Association between serum uric acid level and mortality in China

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Abstract

Background: Whether there is an association between serum uric acid (SUA) level and risk of mortality in the general population remains unclear. Based on the China National Survey of Chronic Kidney Disease linked to mortality data, a population-based cohort study was performed to investigate the association between SUA level and all-cause mortality, cardiovascular disease (CVD) mortality, and cancer mortality in China.

Methods: The survival status of participants in the cross-sectional survey was identified from January 1, 2006 to December 31, 2017. Only 33,268 individuals with complete SUA data among the 47,204 participants were included in the analysis. We determined the rates of all-cause mortality, CVD mortality, and cancer mortality. We used Cox proportional hazards regression models to evaluate the effect of the SUA level on mortality.

Results: During a total of 297,538.4 person-years of follow-up, 1282 deaths occurred. In the Cox proportional hazards regression model, the rate of all-cause mortality, CVD mortality, and cancer mortality had a U-shaped association with SUA levels only in men, whereas no significant associations were detected in women. For all-cause mortality in men, the multivariable-adjusted hazard ratios (HRs) in the first, second, and fourth quartiles compared with the third quartile were 1.31 (95% confidence interval [CI] 1.04–1.67), 1.17 (95% CI 0.92–1.47), and 1.55 (95% CI 1.24–1.93), respectively. For CVD mortality, the corresponding HRs were 1.47 (95% CI 1.00–2.18), 1.17 (95% CI 0.79–1.75), and 1.67 (95% CI 1.16–2.43), respectively. For the cancer mortality rate, only a marginally significant association was detected in the fourth quartile compared with the third quartile with an HR of 1.43 (95% CI 0.99–2.08).

Conclusions: The association between SUA and mortality differed by sex. We demonstrated a U-shaped association with SUA levels for all-cause and CVD mortalities among men in China.

Keywords: Cardiovascular diseases; Sex characteristics; Serum uric acid; China; Cohort study; Mortality; Population-based

Background

Uric acid (UA) is the end product of purine breakdown.[1] The kidney eliminates much of the generated UA. Serum uric acid (SUA) levels are mainly determined by the purine metabolism rate and renal function.[2] In 1988, the Framingham Study was the first investigation on the association between SUA levels and cardiovascular outcomes in the general population; however, no clear link was found by 1999.[3,4] Currently, the role of UA as an independent risk factor for mortality remains a subject of controversy. Classically, high SUA levels are suggested to be a risk factor for various mortalities, including all-cause mortality, cardiovascular disease (CVD) mortality, and cancer mortality, in many epidemiology studies.[5-12] Gradually, several studies have shown that low SUA levels were also significantly associated with increased all-cause mortality in general populations, especially in elderly individuals and patients undergoing hemodialysis.[13-18] The EPOCH-JAPAN Study demonstrated that low SUA levels (<4.6 mg/dL in men and <3.3 mg/dL in women) increase CVD mortality.[13] Cho *et al*[14] investigated whether both low and high SUA levels were predictive of increased specific mortality, supporting a U-shaped association between SUA levels and adverse health outcomes.

Additionally, SUA levels were higher in men compared with women. The distribution of SUA levels according to

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sex was attributed to the influence of estrogens.[19] Considering the sex difference in SUA levels, many studies have analyzed the association between SUA levels and mortality.[3,4,9-11,14] However, there was no agreement about the association between mortality and SUA level based on sex.

In China, the prevalence of hyperuricemia has increased in recent years. In 2014, Liu *et al*[20] found that the adjusted prevalence of hyperuricemia among Chinese adults in 2009 to 2010 was 8.4% to 9.9%. The SUA level might be associated with various mortalities, and the sex-specific relationship was controversial. In addition, research on the association in the Chinese population is limited. Considering the data obtained from the China National Survey of Chronic Kidney Disease with a link to mortality data through the national death registry, we aimed to investigate the association between SUA level and mortality in Chinese adults.

Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Institutional Review Board committee of Peking University First Hospital (No. 2007[053]). Written informed consent was obtained from every participant before the data collection.

Study population

The current study was based on a cross-sectional study named the China National Survey of Chronic Kidney Disease. The participants were non-institutionalized adults (≥18 years) recruited from 13 provinces of China via a multistage, stratified sampling method.[21,22] A total of 50,550 people were invited to participate. Of these invited individuals, 47,204 completed the survey and examination and 33,268 completed SUA measurement.

Data collection

Blood and urine samples were analyzed at the central laboratory in each province. SUA was measured from overnight fasting blood collected by venipuncture. We used two levels of education in the analyses: junior high school or lower (<9 years of education) and high school or higher (≥9 years of education). Current smoking was defined as smoking every day for at least 1 year. Alcohol intake (habitual drinker [drink once per day or more] *vs.* non-habitual drinker [six times per week to once per month or almost never]), height, and weight were measured according to standard protocols. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Blood pressure (BP) was measured using a sphygmomanometer three times at 1-min intervals. The mean of the three readings was calculated. Hypertension was defined as a systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, self-reported use of antihypertensive medications in the last 2 weeks, or any self-reported history of hypertension. Fasting blood glucose was measured enzymatically with a glucose oxidase method. Diabetes was defined as fasting plasma glucose ≥126 mg/dL (7.0 mmol/L), use of hypoglycemic agents, or any self-reported history of diabetes.

Serum creatinine was measured from overnight fasting blood collected by venipuncture, and urinary creatinine was measured from an overnight fasting urine sample. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equations for White or other (not Black) races.[23] Serum triglycerides (TGs) and low-density lipoprotein cholesterol (LDL-C) were measured using a Hitachi 7600 auto-analyzer (Hitachi; Tokyo, Japan).

Outcomes

Data from the China National Survey of Chronic Kidney Disease were linked to the Master Death file (from January 1, 2008, to December 31, 2017) of the China Cause of Death Reporting System to determine all-cause mortality and cause-specific mortality.[24] The system is managed by the Chinese Center for Disease Control and Prevention, and death cases are reported by nearly all hospitals across China with death certificates and the International Classification of Diseases (ICD) coded causes using an internet-based reporting system. The underreporting rate was estimated to be 16.68% in 2006 to 2008.[25] Personal identification numbers were used as the key variable for linking the data, and information, including name, gender, birth date, and home address, was used to verify the accuracy of linkage. Causes of death in ICD codes I00–I99 were classified as CVD. Causes of death in ICD codes C00–C99 were classified as cancer disease. We used the deidentified merged data for the analyses.

Statistical analysis

Men and women were assigned separately to four groups according to SUA level quartiles. Continuous data are presented as the mean ± standard deviation, except for albumin creatinine ratio and TG, which are presented as the median (interquartile range [IQR]) due to large skewness. Categorical variables are presented as numbers and proportions. The follow-up time for each participant in the study was the length of time between the date of on-site examination and the end of follow-up (December 31, 2017) or date of death, whichever came first. All-cause, cardiovascular, and cancer-specific mortality rates were calculated as the number of deaths per 10,000 person-years. We depicted the cumulative survival rates for all-cause mortality, cardiovascular mortality, and cancer mortality according to quartile categories of SUA level and compared these values using a log-rank test.

We used Cox proportional hazards regression models to evaluate the effect of the SUA level on mortality. The reference group was defined as the lowest mortality incidence group in both men and women. Univariable- and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. Three models were used with progressively increased adjustments for

confounding variables that could affect the association between SUA level and mortality. Covariates included in the multivariable-adjusted regression model were age (a continuous variable), sex, education (≥high school *vs.* <high school), current smoker (yes *vs.* no), BMI (continuous), hypertension (yes *vs.* no), diabetes mellitus (yes *vs.* no), rural *vs.* urban resident, TG (continuous), LDL-C (continuous), serum creatinine (continuous), and eGFR (continuous). To further explore the shape of the non-linear association between the SUA level and the risk of all-cause, CVD, and cancer mortalities, restricted cubic splines with knots were used at the 5th, 50th, and 95th percentiles of the UA distribution.[26] The restricted cubic spline survey investigated by Desquilbet and Mariotti[26] has been widely used in dose-response analyses in public health research.[27,28] Because of the heterogeneous association between SUA and mortality reported in a previous study, we performed all analyses stratified by sex.[3,4,9-11,14,19]

All analyses were conducted with SAS software (version 9.4, SAS Institute, Cary, NC, USA). A statistically significant difference was defined as a P value < 0.05.

Results

Patient characteristics and SUA levels

The mean age of the population at baseline was 47.3 ± 15.5 years. A proportion of 44.1% of participants were male. The mean SUA level was 5.02 ± 1.56 mg/dL, and the level was significantly higher in men than in women (5.59 ± 1.60 *vs.* 4.57 ± 1.38 mg/dL, $P < 0.001$). In both men and women, higher SUA levels were associated with advanced age, higher BMI, diastolic BP level, serum creatinine, TGs, and LDL-C levels; the reduced likelihood of attending high school or above and rural residents. Men with higher SUA levels were more likely to be current smokers and habitual drinkers, whereas no significant results were found in women. This finding may be due to the low prevalence of these habits in women [Tables 1 and 2].

Mortality

During a total of 297,538.4 person-years of follow-up, 1282 deaths occurred among 33,268 participants (672 in men and 610 in women). A total of 486 deaths were ascribed to CVD (250 in men and 236 in women) and 393 to cancer (219 in men and 174 in women). The median follow-up duration was 8.89 years (IQR: 7.95–10.10 years).

The participants were grouped according to the SUA quartile level. The probability of all-cause mortality and CVD mortality for men increased with the ascending category of quartile 3, quartile 2, quartile 1, and quartile 4 [Supplementary Figures 1 and 2, http://links.lww.com/CM9/A667, $P < 0.001$ and $P < 0.05$]. The fully adjusted model included age, education, current smoking, alcohol

Table 1: Baseline characteristics of participants by serum uric acid of male participants from China National Survey of Chronic Kidney Disease.

Characteristic	All	SUA, mg/dL				*P* value
		Quartile 1 (<4.475)	Quartile 2 (4.475 to <5.464)	Quartile 3 (5.464 to <6.550)	Quartile 4 (≥6.550)	
N	14,679	3667	3669	3654	3689	
Demographics						
Age, years	47.1 ± 16.0	46.5 ± 16.3	46.2 ± 16.2	47.4 ± 15.9	48.3 ± 15.4	<0.001
BMI*, kg/m^2	23.6 ± 3.4	23.1 ± 3.2	23.3 ± 3.4	23.6 ± 3.4	24.3 ± 3.5	<0.001
Rural residents	8074 (55.0)	2716 (74.1)	2106 (57.4)	1729 (47.3)	1523 (41.3)	<0.001
Educated to high school or above*	6091 (41.5)	1021 (27.8)	1477 (40.2)	1725 (47.2)	1686 (50.6)	<0.001
Current smoker*	7042 (78.0)	1602 (43.7)	1812 (49.4)	1887 (51.6)	1741 (47.2)	<0.001
Habitual drinker*	2730 (18.6)	554 (15.1)	654 (17.8)	716 (19.6)	806 (21.9)	<0.001
Comorbidity						
Hypertension	6287 (42.8)	1533 (41.8)	1496 (40.8)	1535 (42.0)	1723 (46.7)	<0.001
Diabetes mellitus	1038 (7.1)	260 (7.1)	253 (6.9)	235 (6.4)	290 (7.9)	0.110
BP*, mmHg						
Systolic	128.1 ± 16.8	128.8 ± 20.1	128.2 ± 19.3	128.0 ± 19.2	128.7 ± 10.9	0.320
Diastolic	81.9 ± 11.4	82.3 ± 12.0	81.6 ± 11.5	81.7 ± 11.5	82.1 ± 11.0	0.030
Laboratory data						
Creatinine, μmol/L	83.6 ± 20.9	77.0 ± 17.0	82.1 ± 15.8	84.4 ± 15.6	90.8 ± 29.4	<0.001
eGFR, mL·min^{-1}·1.73 m^{-2}	99.3 ± 20.2	105.6 ± 19.6	101.1 ± 19.2	98.1 ± 19.0	92.4 ± 20.6	<0.001
ACR, mg/g	5.1 (1.4, 12.4)	5.4 (1.5, 13.6)	5.2 (1.3,12.9)	5.0 (1.2, 11.5)	5.1 (1.7, 11.9)	0.720
TGs*, mmol/L	1.2 (0.8, 1.9)	0.99 (0.7, 1.4)	1.1 (0.76, 1.6)	1.2 (0.85, 1.9)	1.6 (1.1, 2.5)	<0.001
LDL-C*, mmol/L	2.8 ± 0.8	2.6 ± 0.7	2.7 ± 0.8	2.8 ± 0.8	3.0 ± 1.0	<0.001
Fasting glucose*, mmol/L	5.2 ± 1.6	5.2 ± 1.8	5.2 ± 1.6	5.2 ± 1.6	5.2 ± 1.3	0.250

Data are presented as *n* (%), mean ± standard deviation or median (interquartile). *Missing counts: 132 for BMI; 50 for education level; 18 for triglycerides; 2648 for LDL-C; 11 for current smoker; 38 for alcohol intake; 2899 for BP; 16 for fasting glucose. ACR: Albumin creatinine ratio; BMI: Body mass index; BP: Blood pressure; eGFR: Estimated glomerular filtration rate; IQR: Interquartile range; LDL-C: Low-density lipoprotein cholesterol; SD: Standard deviation; SUA: Serum uric acid; TGs: Triglycerides.

Table 2: Baseline characteristics of participants by serum uric acid of female participants from China National Survey of Chronic Kidney Disease.

Characteristic	All	SUA, mg/dL				*P* value
		Quartile 1 (<4.475)	Quartile 2 (4.475 to <5.464)	Quartile 3 (5.464 to <6.550)	Quartile 4 (≥6.550)	
N	18,589	4646	4665	4630	4648	
Demographics						
Age, years	47.7 ± 15.1	44.7 ± 14.6	46.5 ± 14.8	48.3 ± 14.9	51.4 ± 15.3	<0.001
BMI*, kg/m^2	23.4 ± 3.6	23.0 ± 3.4	23.2 ± 3.7	23.3 ± 3.6	23.9 ± 3.7	<0.001
Rural residents	9119 (49.1)	2938 (63.2)	2415 (51.8)	2065 (44.6)	1701 (36.6)	<0.001
Educated to high school or above*	6390 (34.4)	1273 (27.4)	1642 (35.2)	1739 (37.6)	1736 (37.4)	<0.001
Current smoker*	510 (2.7)	115 (2.5)	143 (3.1)	131 (2.8)	121 (2.6)	0.310
Habitual drinker*	297 (1.6)	56 (1.2)	87 (1.9)	78 (1.7)	76 (1.6)	0.070
Comorbidity						
Hypertension	6999 (37.7)	1593 (34.3)	1602 (34.3)	1728 (37.3)	2076 (44.7)	<0.001
Diabetes mellitus	1246 (6.7)	264 (5.7)	246 (5.3)	289 (6.2)	446 (9.6)	<0.001
BP*, mmHg						
Systolic	125.2 ± 20.8	124.9 ± 21.0	124.2 ± 20.6	124.3 ± 20.6	127.3 ± 21.4	<0.001
Diastolic	79.3 ± 11.4	79.3 ± 11.7	79.0 ± 11.4	79.0 ± 11.2	79.8 ± 11.1	0.002
Laboratory data						
Creatinine, μmol/L	67.6 ± 19.8	65.8 ± 15.7	66.8 ± 20.5	66.9 ± 18.4	70.9 ± 23.3	<0.001
eGFR, mL·min^{-1}·1.73 m^{-2}	96.2 ± 20.5	99.7 ± 18.9	97.9 ± 19.8	96.6 ± 20.3	90.8 ± 21.6	<0.001
ACR, mg/g	7.3 (2.2, 16.6)	8.7 (2.1, 19.6)	7.2 (1.9, 17.1)	6.6 (1.9, 15.2)	7.4 (3.1, 15.0)	0.270
TGs*, mmol/L	1.1 (0.7, 1.7)	0.96 (0.68, 1.4)	1.0 (0.73, 1.5)	1.1 (0.78, 1.7)	1.4 (0.95, 2.1)	<0.001
LDL-C*, mmol/L	2.9 ± 0.90	2.62 ± 0.73	2.76 ± 0.80	2.93 ± 0.87	3.25 ± 1.04	<0.001
Fasting glucose*, mmol/L	5.2 ± 1.5	5.1 ± 1.6	5.1 ± 1.5	5.1 ± 1.4	5.4 ± 1.6	<0.001

Data are presented as *n* (%) or mean ± SD. ACR and TGs are presented as median and interquartile because of high skew. *Missing counts: 182 for BMI; 41 for education level; 16 for triglycerides; 2875 for LDL-C; 22 for current smoker; 48 for alcohol intake; 2984 for BP; 11 for fasting glucose. ACR: Albumin creatinine ratio; BMI: Body mass index; BP: Blood pressure; eGFR: Estimated glomerular filtration rate; IQR: Interquartile range; LDL-C: Low-density lipoprotein cholesterol; SD: Standard deviation; SUA: Serum uric acid; TGs: Triglycerides.

intake, BMI, rural or urban residents, TG, LDL-C, hypertension, diabetes mellitus, and eGFR. In men, compared with the 5.464 to 6.550 mg/dL UA group, the other three quartile groups showed higher mortality, including all-cause, CVD, and cancer mortalities. For all-cause mortality, the multivariable-adjusted HRs in the first, second, and fourth quartiles compared with the third quartile were 1.31 (95% CI: 1.04–1.67), 1.17 (95% CI: 0.92–1.47), and 1.55 (95% CI: 1.24–1.93), respectively. Kaplan-Meier curves for all-cause mortality in men are shown in Supplementary Figure 1, http://links.lww.com/CM9/A667. Regarding the CVD mortality rate, compared with the third quartile, the multivariable-adjusted HRs in the first, second, and fourth quartiles were 1.47 (95% CI: 1.00–2.18), 1.17 (95% CI: 0.79–1.75), and 1.67 (95% CI: 1.16–2.43), respectively. For the cancer mortality rate, compared with the third quartile, the multivariable-adjusted HRs in the first, second, and fourth quartiles were 1.30 (95% CI: 0.87–1.96), 1.01 (95% CI: 0.67–1.53), and 1.43 (95% CI: 0.99–2.08), respectively [Table 3]. In multivariable-adjusted spline regression models for men, a U-shaped association between SUA and mortality was observed, and there was a crossover at SUA levels of 5.5 mg/dL [Figure 1].

In women, the highest level of SUA (≥6.55 mg/dL) was associated with an increased risk of all-cause and CVD mortality in the log-rank test (both $P < 0.01$). In multivariable Cox regression analyses, no significant difference was noted among the four groups [Table 4]. In multivariable-adjusted spline regression models for women, no association was observed between SUA and mortality [Figure 2]. Results for other adjusting variables of all-cause, CVD, and cancer mortalities in the model 3 multivariate analysis for men and women are shown in Supplementary Tables 1 and 2, http://links.lww.com/CM9/A667.

Discussion

In this comprehensive cohort of a general Chinese population, we found that the SUA level was a predictor of all-cause mortality, CVD mortality, and cancer mortality only in men. We found a U-shaped association after adjusting for age, sex, education level, smoking status, alcohol intake status, BMI, hypertension, diabetes mellitus, rural *vs.* urban resident, TG, LDL-C, serum creatinine, and eGFR. The crossover for SUA levels was approximately 5.5 mg/dL.

In general, SUA levels were significantly higher in men compared with women. Sex differences in SUA levels have been confirmed in many previous studies. SUA levels were described as independent risk factors for mortality regardless of sex in some previous studies, whereas others confirmed a definite difference between men and women. The association between mortality and SUA according to sex remains controversial. Recently, a cohort study was performed in South Korea, which also found a U-shaped

Table 3: All-cause, cardiovascular disease, and cancer mortality by uric acid level among male participants from China National Survey of Chronic Kidney Disease ($N = 14,679$).

Items	Person-years	Events	Mortality per 10,000 person-years	*P* value for log-rank test	Multivariable adjusted (HR, 95% CI)* Model 1	Model 2	Model 3
All-cause mortality				0.0001			
Quartile 1	32,055.0	168	52.4		1.35 (1.07–1.69)	1.32 (1.05–1.67)	1.31 (1.04–1.67)
Quartile 2	32,158.9	147	45.7		1.80 (0.93–1.49)	1.17 (0.92–1.48)	1.17 (0.92–1.47)
Quartile 3	32,146.3	135	42.0		Reference	Reference	Reference
Quartile 4	32,919.5	222	68.1		1.55 (1.25–1.91)	1.57 (1.26–1.95)	1.55 (1.24–1.93)
CVD mortality				0.0070			
Quartile 1	32,055.0	69	21.5		1.64 (1.13–2.38)	1.48 (1.01–2.18)	1.47 (1.00–2.18)
Quartile 2	32,158.9	52	16.2		1.23 (0.83–1.83)	1.17 (0.78–1.74)	1.17 (0.79–1.75)
Quartile 3	32,146.3	46	14.3		Reference	Reference	Reference
Quartile 4	32,919.5	83	25.2		1.70 (1.18–2.43)	1.73 (1.20–2.50)	1.67 (1.16–2.43)
Cancer mortality				0.0400			
Quartile 1	32,055.0	54	16.8		1.20 (0.81–1.77)	1.31 (0.88–1.96)	1.30 (0.87–1.96)
Quartile 2	32,158.9	44	13.7		0.98 (0.65–1.1.48)	1.01 (0.67–1.53)	1.01 (0.67–1.53)
Quartile 3	32,146.3	48	14.9		Reference	Reference	Reference
Quartile 4	32,919.5	73	22.4		1.45 (1.00–2.09)	1.43 (0.99–2.07)	1.43 (0.99–2.08)

* Effects of SUA on mortality were expressed as HRs and 95% CIs. Model 1 was adjusted for age. Model 2 was adjusted for all variables in model 1 plus education, current smoking, alcohol intake, BMI, rural or urban residents, TGs, high LDL-C. Model 3 was adjusted for all variables in model 2 plus hypertension, diabetes mellitus, eGFR, as appropriate. BMI: Body mass index; CI: Confidence interval; CVD: Cardiovascular disease; eGFR: Estimated glomerular filtration rate; HR: Hazard ratio; LDL-C: Low-density lipoprotein cholesterol; SUA: Serum uric acid; TGs: Triglycerides; UA: Uric acid.

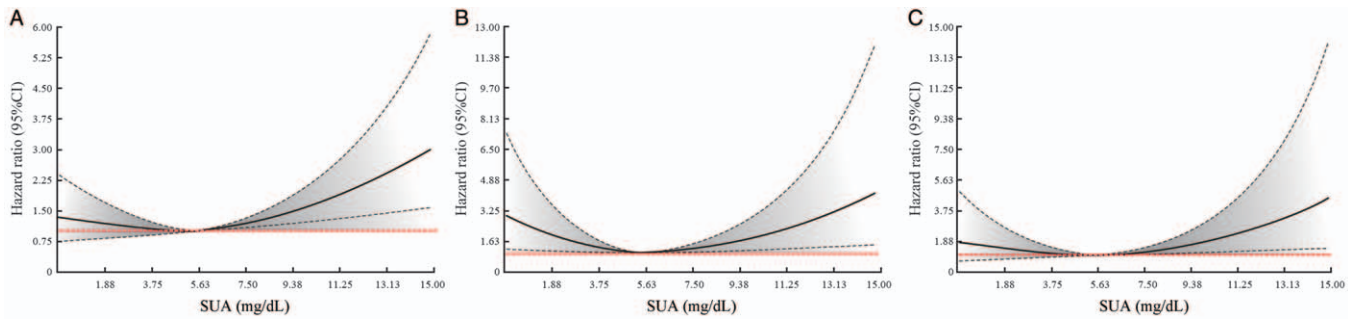

Figure 1: Multivariable-adjusted HRs for (A) all-cause, (B) CVD, and (C) cancer mortality by serum uric acid level among male participants from China National Survey of Chronic Kidney Disease. Solid line indicates estimated HR, dotted line indicates confidence interval, red line is the reference line of HR = 1. CVD: Cardiovascular disease; HR: Hazard ratio; SUA: Serum uric acid.

association between SUA levels and mortality. In contrast to the current study, the SUA level showed predictive value in both men and women.[14] Another study provided novel evidence that the SUA-mortality association differed by sex and demonstrated that a lower SUA was an independent risk factor for all-cause mortality in men.[22] In this study, a U-shaped association between SUA and mortality was exclusively found in men. The inconsistency may be due to the characteristics of the population. In Cho's study,[14] the participants included individuals attending health check-ups. The participants in our cohort included both premenopausal women and postmenopausal women; however, we could not obtain the exact menopausal status, which may also influence the result.

In the current study, the highest UA category (SUA level ≥6.550 mg/dL) of men showed a completely higher risk of variable mortality. High UA levels were associated with gout, hypertension, diabetes, and chronic kidney disease.[8,29-31] Furthermore, it has been confirmed that a high UA level was associated with increased all-cause mortality and CVD mortality in some previous studies.[4,8,9] The pathophysiological mechanism of the association might be attributed to the inflammasome and oxidative stress induced by high uric levels.[32] Oxidative stress with activation of the renin-angiotensin system in human vascular endothelial cells is the main mechanism of UA-induced endothelial dysfunction.[33] These processes might explain the strong association between hyperuricemia and all-cause mortality and CVD mortality.

In addition to the highest level of SUA category, the lowest UA category (SUA level <4.475 mg/dL) in men was also associated with an increased risk of variable mortality. Most interestingly, UA acts as both a potent antioxidant and oxidative stress inducer. More than 50% of human

Table 4: All-cause, cardiovascular disease, and cancer mortality by uric acid level among female participants from China National Survey of Chronic Kidney Disease ($N = 18,589$).

Items	Person-years	Events	Mortality per 10,000 person-years	*P*-value for log-rank test	Multivariable adjusted (HR, 95% CI)* Model 1	Model 2	Model 3
All-cause mortality				<0.001			
Quartile 1	41,539.8	120	28.9		Reference	Reference	Reference
Quartile 2	41,593.7	137	32.9		0.99 (0.77–1.26)	0.93 (0.79–1.29)	1.00 (0.78–1.29)
Quartile 3	41,915.4	151	36.0		0.92 (0.73–1.17)	0.93 (0.78–1.26)	0.98 (0.77–1.25)
Quartile 4	43,329.8	202	46.6		0.92 (0.73–1.15)	1.03 (0.81–1.31)	0.99 (0.78–1.19)
CVD mortality				0.003			
Quartile 1	41,539.8	47	11.3		Reference	Reference	Reference
Quartile 2	41,593.7	53	12.7		0.99 (0.77–1.26)	0.94 (0.50–1.76)	0.93 (0.50–1.76)
Quartile 3	41,915.4	49	11.7		0.92 (0.73–1.72)	1.31 (0.73–2.34)	1.30 (0.73–2.33)
Quartile 4	43,329.8	87	20.1		0.92 (0.73–1.15)	1.44 (0.81–2.54)	1.40 (0.78–2.50)
Cancer mortality				0.050			
Quartile 1	41,539.8	33	7.9		Reference	Reference	Reference
Quartile 2	41,593.7	44	10.6		1.18 (0.75–1.84)	1.13 (0.72–1.78)	1.15 (0.73–1.82)
Quartile 3	41,915.4	37	8.8		0.86 (0.54–1.38)	0.82 (0.51–1.33)	0.85 (0.52–1.37)
Quartile 4	43,329.8	60	13.8		1.01 (0.70–1.66)	0.98 (0.61–1.55)	1.02 (0.64–1.62)

* Effects of SUA on mortality were expressed as HRs and 95% CIs. Model 1 was adjusted for age. Model 2 was adjusted for all variables in model 1 plus education, current smoking, alcohol intake, BMI, rural or urban residents, TGs, high LDL-C. Model 3 was adjusted for all variables in model 2 plus hypertension, diabetes mellitus, eGFR, as appropriate. BMI: Body mass index; CI: Confidence interval; CVD: Cardiovascular disease; eGFR: Estimated glomerular filtration rate; HR: Hazard ratio; LDL-C: Low-density lipoprotein cholesterol; SUA: Serum uric acid; TGs: Triglycerides; UA: Uric acid.

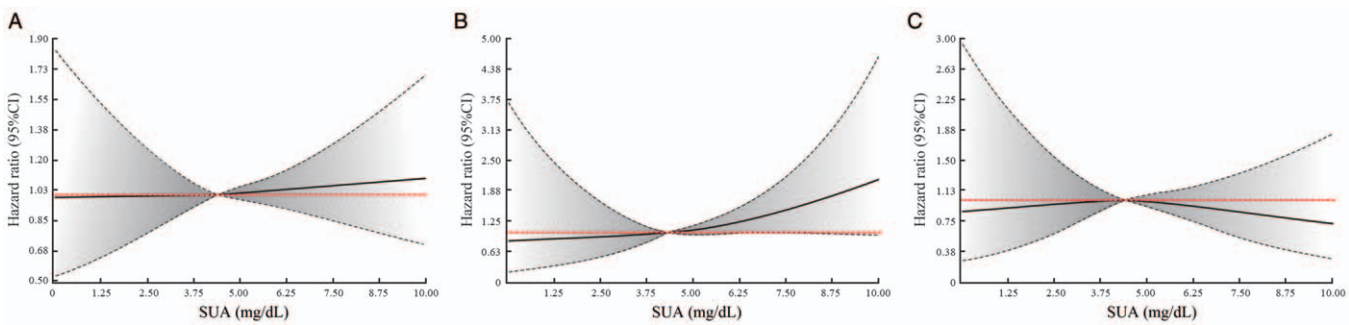

Figure 2: Multivariable-adjusted HRs for (A) all-cause, (B) CVD, and (C) cancer mortality by serum uric acid level among female participants from China National Survey of Chronic Kidney Disease. Solid line indicates estimated HR, dotted line indicates confidence interval, red line is the reference line of HR = 1. CVD: Cardiovascular disease; HR: Hazard ratio; SUA: Serum uric acid.

plasma antioxidant capacity is contributed by UA.[34] Increasing experimental and clinical evidence shows that UA plays an important role *in vivo* as an antioxidant; it increases the production of reactive oxygen species[35] and prevents acute activation of pro-inflammatory cells.[36] An increased risk of atherosclerotic diseases and cancer was observed due to decreased antioxidant potential.[7,37,38] On the other hand, a low SUA level has been proposed as a surrogate marker of malnutrition. In the study of hemodialysis and elderly patients, researchers found that both the lowest and the highest SUA groups were predictive factors for all-cause mortality.[15]

Similar results were observed in previous studies. The predictive value of SUA for mortality was evident. Given that SUA levels are closely related to kidney function, we took the serum creatinine level as one of the most important covariates in this study, which made the conclusions more convincing. Starting from the conclusion of this study, we proposed that controlling SUA levels should be more appropriate than the unchecked lowering of SUA levels without a goal.

Although our study has the advantages of a large sample size of a general population as well as longitudinal validation of adverse outcomes, some limitations should be noted. First, biomarkers were measured in different study centers. Although the measurement was calibrated with the standard sample from the central laboratory and under tight quality control, some variation among different centers might still exist. Second, the mortality rate among different groups of participants in our study might be underestimated. Third, we used baseline status for analyses and did not incorporate changes in UA levels or other changes in lifestyle factors and covariates during follow-up. Finally, due to the limited information, we could not

determine whether UA-lowering agents, anti-uricosuric agents, or uricosuric agents were used in the participants.

In conclusion, the association between SUA and mortality differed by sex. We demonstrated a U-shaped association with SUA levels for all-cause and CVD mortalities among men in China.

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Conflicts of interest

None.

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