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The association of serum uric acid levels with cardiovascular and all-cause mortality in hypertensive patients in China: a cohort study

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Abstract

Purpose

The present study aimed to assess the association of elevated serum uric acid (SUA) and hypouricemia with all-cause mortality and cardiovascular mortality in Chinese hypertensive patients.

Methods

In the present prospective cohort, 9,325 hypertensive patients from Dongguan, China were enrolled from 2014 to 2018 for analysis. Participants were categorized by quintiles of SUA. The hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between SUA, all-cause and cardiovascular mortality were evaluated using the multivariate Cox regression model. After adjusting for multiple confounders, restricted cubic spline analysis was conducted to demonstrate the shape of relationship.

Results

After a median follow-up of 4.18 years for 9,325 participants, there were 409 (4.4%) and 151 (1.6%) reported cases of all-cause and cardiovascular mortality, respectively. By using the third quintile of SUA (6.68 to < 7.55 mg/dL for males, 5.63 to < 6.42 mg/dL for females) as reference, the highest quintiles of SUA was associated with an elevated risk of all-cause (HR: 1.34, 95% CI= 1.00, 1.80) in the crude model, but the association was not significant after adjusting for multiple comparisons. The association between low SUA and mortality, and the dose-response analysis on the non-linearity of SUA-mortality relationship were not statistically significant.

Conclusions

Although the association between SUA levels, all-cause and CVD mortality did not appear to be significant among Chinese hypertensive patients, the findings might be confounded by their medical conditions. Further studies are needed to verify the optimal SUA levels for hypertensive patients.

Keywords

Hyperuricemia, hypouricemia, all-cause mortality, cardiovascular mortality, hypertension

Key Messages

What is already known on this topic

- Elevated levels of serum uric acid (SUA) may increase the risk of all-cause and cardiovascular mortality.
- The magnitude of association between SUA and mortality appears to be inconsistent across different medical conditions.

What this study adds

- This prospective cohort has examined the association of high and low SUA with mortality among hypertensive patients in China.
- The mortality rate did not differ substantially among SUA quintiles, which might be confounded by the medical conditions.

How this study might affect research, practice or policy

- Future studies should explore the optimal SUA levels for hypertensive patients.

INTRODUCTION

Elevated blood pressure (BP) is one of the major risk factors for global disease burden,[1] it can cause severe target organ damage, and a higher risk for mortality. Moreover, serum uric acid (SUA), as the end product of purine metabolism,[2] has been related to hypertension, diabetes, dyslipidemia, and obesity.[3 4] SUA is also being regarded as an independent risk factor for cardiovascular disease (CVD),[5] including heart failure.[6 7] Some studies demonstrated a positive association between hyperuricemia and cardiovascular mortality.[8-11] However, the influence of a low uric acid level on mortality and clinical outcomes has not been established, since only several studies have been performed. A Korean study has demonstrated low uric acid level to be associated with higher all-cause mortality in patients undergoing dialysis.[12] A cohort study in Japan reported that low uric acid level (<4.6 mg/dl in men and<3.3 mg/dl in women) can increase the risk of CVD mortality.[13] Despite the aforementioned studies, the prospective impact of hyperuricemia and hypouricemia in the risk of mortality has not been investigated adequately, including people with hypertension. To address this research gap, we aimed to assess the association of elevated SUA and

hypouricemia with all-cause mortality and cardiovascular mortality in Chinese hypertensive patients.

METHODS

Study population

All participants were essential hypertensive patients aged 18 years or above, who lived in Liaobu community in Dongguan, Guangdong Province of China. Patients were enrolled during January and December 2014 and being followed until 31 December 2018. Participants with missing baseline data on SUA levels or blood pressure (BP), or patients that took diuretic and other uric acid lowering drugs were excluded (Figure 1). Finally, 9,325 participants were included in this analysis. This study was following the principles outlined in the Declaration of Helsinki and was approved by the institutional medical ethical committee of the Guangdong Provincial People's Hospital, Guangzhou, China (reference number: 2012143H). All participants provided informed written consent to participate.

Data collection

To measure the level of SUA, fasting blood samples were drawn after 8 to 10 hours of overnight fasting. After that, the samples were centrifuged at 3,500 rounds per minute for 15 minutes to obtain a serum layer for analysis. The concentration of SUA was measured using an automatic biochemical analyzer (Hitachi 7170A).[14] Demographic data from participants were obtained using a standardized questionnaire, including age, sex, race, lifestyle habits such as smoking (yes or no), alcohol intake (yes or no), history of hypertension (yes or no), coronary heart diseases (CAD) (yes or no), diabetes (yes or no), stroke (yes or no) and antihypertensive medication use (antihypertensive drugs: β-receptor blockers (Beta), calcium channel blockers (CCB), angiotensin converting enzyme inhibitors(ACEI)/angiotensin (ARB)). Height and weight were measured using an automatic scale, and body mass index (BMI) was calculated using these measurements as follow: BMI = body weight/height^2. Diabetes mellitus (DM) was defined as fasting blood glucose (FBG) ≥126 mg/dL, the use of

hypoglycemic agents, or self-reported history of diabetes.[14] Blood samples drawn from the antecubital vein were obtained after overnight fasting. Serum levels of uric acid, FBG, total cholesterol (CHOL), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were measured by standard method in core clinical laboratory. BP and heart rate (HR) were measured by the Omron HBP-1100u professional portable BP monitor (Japan) placed on the right arm, while the individual was in a sitting position more than 5 minutes. The average measurement values of systolic BP (SBP) and diastolic BP (DBP) were used. Hypertension was defined as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg or self-reported use of antihypertensive drug in the last 2 weeks.[14]

Outcome assessment and follow-up

All-cause and cardiovascular mortality were the outcomes of the present study, which were assessed according to the ICD-10.[15] All-cause mortality included deaths from all causes. Cardiovascular mortality was defined by International Classification of Diseases, 10th Edition, Clinical Modification System codes (ICD-10) (I00-I09, I11, I13, and I20-I51) derived from death-certificate data. From the time of enrolment until 31 December 2018, data on mortality were obtained from the local medical insurance administration of Dongguan City, which were investigated by clinic visit or phone call during follow-up.

Statistical methods

Continuous variables were reported as means and standard deviation (SD), and categorical variables were reported as frequencies with percentages. By using pre-defined normal values (3.5 to 7.2 mg/dL for males, 2.6 to 6.0 mg/dL for females) of SUA,[16] only very few patients from the present study sample were low in SUA (0.6% for males and 0.3% for females). Therefore, participants were categorized by sex-specific quintiles in the study population for all analyses instead. For males, the range of quintiles were < 5.76 mg/dL, 5.76 to < 6.68 mg/dL, 6.68 to < 7.55 mg/dL, 7.55 to < 8.68 mg/dL and ≥8.68 mg/dL, respectively. For females, the range of quintiles were < 4.83 mg/dL, 4.83 to < 5.63 mg/dL, 5.63 to < 6.42 mg/dL, 6.42 to < 7.46 mg/dL and ≥

7.46 mg/dL, respectively. These categories were used to explore the nonlinear associations and better delineate the effects of low and high SUA levels on mortality risk. With the use of Cox proportional hazards models (the third quintile as referent), hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated to demonstrate the association between SUA, all-cause and cardiovascular mortality. Two regression models were built. Model 1 only included SUA, while model 2 was additionally adjusted for age, sex, BMI, SBP, DBP, smoking, alcohol intake, TG, HDL-C, CHOL, FBG comorbidities (stroke, DM, CAD) and medication use (Beta, CCB, ACEI/ ARB). Trend analysis was performed by assigning median values of each SUA quintile and treating it as a continuous variable in the regression model.[17] We performed restricted cubic spline analysis with 3 knots (25th, 50th and 75th percentiles) to detect the shape of dose-response relationships of SUA and mortality, using the median of SUA as the reference point, adjusted by all covariates in Model 2.[18] We used Wald-type statistics testing that a beta-coefficient for second spline is not equal to zero.[19] For the subgroup analyses, we stratified participants by age (<80 or ≥80 years), sex (male or female), antihypertensive medication use (yes or no), and BMI (<25 or ≥25 kg/m^2) to investigate potential sources of effect modification. All p values were two sided, and p values <0.05 were considered statistically significant. To avoid false-positive findings due to multiple comparisons, the significance level of all statistical analyses has been adjusted using Bonferroni correction. All analyses were performed with R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

The baseline characteristics of all the participants according to SUA levels are summarized in Table 1. A total of 9,325 (48.5% male) participants with an average age of 62.22±13.62 years were enrolled at baseline. The overall BMI of participants was 24.9 (SD = 3.93), demonstrating that half of the study population tended to be overweight. There were significant differences in age, SUA, SBP, alcohol intake, BMI, the use of antihypertensive drugs, CHOL, HDLC and TG across the quintiles of SUA

(all P<0.05). In general, all aforementioned variables increased across quintiles except for HDLC that decreased across quintiles.

Exploring the non-linear Association Between SUA and Mortality

There were 409 deaths documented during the follow up period (average = 4.18 years). Among the total cases of deaths, 151 (36.9%) events were attributed by CVD. Univariate and multivariate Cox regression analyses were performed to study the association of SUA level with cardiovascular and all-cause mortality (Table 2). When compared to the third quintile, the highest quintile of SUA was associated with the elevated risk of all-cause (HR: 1.34, 95% CI= 1.00, 1.80) in the crude model (Model 1), but the association was not statistically significant after adjusting for multiple comparisons (p= 0.48). Furthermore, the strength of association of the highest quintile of SUA with all-cause mortality attenuated after being fully adjusted in Model 2 (HR: 0.87, 95% CI= 0.64, 1.18). In the trend analysis, SUA was associated with the elevated risk of all-cause (HR: 1.10, 95% CI= 1.05, 1.16) in the crude model after adjusting for multiple comparisons (Model 1), but the association (HR: 0.98, 95% CI= 0.92, 1.04) was not significant after being fully adjusted in Model 2. For the dose-response analysis (Figure 2), the p-value for nonlinearity was not significant for both all-cause (p=0.29) and CVD mortality (p=0.45).

Subgroup Analyses

As shown in Table 3, after multivariate adjustment for confounders, subgroup analyses were performed in age (≥80 yeas vs. <80 years), sex (male vs. female), the use of antihypertensive drug (yes vs. no) and BMI (≥25 kg/m^2 vs. <25 kg/m^2), respectively. The only significant interaction was found between age and SUA in the relationship between SUA and all-cause mortality, but the association between SUA in quintiles, all-cause and cardiovascular mortality were not significant regardless of subgroups.

DISCUSSION

In a cohort of 9,325 patients with hypertension in China, the present study has

examined the association between both higher and low SUA levels and the risk of all-cause and cardiovascular mortality. Although SUA at the highest quintile might associate with an elevated risk of all-cause mortality in the crude model, the magnitude of association was insignificant after adjusting for multiple comparisons. The dose-response analysis on the non-linearity of SUA-mortality relationship was also insignificant.

The association of elevated SUA levels with all-cause and cardiovascular mortality was examined in several studies.[20-24] For example, one study categorized SUA into quartiles,[14] and they found that hyperuricemia was an independent risk factor of mortality from all causes and total CVD in Taiwanese population. Moreover, few studies have explored the role of both high and low uric acid level in mortality risk. Kuo et al found that individuals with either high (>11.4 mg/dl) or low (<2.9 mg/dl) SUA levels were at high risk for all-cause and cardiovascular mortality by setting the reference group as 5-6 mg/dl.[22] However, the study quality of Kuo et al might be affected by not adjusting for smoking, alcohol intake and BMI, which were the key cardiovascular risk factors.

To date, the underlying pathophysiologic mechanism of for the association between low SUA levels and mortality is still unclear. Uric acid is known for two important opposing properties, namely the antioxidant properties and its role in endothelial dysfunction. Several experimental investigations have demonstrated the free radical-scavenging capacity of SUA, while it can induce endothelial dysfunction.[25-27] A Taiwanese study showed that low uric acid level can also be a marker of malnutrition, and further pointed out that low SUA level was only predictive of increased mortality in older people who were malnourished (as defined by Geriatric Nutritional Risk Index, albumin and BMI).[28]

While previous studies have explored the influence of elevated and low SUA levels on the risk of death, inconsistent results were observed for different patient groups. For example, a study on people with diabetes showed that SUA has no independent role on cardiovascular mortality.[29] In another study of 15,366 participants in the Atherosclerosis Risk in Communities, there was a significant association between

hyperuricemia and mortality (HR 1.18, 95% CI= 1.04, 1.33) in a non-CKD population, while the association in the CKD population was not significant.[30] The connection between hypertension and hyperuricemia also attracts people's attention. Zhang et al reported that SUA level was positively associated with DBP and SBP in both men and women in general population.[31] In a study conducted among Chinese hypertensive patients, hyperuricemia was associated with higher risk for all-cause and cardiovascular mortality.[32] Uric acid is the final oxidation product of purine metabolism,[33] which approximately two-thirds of SUA is excreted by the kidneys, and its excretion level is affected by renal function.[20] In hypertensive patients, increased SUA levels may reflect early renal vascular alterations, with reduction in cortical blood flow and depressed tubular secretion of urate as caused by its reduced delivery to the tubular secretory sites.[34] Besides this, the increased activity of the sympathetic nervous system and hyperinsulinemia have been proved to be associated with reduced renal excretion of uric acid.[35 36]

In order words, the insignificant association between SUA and mortality in our study population might be attributed by several reasons. First, when compared to other studies conducted among general population, all participants in the present study were with essential hypertension. Although we have performed multivariable Cox regression analysis to minimize the interference of other potential risk factors and comorbidities, one also must consider the possibility that hypertension itself may be a risk factor for mortality, and consequently, the presence of hypertension may attenuate the association of SUA with mortality. Second, only very few patients (0.6% for males and 0.3% for females) from the present study sample were low in SUA (<3.5 mg/dL for males and <2.6 mg/dL for females).[16] In other words, patient in the present study might not reach the threshold level of exposure to elevate the mortality risk. Third, when compared to the study conducted among Chinese hypertensive patients,[32] the present study has lower all-cause mortality rate (27.4% vs. 4.4%) and a shorter follow-up period (5.75 years vs. 4.18 years on average). The relatively fewer cases of death and shorter follow-up duration for the present study might limit the statistical power to detect associations between SUA and the risk of mortality. To explore the influence of SUA on mortality

risk across a wider range of exposure, more studies among hypertensive from diverse population should be conducted. In long term, optimal SUA levels for hypertensive patients can be established.

Some potential limitations of the present study should be considered. First, we determined uric acid level at a single time point, and might not account for the changes in SUA with time. Second, information such as smoking status, alcohol use and medical history was self-reported through a questionnaire, and could have resulted in recall bias. Third, some cardiovascular risk factors (e.g. diet and mental health) were not adjusted in the present study, and might result in residual confounding effect. Fourth, this study was conducted solely the Chinese population, so therefore the conclusions of the study cannot be extrapolated to other ethnic population.

CONCLUSION

In summary, this study indicated that SUA levels did not have significant association with all-cause and CVD mortality among Chinese hypertensive patients, which might be confounded by their medical conditions. Further studies are needed to verify the optimal SUA levels for hypertensive patients.

FIGURE LEGEND

Figure 1 Flow chart for participant selection

Figure 2 Association of serum uric acid with all-cause (left) and cardiovascular (right) mortality using restricted cubic spline regression models

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Table 1. The baseline characteristic of participants according to the quintiles of serum uric acid

	Overall	Q1	Q2	Q3	Q4	Q5	p^
	9325	1865	1865	1865	1865	1865	
Age, y	62.22 ± 13.62	60.21 ± 14.28	61.42 ± 13.33	62.01 ± 13.31	62.89 ± 13.34	64.56 ± 13.43	<0.001
Male, n,%	4525 (48.5)	905 (48.5)	905 (48.5)	905 (48.5)	905 (48.5)	905 (48.5)	1.00
SUA, mg/dl	6.71 ± 1.78	4.54 ± 0.74	5.73 ± 0.56	6.55 ± 0.59	7.47 ± 0.66	9.25 ± 1.24	<0.001
SBP, mmHg	136.85 ± 18.96	134.97 ± 18.88	136.26 ± 18.60	136.70 ± 18.59	137.57 ± 18.56	138.74 ± 19.96	<0.001
DBP, mmHg	80.46 ± 11.98	79.93 ± 11.95	80.83 ± 11.78	80.63 ± 11.93	80.52 ± 11.66	80.39 ± 12.53	1.00
Smoking, n,%	2628 (28.2)	496 (26.6)	547 (29.3)	540 (29.0)	523 (28.1)	522 (28.0)	1.00
Alcohol intake, n,%	1505 (16.1)	259 (13.9)	276 (14.8)	330 (17.7)	316 (17.0)	324 (17.4)	0.03
BMI, kg/m2	24.91 ± 3.93	23.70 ± 3.71	24.31 ± 3.66	25.08 ± 3.97	25.45 ± 3.86	26.01 ± 4.01	<0.001
Antihypertensive Drugs, n, %							
Beta	655 (7.0)	99 (5.3)	96 (5.1)	116 (6.2)	147 (7.9)	197 (10.6)	<0.001
CCB	2580 (27.7)	474 (25.4)	501 (26.9)	499 (26.8)	546 (29.3)	560 (30.0)	0.08
ACEI/ARB	4025 (43.2)	697 (37.4)	752 (40.3)	790 (42.4)	838 (44.9)	948 (50.8)	<0.001
Comorbidity, n,%							
Diabetes mellitus	1991 (21.4)	414 (22.3)	407 (21.9)	375 (20.2)	377 (20.3)	418 (22.5)	1.00
Coronary artery disease	190 (2.0)	30 (1.6)	34 (1.8)	32 (1.7)	36 (1.9)	58 (3.1)	0.08
Stroke	242 (2.6)	43 (2.3)	41 (2.2)	59 (3.2)	51 (2.7)	48 (2.6)	1.00
CHOL, mg/dl	213.64 ± 46.06	207.78 ± 44.54	212.60 ± 45.56	214.59 ± 43.97	216.07 ± 46.29	217.14 ± 49.19	<0.001
HDLC, mg/dl	56.96 ± 14.72	58.79 ± 13.67	57.85 ± 13.67	56.64 ± 14.96	55.84 ± 12.46	55.67 ± 18.02	<0.001
TG, mg/dl	158.57 ± 144.93	131.13 ± 117.87	144.53 ± 137.19	156.45 ± 135.13	165.25 ± 135.56	195.49 ± 182.62	<0.001
FBG, mmol/L	5.60 ± 1.78	5.72 ± 2.21	5.55 ± 1.74	5.58 ± 1.82	5.53 ± 1.54	5.61 ± 1.52	1.00

Note: Values are mean ± standardized differences or n (%).
^ All p-values are being adjusted by Bonferroni correction.
Abbreviation: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHOL, cholesterol; HDL, high-density lipoprotein; TG, triglycerides; FBG, fasting blood glucose; SUA, serum uric acid.

Table 2. Association between UA level and risks of all-cause and cardiovascular mortality

		Model 1#		Model 2#	
All-cause mortality	Case/total (%)	HRs (95%CI)	P-value^	HRs (95%CI)	P-value^
SUA, mg/dl					
Continuous variable	409/9325 (4.4%)	1.10 (1.05,1.16)	<0.001*	0.98 (0.92,1.04)	1.00
Q1	59/1865 (3.2%)	0.94 (0.67,1.33)	1.00	0.95 (0.67,1.36)	1.00
Q2	60/1865 (3.2%)	0.88 (0.63,1.25)	1.00	0.92 (0.65,1.31)	1.00
Q3	72/1865 (3.9%)	1.00 (Ref)		1.00 (Ref)	
Q4	100/1865 (5.4%)	1.26 (0.93,1.70)	1.00	0.98 (0.71,1.34)	1.00
Q5	118/1865 (6.3%)	1.34 (1.00,1.80)	0.48	0.87 (0.64,1.18)	1.00
Cardiovascular mortality	Case/total (%)	HRs (95%CI)	P-value	HRs (95%CI)	P-value
SUA, mg/dl					
Continuous variable	151/9325 (1.6%)	1.09 (1.00,1.19)	0.47	0.98 (0.88,1.07)	1.00
Q1	21/1865 (1.1%)	0.90 (0.51,1.60)	1.00	0.92 (0.50,1.67)	1.00
Q2	19/1865 (1.0%)	0.75 (0.42,1.35)	1.00	0.79 (0.43,1.45)	1.00
Q3	27/1865 (1.4%)	1.00 (Ref)		1.00 (Ref)	
Q4	42/1865 (2.3%)	1.40 (0.86,2.27)	1.00	1.04 (0.62,1.74)	1.00
Q5	42/1865 (2.3%)	1.26 (0.78,2.05)	1.00	0.75 (0.44,1.26)	1.00

#Model 1 did not adjust for any covariates; Model 2 adjust for age, sex, body mass index, systolic blood pressure, diastolic blood pressure, smoking, alcohol intake, cholesterol, high-density lipoprotein, triglycerides, fasting blood glucose, comorbidities (stroke, diabetes, and coronary artery disease), and medication use (antihypertensive drugs: β-receptor blockers, calcium channel blockers, angiotensin converting enzyme inhibitors). *p<0.05.

^ All p-values are being adjusted by Bonferroni correction.

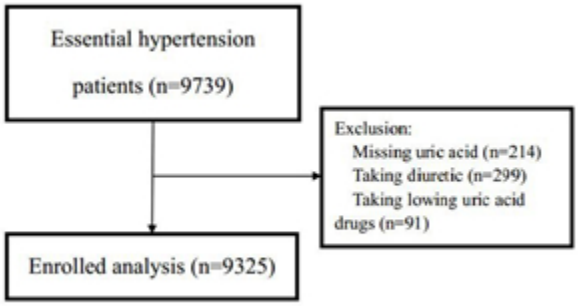
Abbreviations: SUA, serum uric acid; CI, confidence interval; Q, quintile; Ref, reference.

Table 3. Subgroup analyses for the relationship of serum uric acid in quintile with all-cause and cardiovascular mortality

	Continuous	Q1	Q2	Q3	Q4	Q5
			HRs (95%CI)			
All-cause mortality						
Age, years (p-interaction=0.03)						
≥80	0.96 (0.87,1.05)	0.92 (0.52,1.61)	1.28 (0.76,2.15)	1.00 (Ref)	0.81 (0.49,1.33)	0.73 (0.45,1.18)
<80	1.00 (0.92,1.07)	0.93 (0.59,1.48)	0.74 (0.46,1.21)	1.00 (Ref)	1.12 (0.74,1.69)	0.97 (0.64,1.45)
Sex (p-interaction=0.88)						
Male	1.00 (0.93,1.08)	1.11 (0.69,1.77)	0.82 (0.50,1.35)	1.00 (Ref)	1.03 (0.67,1.58)	1.02 (0.67,1.54)
Female	0.97 (0.89,1.06)	0.76 (0.44,1.33)	1.13 (0.68,1.87)	1.00 (Ref)	0.96 (0.61,1.53)	0.79 (0.50,1.24)
Use of antihypertensive drug (p-interaction=0.32)						
Yes	0.95 (0.89,1.02)	0.87 (0.55,1.37)	0.97 (0.64,1.48)	1.00 (Ref)	0.96 (0.67,1.39)	0.77 (0.54,1.12)
No	1.11 (1.09,1.12)	1.09 (0.60,2.00)	0.71 (0.36,1.39)	1.00 (Ref)	0.93 (0.50,1.74)	1.07 (0.60,1.91)
BMI, kg/m² (p-interaction=0.10)						
≥25	0.96 (0.88,1.05)	0.71 (0.40,1.28)	0.76 (0.43,1.35)	1.00 (Ref)	0.86 (0.54,1.38)	0.61 (0.39,0.98)
<25	0.98 (0.91,1.06)	1.13 (0.72,1.79)	1.02 (0.65,1.60)	1.00 (Ref)	1.03 (0.67,1.58)	1.03 (0.68,1.56)
Cardiovascular mortality						
Age, years (p-interaction=0.26)						
≥80	1.00 (0.86,1.15)	0.71 (0.29,1.73)	1.03 (0.45,2.32)	1.00 (Ref)	0.82 (0.39,1.74)	0.73 (0.35,1.52)
<80	0.93 (0.82,1.07)	1.12 (0.49,2.60)	0.56 (0.21,1.50)	1.00 (Ref)	1.31 (0.63,2.71)	0.74 (0.34,1.59)
Sex (p-interaction=0.50)						
Male	1.01 (0.88,1.16)	1.65 (0.69,3.98)	0.77 (0.27,2.20)	1.00 (Ref)	1.40 (0.62,3.18)	1.12 (0.50,2.55)
Female	0.96 (0.84,1.11)	0.48 (0.20,1.19)	0.83 (0.38,1.79)	1.00 (Ref)	0.79 (0.40,1.56)	0.58 (0.29,1.15)
Use of antihypertensive drug (p-interaction=0.85)						
Yes	0.97 (0.87,1.08)	1.05 (0.51,2.17)	0.87 (0.43,1.77)	1.00 (Ref)	1.04 (0.57,1.89)	0.91 (0.50,1.64)
No	0.99 (0.80,1.22)	0.83 (0.27,2.55)	0.54 (0.15,1.96)	1.00 (Ref)	1.08 (0.39,3.01)	0.35 (0.10,1.26)
BMI, kg/m² (p-interaction=0.20)						
≥25	0.96 (0.82,1.12)	0.41 (0.11,1.52)	1.02 (0.40,2.59)	1.00 (Ref)	0.86 (0.37,1.97)	0.56 (0.25,1.27)
<25	1.00 (0.88,1.14)	1.23 (0.59,2.54)	0.65 (0.29,1.47)	1.00 (Ref)	1.22 (0.62,2.38)	0.89 (0.44,1.78)

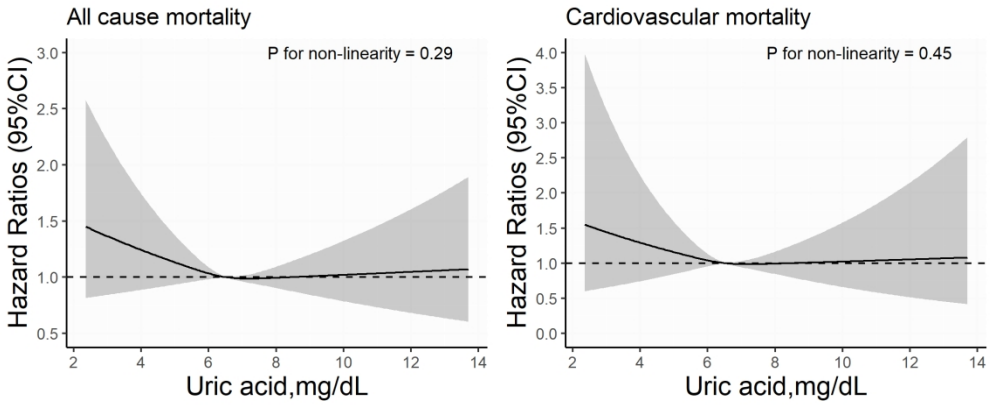
When analyzing a subgroup variable, age, sex, body mass index, systolic blood pressure, diastolic blood pressure, smoking, alcohol intake, cholesterol, high-density lipoprotein, triglycerides, fasting blood glucose, comorbidities (stroke, diabetes, and coronary artery disease), and medication use (antihypertensive drugs: β-receptor blockers, calcium channel blockers, angiotensin converting enzyme inhibitors) were all adjusted except the variable itself.

Abbreviations: BMI, body mass index; HRs, hazard ratios; CI, confidence interval; Q, quintile.



Flow chart for participant selection

53x30mm (144 x 144 DPI)



Association of serum uric acid with all-cause (left) and cardiovascular (right) mortality using restricted cubic spline regression models

203x84mm (300 x 300 DPI)