Journal of Human Hypertension (2021) 35:1020–1028
https://doi.org/10.1038/s41371-020-00455-7

ARTICLE

Hyperuricemia is independently associated with hypertension in men under 60 years in a general Chinese population

Tingting Qian[1] · Hui Sun[2] · Qun Xu[2] · Xujuan Hou[3] · Wenqi Hu[3] · Guang Zhang[3] · Grant R. Drummond[4] · Christopher G. Sobey[4] · Fadi J. Charchar[5] · Jonathan Golledge[6,7] · Yutang Wang[5] · Guang Yang[2]

Received: 6 August 2020 / Revised: 31 October 2020 / Accepted: 16 November 2020 / Published online: 14 December 2020

Abstract

Hyperuricemia has been associated with hypertension, however, whether this association exists across all decades of adult life is unknown. This study aimed to assess the association between hyperuricemia and hypertension in relation to age. This retrospective cross-sectional study included a total of 22,556 adult Chinese people who attended Health Physical Examination in a Chinese hospital. Participants were aged between 18 and 95 years (mean [standard deviation], 45.4 [14.0]). Serum uric acid levels and blood pressure were measured. Associations between serum uric acid and blood pressure, and between hyperuricemia and hypertension diagnosis were analyzed using linear or logistic regression, adjusting for confounding risk factors including age, sex, total cholesterol, high-density lipoprotein cholesterol, and fasting blood glucose. Sub-analysis was stratified by age and sex. Before adjustment, high serum uric acid was associated with higher systolic blood pressure ($\beta = 0.214$, $P < 0.001$) and higher diastolic blood pressure ($\beta = 0.271$, $P < 0.001$). Hyperuricemia was associated with hypertension diagnosis (OR, 1.763; 95% CI, 1.635–1.901; $P < 0.001$) in an unadjusted analysis. These findings remained significant after adjusting for confounding factors. Sub-analysis suggested that the association between uric acid and blood pressure was weaker in older age groups and the association between hyperuricemia and hypertension was limited to people under 60 years. Hyperuricemia was independently associated with hypertension diagnosis in men but not in women, and the independent association between hyperuricemia and hypertension only presented in men under 60 years. This study suggests that hyperuricemia is independently associated with hypertension in Chinese men under 60 years.

Introduction

Uric acid is the end product of the metabolic breakdown of purine compounds [1]. Its concentration in the serum is a balance between its production, which is catalyzed by xanthine oxidase [2], and its excretion, which is mainly through the urinary tract [3]. High circulating uric acid

These authors contributed equally: Tingting Qian, Hui Sun

These authors jointly supervised this work: Yutang Wang, Guang Yang

✉ Yutang Wang
yutang.wang@federation.edu.au

✉ Guang Yang
yangg1972@126.com

[1] Department of Geriatric Medicine, School of Clinical Medicine, Weifang Medical University, Weifang, Shandong, China

[2] Department of Gerontology, The First Affiliated Hospital of Shandong First Medical University, Jinan, Shandong Province, China

[3] The Health Physical Examination Center, The First Affiliated Hospital of Shandong First Medical University, Jinan, Shandong Province, China

[4] Centre for Cardiovascular Biology and Disease Research and Department of Physiology, Anatomy and Microbiology, School of Life Sciences, La Trobe University, Melbourne, VIC 3086, Australia

[5] Discipline of Life Sciences, School of Science, Psychology and Sport, Federation University Australia, Ballarat, VIC 3350, Australia

[6] Queensland Research Centre for Peripheral Vascular Disease, College of Medicine and Dentistry, James Cook University, Townsville, QLD 4811, Australia

[7] Department of Vascular and Endovascular Surgery, The Townsville University Hospital, Townsville, QLD 4814, Australia

(hyperuricemia) has been reported to be associated with many diseases, including metabolic syndrome [4], coronary artery disease [5], stroke [6], preeclampsia [7], and kidney disease [8].

Hyperuricemia is also reported to be associated with hypertension [5, 9–14]. Lowering serum uric acid by treatment with the xanthine oxidase inhibitor allopurinol has been reported to decrease blood pressure in a meta-analysis of 15 randomized clinical trials [15]. These findings suggest that treatments to lower uric acid may be an effective means to manage high blood pressure in selected patients. A number of reports have, however, provided contradictory evidence about the role of hyperuricemia in hypertension. One study reported that hyperuricemia was not associated with hypertension [9] and allopurinol treatment has been reported to not affect blood pressure in some studies of older people [16, 17]. Therefore, it is important to determine whether the association between hyperuricemia and hypertension exists across all decades of adult life.

This study aimed to examine the association between hyperuricemia and blood pressure in a large Chinese general population ($N = 22{,}556$) in relation to the participants' age which was stratified as 18–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years, and 80–95 years.

Methods

Subjects

A total of 22,571 included participants who underwent health examinations between January and May 2019 at the Health Physical Examination Center of the First Affiliated Hospital of Shandong First Medical University, Jinan, Shandong Province, China. Two participants were excluded due to missing uric acid or blood pressure data. Thirteen subjects were excluded due to being aged younger than 18 years. The remaining 22,556 adult participants were included in the study. This retrospective study complied with the Declaration of Helsinki and was approved, and the requirement for obtaining patient informed consent was waived, by the Research Ethics Committee of the First Affiliated Hospital of Shandong First Medical University.

Measurements and definitions

Blood pressure was measured in all participants by trained professionals using electronic sphygmomanometry (Omron HBP-9020 Automatic Blood Pressure Monitor, Omron Healthcare Co. Ltd, Tokyo, Japan). The Omron HBP-9020 Automated Blood Pressure Monitor used in this study was equipped with a cuff with a wide range of arm circumferences from 17 to 42 cm. It had good repeatability (coefficient of variation for systolic blood pressure was 3.9%, $N = 10$; it was 3.2% for diastolic pressure, $N = 10$). Blood pressure was measured in the right arm in the seated position with the arm being placed on an arm rest after the participant rested for 10 min [18]. Blood pressure was measured 2 times at 2-min intervals in all participants and mean systolic and diastolic blood pressure were calculated. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥ 90 mm Hg [19].

Venous blood samples were collected after an overnight fast (≥12 h). Serum uric acid concentrations were measured by the uricaseperoxidase method [20]. Hyperuricemia was defined as serum uric acid concentration ≥7 mg/dL in men or ≥6 mg/dL in women [21]. The following additional serum biochemical parameters were measured using the Olympus AU2700 automatic biochemical analyzer: total cholesterol, high-density lipoprotein-cholesterol, and fasting plasma glucose.

Statistical analysis

All statistical analyses were performed using SPSS version 25.0 (IBM SPSS Statistics for Windows, Armonk, NY, International Business Machines Corporation). Age (Kolmogorov–Smirnov statistic, KS statistic, 0.089, $P < 0.001$), HDL-C (KS statistic 0.062, $P < 0.001$), systolic blood pressure (KS statistic, 0.054, $P < 0.001$), diastolic blood pressure (KS statistic, 0.045, $P < 0.001$), fasting plasma glucose (KS statistic, 0.219, $P < 0.001$), total cholesterol (KS statistic, 0.037, $P < 0.001$) and uric acid (KS statistic, 0.035, $P < 0.001$) were not normally distributed. Descriptive statistics were presented as mean and standard deviation for continuous variables and percentage for categorical variables. Statistical comparisons of continuous data between groups were performed using the Mann–Whitney U test or Kruskal–Wallis test followed by Bonferroni post-hoc tests, and statistical comparisons of categorical data between groups were performed using Fisher's exact test or Chi-square test.

The association between serum uric acid and blood pressure was analyzed by linear regression analysis before and after adjusting for other risk factors, as established by the Framingham Heart Study [22], including age, sex, total cholesterol, high-density lipoprotein-cholesterol, and fasting blood glucose. They are risk factors for both hypertension [19, 23–25] and coronary heart disease [22].

Sub-analyses were conducted limited to different age groups mainly defined by decade. Only 10 participants were aged 18–19 years and 10 aged 90–95 years. Therefore, participants aged 18–19 years were combined with those aged 20–29 years to form an age group of 18–29 years; and participants aged 90–95 years were combined with those

Table 1 Characteristics of the study participants.

	Total	Male	Female	*P* value[a]
Sample size (count)	22,556	13,300	9256	
Age, mean (SD), y	45.4 (14.0)	45.4 (14.2)	45.5 (13.7)	0.193
SBP, mean (SD), mm Hg	129.9 (19.0)	133.8 (17.4)	124.3 (19.8)	<0.001
DBP, mean (SD), mm Hg	78.7 (12.3)	82.1 (11.8)	73.8 (11.3)	<0.001
HTN, %	30.4	36.8	21.2	<0.001
Serum uric acid, mean (SD), mg/dL	5.38 (1.40)	6.03 (1.26)	4.44 (0.99)	<0.001
Hyperuricemia[b], %	15.0	20.7%	6.8%	<0.001
FPG, mean (SD), mmol/L	5.39 (1.35)	5.52 (1.46)	5.19 (1.13)	<0.001
TC, mean (SD), mmol/L	4.72 (0.91)	4.70 (0.88)	4.76 (0.95)	0.011
HDL-C, mean (SD), mmol/L	1.28 (0.28)	1.19 (0.25)	1.41 (0.29)	<0.001

DBP diastolic blood pressure, *HDL-C* high-density lipoprotein-cholesterol, *HTN* hypertension (defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg), *FPG* fasting plasma glucose, *SBP* systolic blood pressure, *TC* total cholesterol.

[a]The difference between males and females was analyzed using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables.

[b]Hyperuricemia was defined as uric acid ≥7 mg/dL for men and ≥6 mg/dL for women.

aged 80–89 years to form an age group of 80–95 years. Sub-analyses were also conducted according to sex and within different age groups in each sex. All tests were two-sided and a *P* value of <0.05 was regarded as statistically significant.

Results

The characteristics of the study sample are shown in Table 1. A total of 22,556 participants aged 18–95 years with a mean [standard deviation; SD] age of 45.4 [14.0] years were included. In this general population, there were 13,300 males and 9256 females. The mean [SD] systolic and diastolic blood pressures were 129.9 [19.0] mm Hg and 78.7 [12.3] mm Hg, respectively. The prevalence of hypertension was 30.4%. The mean [SD] serum uric acid was 5.38 [1.40] mg/dL and the prevalence of hyperuricemia was 15.0% (Table 1). Compared to female participants, male participants had higher systolic and diastolic blood pressure, higher fasting plasma glucose, and lower total cholesterol and lower HDL-cholesterol (Table 1).

The mean systolic and diastolic blood pressures of participants were higher in older compared to younger age groups (Fig. 1). The prevalence of hypertension diagnosis increased with increasing age, being 14.9%, 16.4%, 26.3%, 41.0%, 52.8%, 68.2%, 76.2% ($P < 0.001$, Chi-square test) for people aged 18–29, 30–39, 40–49, 50–59 and 60–69, 70–79, and 80–95 years, respectively, in this general population.

Mean serum uric acid ranged from 5.27 to 5.54 mg/dL and decreased first and then increased over decades of adult life ($P < 0.001$, Kruskal–Wallis test, Fig. 1). The prevalence of hyperuricemia displayed a U curve where it decreased first and then increased over decades of adult life, being 17.7%, 16.1%, 13.5%, 13.2%, 14.4%, 16.2%, 18.6% ($P < 0.001$, Chi-square test) for people aged 18–29, 30–39, 40–49, 50–59 and 60–69, 70–79, and 80–95 years, respectively.

The association between serum uric acid and blood pressure

Both systolic ($\beta = 0.214$, $P < 0.001$) and diastolic ($\beta = 0.271$, $P < 0.001$) blood pressure were significantly correlated with serum uric acid concentration (Fig. 2, Table 2). After adjustment for other risk factors, the significant positive association between blood pressure and serum uric acid remained ($\beta = 0.115$, $P < 0.001$ for systolic blood pressure; $\beta = 0.104$, $P < 0.001$ for diastolic blood pressure, Table 2).

In a subgroup analysis, higher uric acid was significantly associated with both higher systolic and higher diastolic blood pressure across all age groups below 70 years (Table 2). After adjustment, the significant association between uric acid and blood pressure remained, except in the 60–69 year age group. In this group, serum uric acid was only positively associated with systolic ($\beta = 0.057$, $P = 0.010$) but not diastolic blood pressure ($\beta = 0.040$, $P = 0.072$, Table 2).

The association between uric acid and systolic blood pressure became weaker in older age groups. β was 0.392, 0.390, 0.262, 0.145 and 0.052 for people aged 18–29, 30–39, 40–49, 50–59 and 60–69 years, respectively (Table 2). A similar trend was seen for diastolic blood pressure (Table 2).

Further subgroup analysis showed that higher serum uric acid remained associated with both higher systolic and higher diastolic blood pressure in each sex both before and after adjustment (Table 3). These associations were limited to female participants under 60 years and male participants under 80 years (Table 3).

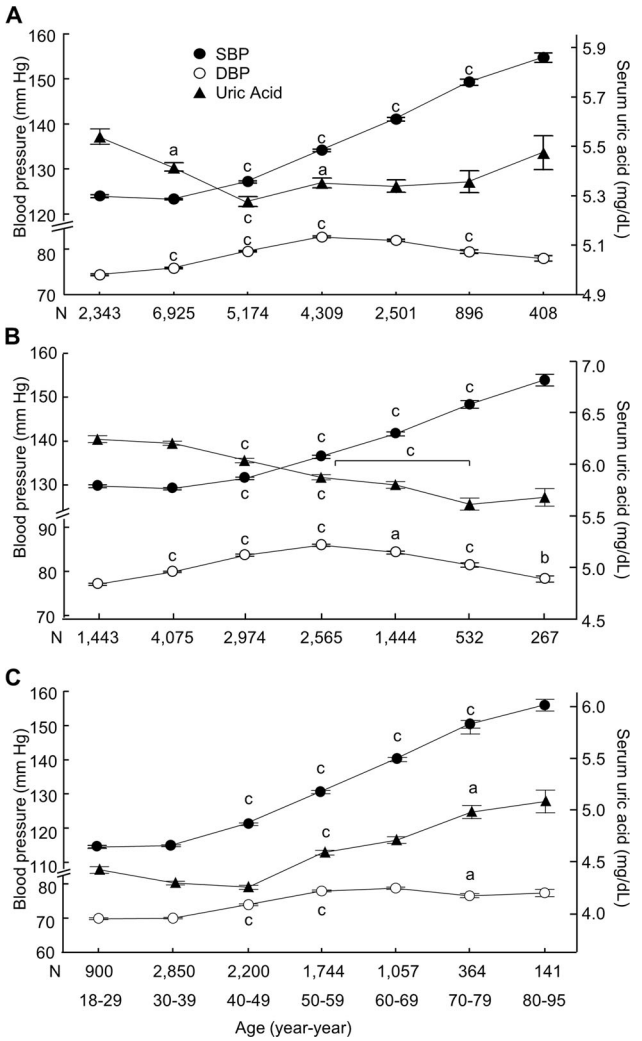

Fig. 1 Uric acid and blood pressure over decades of adult life. Uric acid (triangles) and systolic (filled circles) and diastolic blood pressure (open circles in (**a**) all participants ($N = 22,556$), (**b**) male participants ($N = 13,330$) and (**c**) female participants ($N = 9256$). Data represent mean ± SE. The total number of cases = 22,556. SBP systolic blood pressure, DBP diastolic blood pressure. The difference among groups in each parameter (SBP or DBP or uric acid) was analyzed by the Kruskal–Wallis test followed by Bonferroni post-hoc tests. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ compared to the same parameter in subjects from the immediately younger decade.

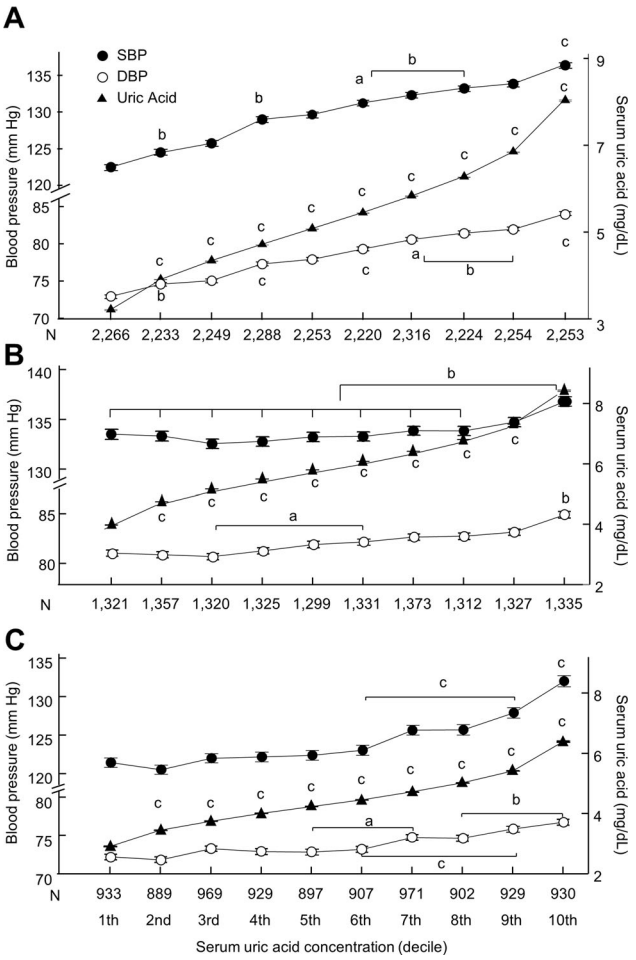

Fig. 2 Blood pressure increases when the concentration of uric acid rises. Uric acid (triangles) and systolic (filled circles) and diastolic blood pressure (open circles) in (**a**) all participants ($N = 22,556$), (**b**) male participants ($N = 13,330$) and (**c**) female participants ($N = 9256$). Data represent mean ± SE. SBP Systolic blood pressure, DBP diastolic blood pressure. The difference among groups in each parameter (SBP or DBP or uric acid) was analyzed by the Kruskal–Wallis test followed by Bonferroni post-hoc tests. $^{a}P < 0.05$, $^{b}P < 0.01$, and $^{c}P < 0.001$ compared to the uric acid concentration or blood pressure in subjects of the immediately lower uric acid decile group or between two specified groups.

The association between hyperuricemia and hypertension

Hyperuricemia was associated with diagnosis of hypertension both before (OR, 1.76; 95% CI, 1.64–1.90; $P < 0.001$, Table 4) and after adjustment for other risk factors (adjusted OR, 1.54; 95% CI, 1.41–1.67; $P < 0.001$; Table 4). In a subgroup analysis hyperuricemia was associated with hypertension diagnosis in all age groups below 60 years (Table 4).

Further subgroup analysis showed that hyperuricemia was associated with hypertension in both men (OR, 1.32; 95% CI, 1.21–1.44; $P < 0.001$; Table 5) and women (OR, 2.46; 95% CI, 2.08–2.92; $P < 0.001$; Table 5). However, the association in women disappeared after adjusting for risk factors (adjusted OR, 1.21; 95% CI, 0.98–1.49; $P = 0.0740$; Table 5). In men, hyperuricemia was an independent risk factor for hypertension (adjusted OR, 1.51; 95% CI, 1.38–1.66; $P < 0.001$; Table 5) and this association was limited to men under 60 years (Table 5).

Discussion

Consistent with past reports [5, 9–15], this study found that higher serum uric acid concentration was associated with higher blood pressure, and that hyperuricemia was associated

Table 2 The association between serum uric acid with blood pressure in the whole general population and across all decadesof adult life analyzed by univariable and multivariable linear regression.

	Univariable				Multivariable[a]			
	SBP		DBP		SBP		DBP	
	β	*P* value	*β*	*P* value	*β*	*P* value	*β*	*P* value
Overall (*N* = 22,556)	0.214	<0.001	0.271	<0.001	0.115	<0.001	0.104	<0.001
Age group, y, (*N*)								
18–29 (2343)	0.392	<0.001	0.306	<0.001	0.064	0.005	0.088	0.001
30–39 (6925)	0.390	<0.001	0.384	<0.001	0.124	<0.001	0.148	<0.001
40–49 (5174)	0.262	<0.001	0.331	<0.001	0.122	<0.001	0.150	<0.001
50–59 (4309)	0.145	<0.001	0.249	<0.001	0.097	<0.001	0.126	<0.001
60–69 (2501)	0.052	0.010	0.127	<0.001	0.057	0.010	0.040	0.072
70–79 (896)	0.044	0.193	0.053	0.113	0.064	0.070	0.000	0.990
80–95 (408)	−0.054	0.279	−0.087	0.08	−0.017	0.742	−0.089	0.092

DBP diastolic blood pressure, *SBP* systolic blood pressure.

[a]Adjusted for age, sex, total cholesterol, high-density lipoprotein-cholesterol, and fasting plasma glucose.

Table 3 The association between serum uric acid with blood pressure among men and women analyzed by the linear regression analyses.

	Univariable				Multivariable[a]			
	SBP		DBP		SBP		DBP	
	β	*P* value	*β*	*P* value	*β*	*P* value	*β*	*P* value
Men (*N* = 13,300)	0.051	<0.001	0.097	<0.001	0.105	<0.001	0.109	<0.001
Women (*N* = 9256)	0.172	<0.001	0.130	<0.001	0.053	<0.001	0.051	<0.001
Age group in men, y, (*N*)								
18–29 (1443)	0.157	<0.001	0.144	<0.001	0.077	0.005	0.063	0.022
30–39 (4075)	0.167	<0.001	0.181	<0.001	0.137	<0.001	0.147	<0.001
40–49 (2974)	0.107	<0.001	0.139	<0.001	0.117	<0.001	0.150	<0.001
50–59 (2565)	0.070	<0.001	0.119	<0.001	0.093	<0.001	0.133	<0.001
60–69 (1444)	0.028	0.280	0.047	0.07	0.059	0.026	0.057	0.032
70–79 (532)	0.107	0.014	0.018	0.681	0.129	0.004	0.008	0.862
80–94 (267)	−0.017	0.785	−0.091	0.137	−0.01	0.909	−0.087	0.172
Age group in women, y, (*N*)								
18–29 (900)	0.043	0.197	0.091	0.006	0.017	0.608	0.086	0.012
30–39 (2,850)	0.082	<0.001	0.106	<0.001	0.045	0.017	0.076	<0.001
40–49 (2,200)	0.118	<0.001	0.135	<0.001	0.066	0.002	0.088	<0.001
50–59 (1,744)	0.114	<0.001	0.118	<0.001	0.065	0.007	0.074	0.002
60–69 (1,057)	0.056	0.067	0.011	0.722	0.028	0.371	−0.002	0.947
70–79 (364)	−0.013	0.809	−0.015	0.777	−0.035	0.514	−0.022	0.685
80–94 (141)	−0.107	0.208	−0.108	0.203	−0.038	0.656	−0.088	0.321

DBP diastolic blood pressure, *SBP* systolic blood pressure.

[a]Adjusted for age, total cholesterol, high-density lipoprotein-cholesterol, and fasting plasma glucose.

with hypertension diagnosis. Sub-analyses showed that higher uric acid was associated with higher blood pressure only in people aged under 70 years and hyperuricemia was associated with hypertension diagnosis only in people aged less than 60 years. These associations remained after adjusting for risk factors for hypertension including age [19], sex [19], total cholesterol [23], high-density lipoprotein-cholesterol [24], and fasting plasma glucose [25], which are the well-established risk factors for coronary heart disease [22]. Multiple mechanisms have been proposed to explain the association of hyperuricemia with hypertension. These include hyperuricemia promoting endothelial dysfunction [26, 27], activating the renin-angiotensin system [28–30], stimulating oxidative stress and inflammation [28, 31, 32] and promoting renal injury [10, 28, 33].

This study found that hyperuricemia was associated with hypertension diagnosis only in people aged under 60 years. This finding is congruent with a prior report that the

Table 4 The association between hyperuricemia and hypertension in the whole general population and across all decades of adult life using binary logistic regression.

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P* value	aOR[a] (95% CI)	*P* value
Overall (*N* = 22,556)	1.76 (1.64–1.90)	<0.001	1.54 (1.41–1.67)	<0.001
Age group, y, (*N*)				
18–29 (2343)	2.90 (2.25–3.73)	<0.001	1.49 (1.12–1.98)	0.006
30–39 (6925)	2.67 (2.30–3.09)	<0.001	1.55 (1.32–1.82)	<0.001
40–49 (5174)	2.08 (1.76–2.46)	<0.001	1.44 (1.21–1.72)	<0.001
50–59 (4309)	1.63 (1.37–1.95)	<0.001	1.43 (1.19–1.71)	<0.001
60–69 (2501)	1.22 (0.98–1.53)	0.079	1.21 (0.96–1.52)	0.113
70–79 (896)	1.38 (0.93–2.06)	0.115	1.35 (0.89–2.04)	0.154
80–95 (408)	1.10 (0.61–2.00)	0.750	1.19 (0.64–2.20)	0.581

aOR adjusted odds ratio, *CI* confidence interval.

[a]Adjusted for age, sex, total cholesterol, high-density lipoprotein-cholesterol, and fasting plasma glucose.

Table 5 The association between hyperuricemia and hypertension in men and women and across all decades of adult life using binary logistic regression.

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P* value	aOR[a] (95% CI)	*P* value
Men (*N* = 13,300)	1.32 (1.21–1.44)	<0.001	1.51 (1.38–1.66)	<0.001
Women (*N* = 9256)	2.46 (2.08–2.92)	<0.001	1.21 (0.98–1.49)	0.740
Age group in men, y, (*N*)				
18–29 (1443)	2.04 (1.55–2.67)	<0.001	1.51 (1.13–2.03)	0.006
30–39 (4075)	1.75 (1.50–2.05)	<0.001	1.58 (1.34–1.87)	<0.001
40–49 (2974)	1.45 (1.21–1.74)	<0.001	1.43 (1.19–1.73)	<0.001
50–59 (2565)	1.61 (1.31–1.98)	<0.001	1.65 (1.33–2.03)	<0.001
60–69 (1444)	1.07 (0.81–1.42)	0.625	1.11 (0.83–1.47)	0.516
70–79 (532)	1.38 (0.80–2.39)	0.245	1.45 (0.83–2.55)	0.190
80–94 (267)	0.78 (0.39–1.56)	0.475	0.81 (0.40–1.66)	0.570
Age group in women, y, (*N*)				
18–29 (900)	2.00 (0.68–5.85)	0.208	1.22 (0.39–3.79)	0.737
30–39 (2850)	1.85 (0.98–3.53)	0.060	1.22 (0.61–2.43)	0.568
40–49 (2200)	2.18 (1.33–3.57)	0.002	1.66 (0.99–2.79)	0.057
50–59 (1744)	1.11 (0.77–1.60)	0.579	0.87 (0.59–1.28)	0.475
60–69 (1057)	1.49 (1.02–2.17)	0.039	1.39 (0.93–2.05)	0.105
70–79 (364)	1.36 (0.75–2.45)	0.309	1.18 (0.64–2.19)	0.600
80–94 (141)	2.48 (0.69–8.89)	0.162	4.25 (1.08–16.76)	0.039

aOR adjusted odds ratio, *CI* confidence interval, *UA* uric acid.

[a]Adjusted for age, total cholesterol, high-density lipoprotein-cholesterol, and fasting plasma glucose.

xanthine oxidase inhibitor allopurinol did not lower either systolic or diastolic blood pressure in older-aged cohorts of people [16, 17]. This is also consistent with the finding from the Framingham Study that hyperuricemia was associated with an increased risk of coronary heart disease in people aged below 60 years and this association diminished in people aged 60 years and over [5]. These findings suggest that trials designed to test the value of treating hyperuricemia in people with hypertension should focus on including younger participants. A recent meta-analysis reported that high circulating uric acid is associated with a 10% higher risk for coronary heart disease mortality and an 8% higher risk for stroke mortality [34]. Overall this suggests treating hyperuricemia may have value in reducing cardiovascular risk, particularly in younger people.

This study found a biphasic association of diastolic blood pressure with age. Diastolic blood pressure increased after 30 years of age, reached a peak at 50–59 years and slightly decreased at 60–69 years. Diastolic blood pressure significantly decreased in people over 70 years. The early increase in diastolic blood pressure may be related to increased peripheral vascular resistance in small vessels associated with aging [35]. The continuous decrease in diastolic blood pressure after 60 years may be related to the

worsening of large artery stiffness [35]. Healthy elastic large arteries expand during systole and serve as an energy reservoir to maintain peripheral perfusion during diastole. A previous study showed that, in aged people (mean age of 60 years), higher carotid-femoral pulse wave velocity (cfPWV, an indicator of arterial stiffness) at baseline was associated with a decrease in diastolic blood over approximately 8 years [36]. Therefore, aged people with large artery stiffness may have lower diastolic blood pressure [37].

Large arteries become stiffer in older people. The observation that higher uric acid was only associated with hypertension in people under 60 years may suggest that the effect of uric acid on blood pressure relies on a relatively healthy and elastic blood vessel. This theory was supported by the observation that the association between higher blood pressure and higher uric acid became weaker in older people, which was consistent with literature reports [12, 38, 39]. This could be suggestive of direct effects of uric acid on the blood vessel wall as explaining its relationship with hypertension.

This study found that serum uric acid levels were higher in men than those in women, which is consistent with literature reports [40, 41]. Higher serum uric acid was independently associated with both higher systolic and higher diastolic blood pressure in both men and women, which is in agreement with literature reports [39, 42]. This study found that hyperuricemia was associated with hypertension in both men and women, with the unadjusted association being stronger in women than in men which are consistent with previous reports [43, 44]. However, the association in women was lost after adjusting for risk factors for both hypertension and cardiovascular disease (age, sex, total cholesterol, high-density lipoprotein cholesterol, and fasting blood glucose), indicating that hyperuricemia was not an independent risk factor for hypertension in women. The underlying mechanism is unknown. Future studies need to investigate whether hyperuricemia is an independent risk factor for hypertension in females in other ethnic groups and whether lowering serum uric acid would benefit males more than females in reducing the risk of hypertension and cardiovascular events.

This study found that the prevalence of hyperuricemia was high (17.7%) in people aged 18–29 years and then slightly and steadily decreased over a few decades to 13.2% in people aged 50–59 years. Hyperuricemia steadily increased to 18.6% in people aged 80–95 years. This biphasic pattern of the prevalence of hyperuricemia was consistent with the National Health and Nutrition Examination Survey 2007–2008 in US subjects [45]. Therefore, the current consensus that the prevalence of hyperuricemia increases with age [40] may not be accurate.

A strength of this study was the large sample size with subjects from all decades of adult life which allowed the analysis of the association between hyperuricemia and hypertension across all decades of adult life. This study has a number of limitations. First, the participants' smoking behavior was not assessed. The Framingham Heart Study [22] established risk factor for coronary heart disease include age, sex, blood pressure, total cholesterol, high-density lipoprotein-cholesterol, diabetes, and smoking, which are also risk factors for hypertension [19, 23–25]. The association between blood pressure and uric acid was adjusted for these risk factors except for smoking as the data on smoking were not available. Second, the participants' dietary habits were not assessed. Salt consumption is associated with hypertension [46], and a diet rich in vegetables, fruits, and low-fat dairy foods with reduced saturated and total fat may lower blood pressure [47]. Higher levels of alcohol consumption (≥2 drinks per day) are associated with an increased risk of hypertension [48]. These potential confounding factors were not recorded and therefore could not be adjusted for. Third, physical activity [49], family history of hypertension [50], and other confounding factors that may affect blood pressure were not assessed. Fourth, only a small number of adult participants aged between 18 and 19 years or aged over 90 years were included. The findings may therefore not apply to these people. Fifth, the results from this study may not be able to be directly extrapolated to other countries or ethnicities, as uric acid levels in people from other places may be different from Chinese populations [45]. Sixth, blood pressure readings from electronic sphygmomanometers may be inaccurate in some situations, such as when the patient or observer is talking during blood pressure taking [51].

In conclusion, this study found that the association between higher uric acid and higher blood pressure becomes weaker over decades of adult life. In addition, hyperuricemia is associated with hypertension only people under 60 years. Future clinical trials are needed to establish whether treating hyperuricemia in younger rather than older people is beneficial as a therapy for hypertension.

Perspectives

High serum uric acid was associated with both higher systolic and higher diastolic blood pressure after adjusting for confounding risk factors for both hypertension and coronary heart disease. The association between uric acid and blood pressure became weaker in older age groups. Hyperuricemia was associated with hypertension after adjusting for confounding risk factors. The association was limited to people aged under 60 years. This study suggests that trials designed to test the value of treating hyperuricemia in people with hypertension should focus on including younger participants, and treating hyperuricemia

may have value in reducing cardiovascular risk, particularly in younger people.

Summary

What is known about topic

- Uric acid is associated with blood pressure.
- Hyperuricemia is associated with hypertension.

What this study adds

- The association between uric acid and blood pressure is weaker in older age groups.
- The independent association between hyperuricemia and hypertension is limited to men under 60 years.

Funding This work was funded by the Shandong Natural Fund (ZR2015HL008), Shandong Province, China. Yutang Wang is supported by a grant from the National Health and Medical Research Council of Australia (1062671). JG holds a Practitioner Fellowship from the National Health and Medical Research Council of Australia (NHMRC; 1117061) and a Senior Clinical Research Fellowship from the Queensland Government, Australia.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Wu XW, Lee CC, Muzny DM, Caskey CT. Urate oxidase: primary structure and evolutionary implications. Proc Natl Acad Sci USA. 1989;86:9412–6.
2. Mandal AK, Mount DB. The molecular physiology of uric acid homeostasis. Annu Rev Physiol. 2015;77:323–45.
3. 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.
4. Ford ES, Li C, Cook S, Choi HK. Serum concentrations of uric acid and the metabolic syndrome among US children and adolescents. Circulation. 2007;115:2526–32.
5. Brand FN, McGee DL, Kannel WB, Stokes J 3rd, Castelli WP. Hyperuricemia as a risk factor of coronary heart disease: the Framingham study. Am J Epidemiol. 1985;121:11–8.
6. Lehto S, Niskanen L, Rönnemaa T, Laakso M. Serum uric acid is a strong predictor of stroke in patients with non-insulin-dependent diabetes mellitus. Stroke. 1998;29:635–9.
7. Roberts JM, Bodnar LM, Lain KY, Hubel CA, Markovic N, Ness RB, et al. Uric acid is as important as proteinuria in identifying fetal risk in women with gestational hypertension. Hypertension. 2005;46:1263–9.
8. Siu YP, Leung KT, Tong MK, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis. 2006;47:51–9.
9. Forman JP, Choi H, Curhan GC. Plasma uric acid level and risk for incident hypertension among men. J Am Soc Nephrol. 2007;18:287–92.
10. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N. Engl J Med. 2008;359:1811–21.
11. 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.
12. Feig DI, Johnson RJ. Hyperuricemia in childhood primary hypertension. Hypertension. 2003;42:247–52.
13. Syamala S, Li J, Shankar A. Association between serum uric acid and prehypertension among US adults. J Hypertens. 2007;25:1583–9.
14. Cheng W, Wen S, Wang Y, Qian Z, Tan Y, Li H, et al. The association between serum uric acid and blood pressure in different age groups in a healthy Chinese cohort. Medicine. 2017;96:e8953.
15. Qu LH, Jiang H, Chen JH. Effect of uric acid-lowering therapy on blood pressure: systematic review and meta-analysis. Ann Med. 2017;49:142–56.
16. Goicoechea M, de Vinuesa SG, Verdalles U, Ruiz-Caro C, Ampuero J, Rincón A, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol. 2010;5:1388–93.
17. Khan F, George J, Wong K, McSwiggan S, Struthers AD, Belch JJ. Allopurinol treatment reduces arterial wave reflection in stroke survivors. Cardiov Therapeut. 2008;26:247–52.
18. Clark CE, Taylor RS, Shore AC, Ukoumunne OC, Campbell JL. Association of a difference in systolic blood pressure between arms with vascular disease and mortality: a systematic review and meta-analysis. Lancet. 2012;379:905–14.
19. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr., et al. Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension. 2003;42:1206–52.
20. Domagk GF, Schlicke HH. A colorimetric method using uricase and peroxidase for the determination of uric acid. Anal Biochem. 1968;22:219–24.
21. Guo L. Interpretation of the Chinese expert consensus: recommendations for diagnosis and treatment of asymptomatic hyperuricemia complicated with cardiovascular diseases. J Transl Int Med. 2014;2:93–6.
22. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97:1837–47.
23. Ivanovic B, Tadic M. Hypercholesterolemia and hypertension: two sides of the same coin. Am J Cardiovasc Drugs. 2015;15:403–14.
24. Cho KH, Park HJ, Kim JR. Decrease in serum HDL-C level is associated with elevation of blood pressure: correlation analysis from the Korean National Health and Nutrition Examination Survey 2017. In J Environ Res Public Health 2020;17.
25. Kuwabara M, Chintaluru Y, Kanbay M, Niwa K, Hisatome I, Andres-Hernando A, et al. Fasting blood glucose is predictive of hypertension in a general Japanese population. J Hypertens. 2019;37:167–74.
26. Mercuro G, Vitale C, Cerquetani E, Zoncu S, Deidda M, Fini M, et al. Effect of hyperuricemia upon endothelial function in patients at increased cardiovascular risk. Am J Cardiol. 2004;94:932–5.
27. Kanbay M, Huddam B, Azak A, Solak Y, Kadioglu GK, Kirbas I, et al. A randomized study of allopurinol on endothelial function and estimated glomular filtration rate in asymptomatic

hyperuricemic subjects with normal renal function. Clin J Am Soc Nephrol. 2011;6:1887–94.
28. Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL, et al. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension. 2001;38: 1101–6.
29. Saito I, Saruta T, Kondo K, Nakamura R, Oguro T, Yamagami K, et al. Serum uric acid and the renin-angiotensin system in hypertension. J Am Geriatrics Soc. 1978;26:241–7.
30. 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.
31. 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.
32. Ogino K, Kato M, Furuse Y, Kinugasa Y, Ishida K, Osaki S, et al. Uric acid-lowering treatment with benzbromarone in patients with heart failure: a double-blind placebo-controlled crossover preliminary study. Circulat Heart Fail. 2010;3:73–81.
33. Soletsky B, Feig DI. Uric acid reduction rectifies prehypertension in obese adolescents. Hypertension. 2012;60:1148–56.
34. Mazidi M, Katsiki N, Mikhailidis DP, Banach M. Associations of serum uric acid with total and cause-specific mortality: Findings from individuals and pooling prospective studies. Atherosclerosis. 2020;296:49–58.
35. Pinto E. Blood pressure and ageing. Postgrad Med J. 2007;83: 109–14.
36. Coutinho T, Bailey KR, Turner ST, Kullo IJ. Arterial stiffness is associated with increase in blood pressure over time in treated hypertensives. J Am Soc Hypertens. 2014;8:414–21.
37. Ogola BO, Zimmerman MA, Clark GL, Abshire CM, Gentry KM, Miller KS, et al. New insights into arterial stiffening: does sex matter? Am J Physiol Heart Circ Physiol. 2018;315:H1073–87.
38. Wang Y, Hu J-W, Lv Y-B, Chu C, Wang K-K, Zheng W-L, et al. The role of uric acid in hypertension of adolescents, prehypertension and salt sensitivity of blood pressure. Med Sci Monit. 2017;23:790–5.
39. Sundström J, Sullivan L, D'Agostino RB, Levy D, Kannel WB, Vasan RS. Relations of serum uric acid to longitudinal blood pressure tracking and hypertension incidence. Hypertension. 2005;45:28–33.
40. Multidisciplinary Expert Task Force on Hyperuricemia and Related Diseases. Chinese multidisciplinary expert consensus on the diagnosis and treatment of hyperuricemia and related diseases. Chin Med J. 2017;130:2473–88.
41. 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;2015:762820.
42. Scheepers L, Boonen A, Dagnelie PC, Schram MT, van der Kallen CJH, Henry RMA, et al. Uric acid and blood pressure: exploring the role of uric acid production in The Maastricht study. J Hypertens. 2017;35:1968–75.
43. Bawazier LA, Sja'bani M, Irijanto F, Zulaela Z, Widiatmoko A, Kholiq A, et al. Association of serum uric acid, morning home blood pressure and cardiovascular risk factors in a population with previous prehypertension: a cross-sectional study. BMJ Open. 2020;10:e038046.
44. Lee JJ, Ahn J, Hwang J, Han SW, Lee KN, Kim JB, et al. Relationship between uric acid and blood pressure in different age groups. Clin Hypertens. 2015;21:14.
45. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-8. Arthritis Rheum. 2011;63:3136–41.
46. Stamler J, Rose G, Stamler R, Elliott P, Dyer A, Marmot M. INTERSALT study findings. public health and medical care implications. Hypertension. 1989;14:570–7.
47. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N. Engl J Med. 1997;336:1117–24.
48. Stranges S, Wu T, Dorn JM, Freudenheim JL, Muti P, Farinaro E, et al. Relationship of alcohol drinking pattern to risk of hypertension: a population-based study. Hypertension. 2004;44:813–9.
49. Farpour-Lambert NJ, Aggoun Y, Marchand LM, Martin XE, Herrmann FR, Beghetti M. Physical activity reduces systemic blood pressure and improves early markers of atherosclerosis in prepubertal obese children. J Am Coll Cardiol. 2009;54:2396–406.
50. Selby JV, Friedman GD, Quesenberry CP Jr. Precursors of essential hypertension: pulmonary function, heart rate, uric acid, serum cholesterol, and other serum chemistries. Am J Epidemiol. 1990;131:1017–27.
51. Muntner P, Shimbo D, Carey RM, Charleston JB, Gaillard T, Misra S, et al. Measurement of blood pressure in humans: a scientific statement from the american heart association. Hypertension. 2019;73:e35–66.