationship between serum uric acid and obesity: a study on Bangladeshi adults. *PLoS One*. 2018;13:e0206850.
- 8 Ali N, Mahmood S, Islam F, Rahman S, Haque T, Islam S, et al. Relationship between serum uric acid and hypertension: a cross-sectional study in Bangladeshi adults. *Sci Rep*. 2019;9:9061.
- 9 Liu F, Hui S, Hidru TH, Jiang Y, Zhang Y, Lu Y, et al. The prevalence, distribution, and extent of subclinical atherosclerosis and its relation with serum uric acid in hypertension population. *Front Cardiovasc Med*. 2021;8:638992.
- 10 Ali N, Rahman S, Islam S, Haque T, Molla NH, Sumon AH, et al. The relationship between serum uric acid and lipid profile in Bangladeshi adults. *BMC Cardiovasc Disord*. 2019;19:42.
- 11 Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension*. 2003;41:1183–90.
- 12 Mazzali M, Kanbay M, Segal MS, Shafiu M, Jalal D, Feig DI, et al. Uric acid and hypertension: cause or effect? *Curr Rheumatol Rep*. 2010;12:108–17.
- 13 Corry DB, Eslami P, Yamamoto K, Nyby MD, Makino H, Tuck ML. Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin-angiotensin system. *J Hypertens*. 2008;26:269–75.
- 14 Kang DH, Han L, Ouyang X, Kahn AM, Kanellis J, Li P, et al. Uric acid causes vascular smooth muscle cell proliferation by entering cells via a functional urate transporter. *Am J Nephrol*. 2005;25:425–33.
- 15 Borghi C, Agabiti-Rosei E, Johnson RJ, Kielstein JT, Lurbe E, Mancia G, et al. Hyperuricaemia and gout in cardiovascular, metabolic and kidney disease. *Eur J Intern Med*. 2020;80:1–11.
- 16 Sanchez-Lozada LG, Rodriguez-Iturbe B, Kelley EE, Nakagawa T, Madero M, Feig DI, et al. Uric acid and hypertension: an update with recommendations. *Am J Hypertens*. 2020;33:583–94.
- 17 Song Y, Xing-Xiang LI. Survey on level of serum uric acid in population of healthy cheek of Yugur, Tibetan and Han in Sunan County. *Chin J Dis Contr Prev*. 2011;15:657–9.
- 18 Deng R. Survey on epidemiology of essential hypertension in Chinese Yugu population and other related factors. *J Lanzhou Univ*. 2008;34:57–9.
- 19 Yin C, Xi-Jiang WU, Meng LH. Logistic regression analysis between uric acid level and hypertension in workers. *Gansu Med J*. 2015;34:484–8.
- 20 He H, Pan L, Pa L, Cui Z, Ren X, Wang D, et al. Data resource profile: the China national health survey (CNHS). *Int J Epidemiol*. 2018;47:1734–5f.
- 21 James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507.
- 22 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *JAMA*. 2003;289:2560–72.
- 23 Sui X, Church TS, Meriwether RA, Lobelo F, Blair SN. Uric acid and the development of metabolic syndrome in women and men. *Metabolism*. 2008;57:845–52.
- 24 Nishida C, Ko GT, Kumanyika S. Body fat distribution and noncommunicable diseases in populations: overview of the 2008 WHO Expert Consultation on waist circumference and waist-hip ratio. *Eur J Clin Nutr*. 2010;64:2–5.
- 25 He H, Pan L, Cui Z, Sun J, Yu C, Cao Y, et al. Smoking prevalence, patterns, and cessation among adults in Hebei province, central China: implications from China national health survey (CNHS). *Front Public Health*. 2020;8:177.
- 26 Desapriya E, Stockwell T, Doll SR, Room R. *International guide for monitoring alcohol consumption and related harm*. Geneva: World Health Organization; 2000.
- 27 Shan G, Wei D, Wang C, Zhang J, Wang B, Ma M, et al. Trends of overweight and obesity in Yi people between 1996 and 2007: an Yi migrant study. *Biomed Environ Sci*. 2011;24:467–74.
- 28 Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. *Stat Med*. 2010;29:1037–57.
- 29 Zhou G, Holzman C, Luo Z, Margerison C. Maternal serum uric acid levels and blood pressure during pregnancy: a community-based cohort study. *Eur J Obstet Gynecol Reprod Biol*. 2018;222:64–9.

- 30 Lee SW, Kim HC, Nam C, Lee HY, Ahn SV, Oh YA, et al. Age-differential association between serum uric acid and incident hypertension. *Hypertens Res*. 2019;42:428–37.
- 31 Zhang W, Sun K, Yang Y, Zhang H, Hu FB, Hui R. Plasma uric acid and hypertension in a chinese community: prospective study and metaanalysis. *Clin Chem*. 2009;55:2026–34.
- 32 Yokokawa H, Fukuda H, Suzuki A, Fujibayashi K, Naito T, Uehara Y, et al. Association between serum uric acid levels/hyperuricemia and hypertension among 85,286 Japanese workers. *J Clin Hypertens*. 2016;18:53–9.
- 33 Wei F, Sun N, Cai C, Feng S, Tian J, Shi W, et al. Associations between serum uric acid and the incidence of hypertension: a Chinese senior dynamic cohort study. *J Transl Med*. 2016;14:110.
- 34 Taniguchi Y, Hayashi T, Tsumura K, Endo G, Fujii S, Okada K. Serum uric acid and the risk for hypertension and type 2 diabetes in Japanese men: the Osaka health survey. *J Hypertens*. 2001;19:1209–15.
- 35 Shankar A, Klein R, Klein BE, Nieto FJ. The association between serum uric acid level and long-term incidence of hypertension: population-based cohort study. *J Hum Hypertens*. 2006;20:937–45.
- 36 Nagahama K, Inoue T, Kohagura K, Kinjo K, Ohya Y. Associations between serum uric acid levels and the incidence of hypertension and metabolic syndrome: a 4-year follow-up study of a large screened cohort in Okinawa, Japan. *Hypertens Res*. 2015;38:213.
- 37 Kuwabara M, Niwa K, Nishi Y, Mizuno A, Asano T, Masuda K, et al. Relationship between serum uric acid levels and hypertension among Japanese individuals not treated for hyperuricemia and hypertension. *Hypertens Res*. 2014;37:785–9.
- 38 Kawamoto R, Ninomiya D, Senzaki K, Kumagi T. Interaction between body mass index and serum uric acid in relation to blood pressure in community-dwelling Japanese men. *Clin Hypertens*. 2018;24:1.
- 39 Hwang J, Lee MY, Ahn JK, Cha HS. Relationship between changing the body mass index and serum uric acid alteration among clinically apparently healthy Korean men. *Arthritis Care Res*. 2021 Feb 5. Epub ahead of print.
- 40 Zhang W, Sun K, Yang Y, Zhang H, Hu FB, Hui R. Plasma uric acid and hypertension in a chinese community: prospective study and metaanalysis. *Clin Chem*. 2009;55:2026–34.
- 41 Yokoi Y, Kondo T, Okumura N, Shimokata K, Osugi S, Maeda K, et al. Serum uric acid as a predictor of future hypertension: stratified analysis based on body mass index and age. *Prev Med*. 2016;90:201–6.
- 42 Feig DI, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. *JAMA*. 2008;300:924–32.
- 43 Soletsky B, Feig DI. Uric acid reduction rectifies prehypertension in obese adolescents. *Hypertension*. 2012;60:1148–56.
- 44 Choi HK, Soriano LC, Zhang Y, Rodríguez LA. Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study. *BMJ*. 2012;344:d8190.
- 45 Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M, et al. A role for uric acid in the progression of renal disease. *J Am Soc Nephrol*. 2002;13:2888–97.
- 46 Mazzali M, Kanellis J, Han L, Feng L, Xia YY, Chen Q, et al. Hyperuricemia induces a primary renal arteriopathy in rats by a blood pressure-independent mechanism. *Am J Physiol Renal Physiol*. 2002;282:F991–7.
- 47 Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, et al. Hyperuricemia induces endothelial dysfunction. *Kidney Int*. 2005;67:1739–42.
- 48 Feig DI, Nakagawa T, Karumanchi SA, Oliver WJ, Kang DH, Finch J, et al. Hypothesis: uric acid, nephron number, and the pathogenesis of essential hypertension. *Kidney Int*. 2004;66:281–7.
- 49 Corry DB, Eslami P, Yamamoto K, Nyby MD, Makino H, Tuck ML. Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin-angiotensin system. *J Hypertens*. 2008;26:269–75.
- 50 Ruiz-Hurtado G, Ruilope LM. Hypertension and obesity: correlates with renin-angiotensin-aldosterone system and uric acid. *J Clin Hypertens*. 2014;16:559–60.
- 51 Puig JG, Ruilope LM. Uric acid as a cardiovascular risk factor in arterial hypertension. *J Hypertens*. 1999;17:869–72.