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U-Shaped Relationship Between Cardiovascular Mortality and Serum Uric Acid May Be Attributed to Stroke- and Heart-Specific Mortality, Respectively, Among Hypertensive Patients: A Nationally Representative Cohort Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Serum uric acid (UA) is involved in the development of hypertension. However, its impact on mortality in hypertension remains unclear. We aimed to assess the association of cardiovascular and all-cause mortality with UA in a hypertensive population.

Material/Methods: This study included 15 583 hypertensive patients from the NHANES study during 1999-2014. Weighted Cox regression analyses and cubic spline fitting were used to assess the relationship between UA and mortality risk.

Results: Over a median follow-up of 7.4 years (116 351 person-years), a total of 3291 deaths occurred. Mortality was examined according to 5 predefined UA levels: ≤3.5, 3.5-5, 5-6, 6-7.5, and >7.5 mg/dL. In multivariable analysis with 5-6 mg/dL as a reference, the hazard ratios (95% confidence interval) of total mortality across the 5 groups were 1.40 (1.05-1.88), 1.08 (0.95-1.21), 1.00 (reference), 1.14 (1.02-1.29), and 1.74 (1.50-2.02), respectively. According to a restricted cubic spline, we noted a U-shaped relationship between UA and total mortality. The U-shaped relationship between UA and cardiovascular mortality remained in both females and males. The increased cardiovascular mortality in the lowest and highest UA groups was attributed to stroke and heart-specific mortality, respectively. However, serum UA was not significantly associated with cancer mortality.

Conclusions: Our findings showed a U-shaped relationship between serum UA levels and total and cardiovascular mortality in patients with hypertension. Furthermore, low UA was associated with stroke mortality, while higher UA was associated with heart-related mortality. Further research is needed to identify the potential mechanisms of UA in hypertension.

Keywords: Antioxidant Response Elements • Cardiovascular Diseases • Hypertension • Oxidative Stress • Uric Acid

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Background

Hypertension is a well-known and strong risk factor for cardiovascular diseases (CVD), which are the major cause of mortality [1,2]. Uric acid (UA), an end-product metabolite of purine nucleotide in great apes and humans, has been considered as one of the cardiometabolic risk factors in CVD, diabetes, and hypertension [3-5]. Increased serum UA is one of the strongest factors for hypertensive development [6]. Experimental results support that raising uric acid levels causes hypertension in rats [7]. Moreover, pilot studies indicate that lowering serum UA levels can decrease blood pressure in hypertensive patients [8-10].

Interestingly, numerous experimental studies demonstrated that uric acid exerts a beneficial role due to its antioxidant properties [3,11]. It has been demonstrated that uric acid explains about 50% of the total antioxidant capacity in vivo [3]. However, under the setting of pathological acidic or hydrophobic milieu, such as atherosclerotic plaque and cytoplasm, UA becomes a pro-oxidant factor that promotes redox disorder and exerts a deleterious effect in the development and progression of cardiovascular disease [3,11].

Currently, the association of UA levels with adverse outcomes is largely controversial. So far, previous studies noted positive [12-14], negative [15,16], and neutral [17,18] relationships between serum UA concentrations and risks of cardiovascular and total mortality in general adult populations, CVD, and renal disease. Insufficient sample size and variations in study populations and analysis strategies may partly account for the heterogenicity. Two recent large population-based cohorts noted a U-shaped association of total mortality with serum UA in general adult populations [19,20]. The increased mortality risk in adults with hypo- or hyper-uricemia suggests the complex biological roles of UA in humans. In particular, the benefit and harm of strict hypouricemic therapy should be considered.

However, the evidence regarding the link between UA levels and cardiovascular mortality in hypertensive individuals is unclear. To identify this association may provide new insights into the management of UA levels in hypertension, especially the intensive anti-uric acid therapy for hypertensive patients with hyperuricemia. This study aimed to assess the association of serum UA with all-cause and cause-specific mortality among 15 583 participants with hypertension.

Material and methods

Study Population and Design

Our analysis was based on a dataset from a nationally representative study, the National Health and Nutrition Examination Surveys (NHANES) of the United States [21], which is a stratified and multistage probability-sampling study to assess the characteristics of the nationally non-institutionalized population. The protocols of NHANES have been reported previously [21-23]. The dataset has been built since 1999 and is released in 2-year survey cycles. The protocols and procedures of this study were agreed to by the Research Ethics Review Board of the Centers of Disease Control and Prevention of the United States (Protocol Number. 98-12, 2005-06, and 2011-17). All participants provided written informed consent. The NHANES datasets are available to all researchers to reproduce the results. (*https://www.cdc.gov/nchs/index.htm*) [21].

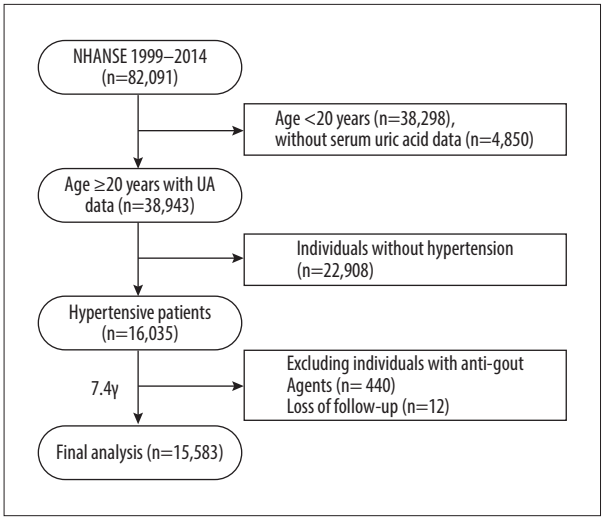

Figure 1. Flow diagram of this study.

We performed the primary analysis using the datasets of 8 two-year survey cycles from 1999-2000 to 2013-2014. In those cycles, there were 38 943 participants aged ≥20 years old with serum UA measurements. Hypertension was defined by blood pressure-lowering treatment and systolic/diastolic blood pressure ≥140/90 mmHg at baseline [21]. We excluded individuals without hypertension (n=22 908). Given the possibility of reverse causality, we further excluded individuals with hypouricemic therapy in the preceding month at baseline (n= 440). Further, we excluded individuals with missing information on mortality status (n=12). In total, 15 583 hypertensive individuals were included for analysis. The flow of the study is presented in **Figure 1**.

Serum Uric Acid Measurement

The exposure variable of interest was serum uric acid concentrations as tested by the Roche Hitachi Model 917/704 multichannel analyzer, Beckman Synchron LX20, or Beckman UniCel® DxC800 Synchron, as described in prior studies [19]. The protocols have been validated. In brief, UA was oxidized with specific enzyme uricase to generate allantoin and H_2O_2. The H_2O_2 further reacted with 2,4,6-tribromo-3-hydroxybenzoic

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acid and 4-aminophenazone to form quinone-imine dye and hydrogen bromide [19]. The intensity of red color was used to quantify results. The coefficient of variation for UA measurements in each cycle was approximately 2%, suggesting good repeatability. All laboratory variables were assessed by validated protocols and procedures. The details were available at *https://www.cdc.gov/nchs/nhanes*.

Covariates

Demographic and lifestyle factors at baseline, including age, gender, race/ethnicity, smoke, alcohol intake, and physical activity, and family income level were recorded during personal interviews via standardized questionnaires [21,22]. Physical examinations were performed according to standardized protocols and processes at a mobile examination center. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared [21]. Average systolic blood pressure and diastolic pressure were assessed as the means of 3 measurements. The detection of biosamples was conducted in special central laboratories with validated methods. Laboratory determinations of triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), glycosylated hemoglobin (HbA1c), and creatinine were detected in each survey cycle [21]. C-reactive protein (CRP) was measured in NHANES 1999-2006. The Chronic Kidney Disease Epidemiology Collaboration method was applied to calculate the estimated glomerular filtration rate (eGFR) [21]. History of diseases and prescription agents in the preceding 30 days was also solicited at a screening interview. Diabetes mellitus was defined as taking diabetic medication or HbA1c ≥6.5% [21]. Emphysema or chronic bronchitis was identified as chronic obstructive pulmonary disease (COPD). Malignant disease was identified according to self-report [21]. Antihypertensive agents were categorized as angiotensin-converting enzyme inhibitor/angiotensin II receptor antagonist (ACEI/ARBs), β-blocker, calcium-channel blockers (CCB), diuretics, and other antihypertensive drugs [4].

Outcomes

The outcomes of this study were total and cause-specific mortality. All participants were linked to the National Death Index in the National Center for Health Statistics of the US [21,22]. Mortality data were available through December 31, 2015. Using the codes of International Classification of Diseases 10th Revision (ICD-10), cause-specific mortality was categorized as death caused by CVD (heart disease: I00-I09, I11, I13, and I20-I51; stroke: I60-I69), and malignant neoplasms (C00-C97) [21].

Statistical Analysis

The statistical analyses were conducted following the analytical guidelines. Sampling weights, the masked variance of the primary sampling unit, and strata were used to explain the complex study design and acquire nationally representative estimates [21]. Variables are presented as weighted means (standard error, SE) and proportions unless otherwise noted. We used weighted linear regression or logistics regression to assess the difference across serum UA groups, when necessary. Restricted cubic spline based on Cox regression was applied to show the link between serum UA and total mortality, after adjustment for age, sex, race, smoking, alcohol intake, exercise, poverty-to-income ratio (PIR), BMI, cancer, COPD, diabetes, cardiovascular disease, TG, TC, HDL-C, eGFR, lipid-lowering agents, antiplatelet treatment, ACEI/ARBs, β-blocker, CCB, diuretics, and other antihypertensive drugs [21,24]. All hypertensive patients were stratified into 5 prespecified groups according to uric acid levels: ≤3.5, 3.5-5, 5-6, 6-7.5, and >7.5 mg/dL. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by crude and multivariable Cox regression models for the relationship between UA and total or cause-specific mortality, with UA 5-6 mg/dL as a reference. Three multivariable models were applied. Model 1 was adjusted for demographic variables, including age, sex, and race/ethnicity (non-Hispanic white, black, Hispanic-Mexican, or other). Model 2 was further adjusted for PIR, BMI, smoking status, alcohol intakes, physical activity, TG, TC, HDL-C, eGFR, CVD, diabetes, COPD, and cancer. Model 3 was additionally adjusted for lipid-lowering agents, antiplatelet drugs, ACEI/ARBs, β-blocker, CCB, diuretics, and other antihypertensive drugs [21]. In secondary analyses, the association between baseline UA and all-cause, cardiovascular, heart-specific, and stroke mortality was ascertained in subgroups by age (<65 and ≥65 years), sex (female and male), race (non-Hispanic white and non-white), BMI (<30 and ≥30 kg/m^2), eGFR (<60 and ≥60 mL/min/1.73 m^2), and anti-hypertension medications (yes/no), with the fully adjusted model except for stratification factors [21]. We also assessed whether the main results were altered after additional adjustment for inflammation marker CRP in NHANES 1999-2006. All tests with a 2-sided *P* value <0.05 were considered significant using Stata (version 15) software.

Results

Baseline Characteristics

Overall, 15 583 participants with hypertension (7524 men and 8059 women) were identified in the dataset from NHANES 1999-2000 to 2013-2014 cycles (**Figure 1**). The mean age was 55.8 years, and 47.6% were males in the study population. The median of serum UA level was 5.7 mg/dL (interquartile range [IQR], 4.8-6.7 mg/dL). Baseline characteristics of hypertensive patients across the strata of uric acid (≤3.5, 3.5-5, 5-6, 6-7.5, and >7.5 mg/dL) are shown in **Table 1**. Compared to those with lower UA, the participants with higher levels of UA were

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Table 1. Characteristics of patients with hypertension in NHANES 1999-2014 at baseline.

Variables	Serum uric acid, mg/dl				
	≤3.5	3.5-5.0	5.0-6.0	6.0-7.5	>7.5
Age,year	55.5 (0.93)	56.8 (0.33)	57.2 (0.33)	56.4 (0.34)	57.4 (0.52)
Male, %	12.63	26.07	48.26	62.6	69.67
Race/ethnicity, %					
Hispanic-Mexican	65.78	70.58	73.13	74.25	72.00
Other ethnicity	13.8	12.33	12.47	12.68	15.68
Non-Hispanic White	7.898	6.969	5.343	4.52	3.563
Non-Hispanic Black	12.52	10.12	9.065	8.554	8.756
Poverty to income ratio	2.6 (0.10)	2.8 (0.04)	3.0 (0.05)	3.0 (0.04)	2.9 (0.06)
Alcohol intakes, g	2.6 (0.34)	3.5 (0.28)	5.8 (1.07)	6.6 (0.53)	6.7 (0.43)
Smoking status, %					
Never smoking	52.69	52.46	50.87	46.78	44.37
Former smoker	25.51	27.01	30.03	34.39	38.36
Current smoker	21.8	20.54	19.1	18.83	17.27
Physical activity, %					
Inactive	49.84	49.49	49.52	50.13	54.03
Moderate activity	30.12	31.51	32.04	31.96	29.29
Vigorous activity	20.04	19.01	18.44	17.91	16.69
BMI, kg/m^2	26.5 (0.33)	28.8 (0.12)	30.4 (0.14)	31.6 (0.13)	32.7 (0.24)
Waist circumference, cm	91.6 (0.79)	98.2 (0.31)	103.7 (0.31)	107.5 (0.29)	110.5 (0.51)
Systolic BP, mmHg	136.5 (1.50)	136.6 (0.40)	135.3 (0.38)	134.4 (0.42)	134.5 (0.57)
Diastolic BP, mmHg	73.7 (0.83)	73.5 (0.34)	73.8 (0.30)	74.4 (0.31)	73.2 (0.59)
Triglycerides, mmol/L	1.6 (0.12)	1.7 (0.03)	1.8 (0.03)	2.1 (0.04)	2.4 (0.07)
Total cholesterol, mmol/L	5.2 (0.06)	5.2 (0.02)	5.2 (0.03)	5.2 (0.02)	5.3 (0.04)
HDL-C, mmol/L	1.6 (0.02)	1.5 (0.01)	1.4 (0.01)	1.3 (0.01)	1.2 (0.01)
eGFR,mL/min per 1.73 m^2	95.8 (1.18)	90.9 (0.44)	86.0 (0.51)	82.7 (0.47)	74.7 (0.70)
Cretinine,umol/L	67.0 (1.26)	73.1 (0.85)	81.5 (0.83)	88.3 (0.63)	102.3 (0.99)
C-reactive protein, mg/dL	0.4 (0.04)	0.5 (0.02)	0.5 (0.02)	0.5 (0.02)	0.7 (0.03)
CVD, %	12.95	14.13	15.44	17.94	24.69
Diabetes, %	16.84	17.33	16.37	17.75	21.74
Cancer, %	12.79	14.56	13.8	13.61	14.07
COPD, %	14.23	11.53	9.671	9.39	9.344
Lowering lipid, %	25.58	26.23	29.92	29.79	31.47
Antiplatelet agents, %	2.877	4.201	4.199	4.472	6.534
Antihypertensive agents, %	48.36	55.01	59.99	62.63	71.28

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Table 1 continued. Characteristics of patients with hypertension in NHANES 1999-2014 at baseline.

Variables	Serum uric acid, mg/dl				
	≤3.5	3.5-5.0	5.0-6.0	6.0-7.5	>7.5
ACEI/ARBs, %	28.42	33.65	38.06	40.25	45.77
Beta-blockers, %	17.64	18.33	21.00	23.51	29.61
Calcium-channel blockers, %	16.23	16.05	17.02	17.26	19.64
Diuretics, %	12.07	19.05	24.86	30.62	47.22
Other antihypertensive drugs, %	2.649	4.087	4.856	6.475	10.13

All variables are shown as the weighted mean±standard error or proportion (%). BMI – body mass index; BP – blood pressure; HDL-C – high-density lipoprotein cholesterol; eGFR – estimated glomerular filtration rate; ACEI – angiotensin-converting enzyme inhibitor; ARBs – angiotensin II receptor antagonist; COPD – chronic obstructive pulmonary disease; CVD – cardiovascular disease.

older and mostly males, and had higher alcohol consumption, TG, and CRP levels. The higher-UA groups were more likely to have adiposity, prior CVD, and to be taking antihypertensive agents. They also had less smoking and vigorous exercise, as well as lower eGFR.

Associations of UA with Total and Cause-specific Mortality

The median duration of follow-up was 7.4 (IQR, 4.1-11.3) years. Over 116 351 person-years of follow-up, 3291 deaths occurred among the 15 583 patients with hypertension, including 639 (19.4%) heart-related deaths and 630 (19.1%) cancer deaths. Among hypertensive participants in NHANES 1999-2006, 152 died due to stroke. The weighted mortality rates per 1000 person-years of follow-up are shown in **Table 2**, with 21.2 (95% CI, 20.3-22.1) for all-cause mortality, 3.9 (95% CI, 3.5-4.3) for heart-related and 4.1 (95% CI, 3.7-4.5) for cancer-related mortality, and 1.3 (95% CI 1.1-1.6) for stroke mortality. In multiple restricted cubic spline fitting, there was a U-shaped trend between UA and risks of total and cardiovascular mortality (**Figure 2**).

The relationships between serum UA levels and risks of all-cause, heart disease, stroke, and cancer-related mortality are shown in **Table 2**, assessed by several weighted multivariable Cox regression analyses with UA 5.0-6.0 mg/dL as reference. The age- and sex-adjusted HRs (95% CIs) of total mortality from ≤3.5 mg/dL to 3.5-5 mg/dL, 5-6 mg/dL, 6-7.5 mg/dL, and >7.5 mg/dL were 1.40 (1.05-1.88), 1.08 (0.95-1.21), 1.00 (reference), 1.14 (1.02-1.29), and 1.74 (1.50-2.02), respectively. The risks remained significant after adjusting for demographics, income, smoking, amateur sports activity, alcohol intakes, BMI, cancer, COPD, diabetes, cardiovascular disease, TG, TC, HDL-C, eGFR, lipid-lowering agents, antiplatelet treatment, ACEI/ARBs, β-blocker, CCB, diuretics, and other antihypertensive drugs. Compared with patients with UA 5-6 mg/dl, those with UA ≤3.5 and >7.5 mg/dL had an elevated risk of all-cause mortality, by 47% and 35%, respectively.

As expected, a similar trend of association of UA with cardiovascular mortality was noted (**Table 2**). In multivariable-adjusted model, the HRs (95% CI) of cardiovascular mortality from the lowest to the highest group were 1.92 (1.08-3.42), 1.27 (0.88-1.81), 1.00 (ref.), 1.19 (0.92-1.55), and 1.37 (1.00-1.90), respectively. Further, compared with patients with UA 5-6 mg/dl, the increased cardiovascular mortality in patients with UA ≤3.5 mg/dl was mainly due to stroke (HR 4.34, 95% CI 1.66-11.35), while the increased mortality in patients with UA >7.5 mg/dl was mainly due to ischemic heart disease (HR 1.46, 95% CI 1.10-1.95). However, neither lower serum UA nor higher UA was significantly related to cancer mortality.

In prespecified stratification analyses (**Supplemenatry Tables 1-6**), the associations of serum concentrations of UA with total and cardiovascular mortality were similar in the subgroups of hypertensive patients regarding sex (female versus male), eGFR (≥60 versus <60), and other subgroups. In the further sensitivity analysis, we assessed the relationship between UA and mortality in participants with CRP measurement. After additionally adjusting for CRP, the results did not alter significantly (**Supplemenatry Table 7**).

Discussion

In this nationally representative sample of hypertensive patients, both lower and higher serum UA levels were significantly associated with elevated risks of total and cardiovascular mortality after fully adjusting for potential confounders. This association remained statistically significant in males and females. Our findings highlight the significantly increased stroke mortality in patients with low UA (≤3.5mg/dL) and increased heart-specific mortality in patients with high UA levels (>7.5 mg/dl).

Previous observational studies suggested that serum UA is an independent predictor for the development from

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Table 2. The relationship between serum uric acid and all-cause and cause-specific mortality in hypertensive patients.

Uric acid, mg/dl	Person-years*	Events*	Mortality rate	Model1	p Value	Model 2	p Value	Model 3	p Value
				HR (95% CI)		HR (95% CI)		HR (95% CI)	
All-cause mortality	116350.6	3291	28.3						
≤3.5	5241.8	130	24.8	1.40 (1.05-1.88)	0.024	1.50 (1.09-2.07)	0.014	1.47 (1.07-2.03)	0.019
3.5-5.0	34376.8	838	24.4	1.08 (0.95-1.21)	0.236	1.13 (0.98-1.29)	0.090	1.12 (0.97-1.28)	0.112
5.0-6.0	28414.9	721	25.4	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
6.0-7.5	33643.8	964	28.7	1.14 (1.02-1.29)	0.027	1.10 (0.96-1.27)	0.168	1.09 (0.95-1.25)	0.231
>7.5	14673.3	638	43.5	1.74 (1.50-2.02)	0.000	1.41 (1.19-1.67)	0.000	1.35 (1.16-1.59)	0.000
CVD mortality**	75196.8	622	8.3						
≤3.5	3664.6	24	6.5	1.69 (1.06-2.68)	0.027	1.92 (1.08-3.42)	0.027	1.92 (1.08-3.42)	0.027
3.5-5.0	23074.5	150	6.5	1.15 (0.82-1.60)	0.409	1.27 (0.89-1.81)	0.184	1.27 (0.88-1.81)	0.194
5.0-6.0	18322.9	139	7.6	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
6.0-7.5	21187.9	190	9.0	1.24 (0.98-1.59)	0.076	1.25 (0.96-1.64)	0.101	1.19 (0.92-1.55)	0.191
>7.5	8946.9	119	13.3	2.03 (1.50-2.74)	0.000	1.52 (1.10-2.10)	0.012	1.37 (1.00-1.90)	0.053
Heart-related mortality	116350.6	639	5.5						
≤3.5	5241.8	20	3.8	1.31 (0.79-2.16)	0.296	1.31 (0.74-2.33)	0.346	1.31 (0.73-2.36)	0.361
3.5-5.0	34376.8	140	4.1	1.13 (0.82-1.56)	0.464	1.17 (0.84-1.63)	0.358	1.16 (0.84-1.62)	0.364
5.0-6.0	28414.9	139	4.9	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
6.0-7.5	33643.8	201	6.0	1.29 (1.02-1.64)	0.036	1.24 (0.95-1.62)	0.109	1.18 (0.91-1.52)	0.218
>7.5	14673.3	139	9.5	2.26 (1.73-2.94)	0.000	1.64 (1.21-2.21)	0.002	1.46 (1.10-1.95)	0.010
Stroke mortality**	75196.8	152	2.0						
≤3.5	3664.6	11	3.0	4.09 (1.86-9.01)	0.001	4.32 (1.66-11.21)	0.003	4.34 (1.66-11.35)	0.003
3.5-5.0	23074.5	41	1.8	1.20 (0.69-2.08)	0.503	1.35 (0.73-2.49)	0.337	1.30 (0.71-2.39)	0.393
5.0-6.0	18322.9	31	1.7	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
6.0-7.5	21187.9	44	2.1	1.23 (0.64-2.36)	0.520	1.34 (0.67-2.68)	0.396	1.32 (0.67-2.58)	0.413
>7.5	8946.9	25	2.8	1.80 (0.89-3.64)	0.100	1.40 (0.61-3.19)	0.422	1.27 (0.54-3.01)	0.574

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Table 2 continued. The relationship between serum uric acid and all-cause and cause-specific mortality in hypertensive patients.

Uric acid, mg/dl	Person-years*	Events*	Mortality rate	Model1	p Value	Model 2	p Value	Model 3	p Value
				HR (95% CI)		HR (95% CI)		HR (95% CI)	
Cancer mortality	116350.6	630	5.4						
≤3.5	5241.8	31	5.9	1.68 (0.97-2.92)	0.064	1.73 (0.98-3.04)	0.060	1.72 (0.97-3.04)	0.063
3.5-5.0	34376.8	162	4.7	1.07 (0.81-1.39)	0.639	1.04 (0.78-1.40)	0.785	1.05 (0.78-1.41)	0.758
5.0-6.0	28414.9	148	5.2	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
6.0-7.5	33643.8	179	5.3	1.15 (0.85-1.56)	0.354	1.13 (0.83-1.54)	0.434	1.12 (0.82-1.52)	0.474
>7.5	14673.3	110	7.5	1.37 (0.94-2.01)	0.102	1.29 (0.86-1.94)	0.220	1.26 (0.86-1.86)	0.235

* Unweighted values; ** estimated in NHANES 1999-2006. **Model 1** (n=15 583): adjusted for age, sex, and race/ethnicity. **Mode 2** (n=15 159): additionally adjusted for PIR (<1.3, 1.3-3.5, ≥3.5, or missing), BMI (<18.5, 18.5-25, 25-30, or ≥30 kg/m^2), smoking status, alcohol intake (none, <5, 5-30, ≥30 g/d, or missing), leisure physical activity, TG, TG, HDL-C, eGFR, diabetes, COPD, CVD, and cancer. **Model 3** (n=15 159): additionally adjusted for lipid-lowing agents, antiplatelet treatment, ACEI/ARBs, β-blocker, CCB, diuretics, and other antihypertensive drugs.

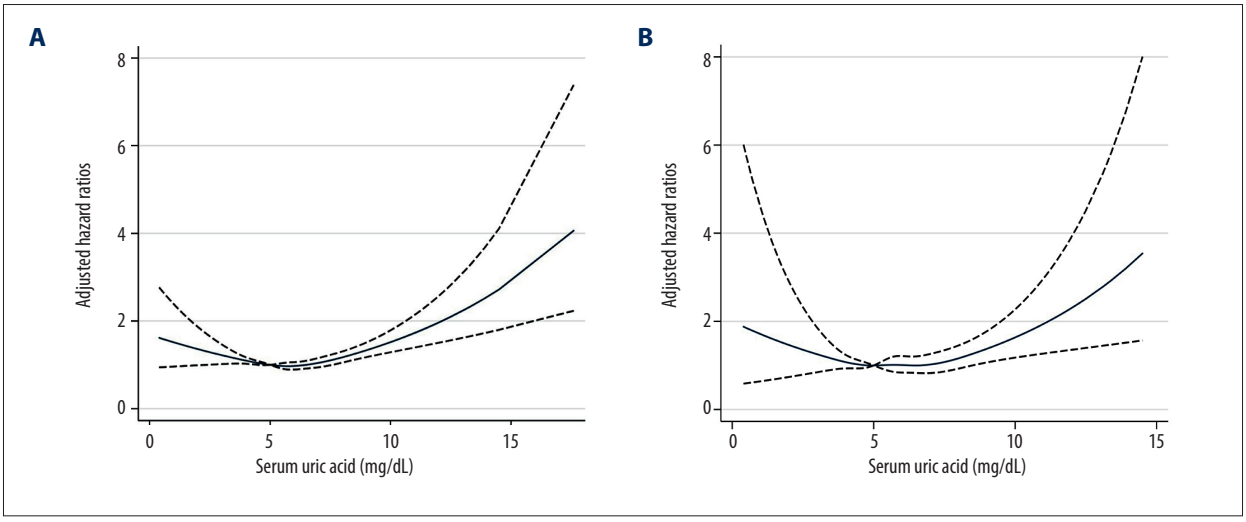

Figure 2. The non-linear associations between uric acid levels and all-cause and cardiovascular mortality. The restricted cubic spline shows the relationship between UA and all-cause (**A**) and cardiovascular (**B**) mortality risk. The fitting includes 5 knots: the 5th, 27.5th, 50th, 72.5th, and 95th percentiles. HR (95% CI) was estimated with multivariable Cox regression analysis after adjustment for Model 3. The solid and dashed lines represent point estimates and 95% CIs, respectively. The non-linear trend was significant for the relationship between UA and all-cause and cardiovascular mortality (*P* for non-linearity ≤0.035).

prehypertension to hypertension [4,6]. Compared with individuals with normal uric acid, hyperuricemic individuals with normal blood pressure had a more than 2-fold elevated risk of hypertension over a 5-year follow-up [4]. A prospective cohort study of 2757 Chinese hypertensive patients found that hyperuricemia significantly predicted increased cardiovascular and total mortality during the 6 years of follow-up compared with those with non-hyperuricemia. Although they distinguished between hyperuricemia and non-hyperuricemia, whether lower uric acid level had advantageous or disadvantageous effects in the progression of hypertension remained unclear [25]. To the best of our knowledge, the present study is the first to report a U-shaped association between serum UA and all-cause and CVD mortality in patients with hypertension independent of various potential confounders. The present results and those of others support that hyperuricemic individuals may be the

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ideal group to target to evaluate the role of uric acid-lowering treatment to prevent mortality risk in hypertensive patients [4,6,25]. Although our findings highlight the increased mortality risk in patients with low UA levels (<3.5 mg/dL), the benefits of intensive hypouricemic therapy should be rigorously assessed in clinical trials of anti-uric acid therapy.

The association of serum UA with mortality risk has been reported by numerous cohort studies, but results varied widely. Most studies only observed that higher UA was linearly associated with increased risks of total and cardiovascular mortality in the general population, and in patients with diabetes, kidney disease, and CVD [5,12-14,25]. Two small-cohort studies indicated that serum UA was inversely related to all-cause and CVD mortality in patients receiving hemodialysis and peritoneal dialysis [15,16]. The heterogeneous conclusions may be partly due to the discrepancy in subjects, clinical characteristics, sample size, grouping strategy, and adjustment for confounders [19]. Although the severity of renal disease and treatment may also influence the relationship, our limited simple size may hinder the power of the test. Grouping methods to estimate hazard ratios may also conceal the increased mortality in participants with low UA, such as tertiles or quartiles of UA, hyperuricemia (>6.5 mg/dL) or not, and per 1 mg/dL increase of UA. Use of predefined groups according to UA levels may be a good approach to identify the non-linear association.

Recently, several studies noted a U-shaped association of mortality risk with UA in the general population. According to the Taipei City Elderly Health Examination Program, which included 127 771 elderly adults, compared with UA 4-5 mg/dL, serum UA< 4 and ≥8 mg/dL independently predicted the elevated risks of cardiovascular and total mortality in elderly people, especially in participants with malnutrition [26]. Another prospective cohort study of 9118 general adults from the US also found a U-shaped relationship between UA levels and mortality risk [19]. Consistently, another cohort study, including 375 163 adults in South Korea, demonstrated that both low and high levels of serum UA were significantly related to higher all-cause and CVD mortality [20]. In the present study, a similar U-shaped relationship between UA and total and CVD mortality was observed in hypertensive patients. Interestingly, we found that the increased cardiovascular mortality in the lowest and highest UA groups was attributed to stroke and heart-specific mortality, respectively, which has not been previously reported. Indeed, the occurrence of stroke or ischemic heart disease has distinct pathophysiological mechanisms, such as poor blood pressure control and vulnerable atherosclerotic plaque, respectively. Although the difference was statistically insignificant, systolic blood pressure at baseline was higher in the low-UA groups, which may help explain our conclusions. Our findings show that uric acid plays complex roles in the regulation of blood pressure and plaque instability. However, the particular mechanism by which UA affects the progression of hypertension warrants further clarification.

The relationship between serum UA and cancer-related deaths was statistically insignificant in our analysis, consistent with the findings of Cho et al in the general population [20]. The heterogeneity of types of tumors may partly explain the neutral results, and more research with larger sample sizes is required.

The biological mechanism underlying this link remain unclear [19,27]. Endothelial dysfunction and arterial stiffness are thought to be early manifestations of vascular dysfunction in the development of prehypertension and hypertension [28]. UA is involved in the progression of endothelial dysfunction. Intracellular uric acid stimulates adenosine monophosphate dehydrogenase to inhibit the enzyme activity of adenosine monophosphate kinase and decreases endothelial NO synthase (eNOS) activity [29]. Treatment of hyperuricemia with allopurinol for 3 months resulted in a significant decrease in inflammation biomarkers [30]. High UA exposure activates the inflammatory cascade process via inducing NLRP3 inflammasome and interleukin-1β [19,31]. Experimental studies demonstrated that intracellular UA activates the generation of reactive oxygen species/reactive nitrogen species to aggravate endothelial dysfunction [29]. According to prior studies, UA may act as a crucial antioxidant molecule that takes 50% of the total antioxidant capacity. It has been suggested that high uric acid levels are an adaptive alteration to protect from atherosclerosis progression, due to its antioxidant function [3]. Also, lower uric acid levels may reflect the insufficient intake of purine-rich foods, which may indicate poor nutritional conditions, and a study observed lower UA level was associated with vitamin deficiency [26,32]. Those reports may partly explain the U-shaped relationship between UA and mortality. The potential mechanisms underlying this link need further investigation.

Strengths and Limitations

Our study has several limitations. First, the residual confounders unmeasured may not be completely ruled out. Second, the causality of this link between serum UA and mortality risk could not be determined because of the observational nature of the study, although prior experimental studies observed that UA-related metabolism activated inflammation and oxidative stress in the process of cardiovascular disease. Third, the enrolled participants in this study were US civilians, so the results extrapolated to other populations need further verification. Fourth, information on distinguishing primary and secondary hypertension was lacking in this community-based cohort, and further investigation in special hospital-based cohorts is warranted. This study may have some strengths. The NHANES study was a national sampling dataset that favored repeatability and generalization. The sample size and long-term follow-up

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provide favorable statistical effectiveness. We have adjusted for a variety of potential confounders, including lifestyle, laboratory data, chronic disease, and detailed information of antihypertensive agents, and the relationship between UA and all-cause and cardiovascular mortality remained significant.

Conclusions

Our findings suggest a U-shaped relationship between serum UA and risks of total and cardiovascular mortality in hypertensive patients. Both low and high levels of uric acid were independently associated with increased risks of cardiovascular mortality. Nonetheless, low UA may mainly increase stroke-related mortality, and high UA may mainly increase heart-related mortality. Further investigations are needed to elucidate the potential mechanisms and validate the role of uric acid in the progression of hypertension.

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Conflict of Interest

None.

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Supplementary data

Supplementary Table 1. Stratification analysis of the association between uric acid and mortality by sex.

Uric acid, mg/dl	Female (n=7,850)	p Value	Male (n=7,309)	p Value
	HR (95% CI)		HR (95% CI)	
All-cause mortality				
≤3.5	1.33 (0.93-1.91)	0.118	2.46 (1.57-3.86)	0.000
3.5-5.0	1.11 (0.90-1.35)	0.322	1.17 (0.96-1.42)	0.115
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	1.27 (1.04-1.56)	0.022	0.97 (0.81-1.16)	0.736
>7.5	1.48 (1.18-1.85)	0.001	1.29 (1.04-1.60)	0.019
CVD mortality*				
≤3.5	2.28 (1.14-4.55)	0.020	1.52 (0.45-5.14)	0.491
3.5-5.0	1.23 (0.75-2.03)	0.407	1.41 (0.92-2.17)	0.112
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	1.48 (0.89-2.44)	0.126	1.04 (0.70-1.54)	0.849
>7.5	1.56 (0.90-2.68)	0.108	1.49 (0.92-2.42)	0.105
Heart-related mortality				
≤3.5	1.34 (0.66-2.73)	0.419	1.16 (0.27-5.08)	0.840
3.5-5.0	1.02 (0.62-1.67)	0.937	1.39 (0.92-2.09)	0.114
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	1.28 (0.82-2.02)	0.278	1.10 (0.77-1.57)	0.611
>7.5	1.47 (0.86-2.52)	0.160	1.55 (1.04-2.31)	0.032
Stroke mortality*				
≤3.5	2.28 (1.16-4.50)	0.018	1.50 (0.13-17.07)	0.741
3.5-5.0	1.21 (0.73-2.01)	0.460	1.47 (0.58-3.76)	0.411
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	1.39 (0.83-2.30)	0.203	1.23 (0.47-3.22)	0.665
>7.5	1.36 (0.79-2.34)	0.256	1.26 (0.35-4.60)	0.719

* Estimated in NHANES 1999-2006. Hazard ratio (95% confidence interval) was estimated via weighted cox regression analysis after adjustment for age (years, continuous), race/ethnicity (non-Hispanic white, black, Hispanic-Mexican, or other), poverty to income ratio (<1.3, 1.3-3.5, ≥3.5, or missing), body mass index (<18.5, 18.5-25, 25-30, or ≥30 kg/m^2), smoking status, alcohol intake (no, <5, 5-30, ≥30 g/d, or missing), physical activity (inactive, moderate, or vigorous), TG, total cholesterol (mmol/L, continuous), high-density lipoprotein cholesterol (mmol/L, continuous), estimated glomerular filtration rate (mL/min/1.73 m^2, continuous), cardiovascular diseases (no/yes), diabetes (no/yes), chronic obstructive pulmonary disease (no/yes), cancer (no/yes), lowing lipid agents (no/yes), antiplatelet treatment (no/yes), ACEI/ARBs (no/yes), β-blocker (no/yes), CCB (no/yes), diuretics (no/yes) and other antihypertensive drugs (no/yes).

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Supplementary Table 2. Stratification analysis by estimated glomerular filtration rate.

Uric acid, mg/dl	Non-CKD (n=12,643)	p Value	CKD* (n=2,516)	p Value
	HR (95% CI)		HR (95% CI)	
All-cause mortality				
≤3.5	1.42 (1.02-1.98)	0.036	1.57 (0.77-3.21)	0.211
3.5-5.0	1.09 (0.93-1.27)	0.311	1.10 (0.86-1.41)	0.435
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	0.99 (0.84-1.18)	0.948	1.31 (1.06-1.62)	0.013
>7.5	1.37 (1.09-1.71)	0.007	1.52 (1.21-1.90)	0.000
CVD mortality*				
≤3.5	1.73 (0.94-3.21)	0.078	4.95 (1.29-19.01)	0.021
3.5-5.0	1.25 (0.81-1.93)	0.308	1.32 (0.70-2.49)	0.383
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	0.94 (0.65-1.35)	0.731	1.69 (0.97-2.94)	0.063
>7.5	1.79 (1.06-3.00)	0.029	1.43 (0.80-2.58)	0.226
Heart-related mortality				
≤3.5	1.31 (0.67-2.55)	0.421	1.49 (0.15-14.55)	0.727
3.5-5.0	1.19 (0.78-1.80)	0.420	1.12 (0.63-1.99)	0.706
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	1.05 (0.78-1.43)	0.731	1.43 (0.86-2.36)	0.166
>7.5	1.75 (1.11-2.77)	0.017	1.57 (0.93-2.67)	0.092
Stroke mortality*				
≤3.5	4.04 (1.32-12.44)	0.016	13.12 (2.33-73.86)	0.004
3.5-5.0	1.22 (0.55-2.70)	0.625	1.04 (0.26-4.16)	0.958
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	0.93 (0.37-2.32)	0.878	2.23 (0.84-5.92)	0.107
>7.5	1.18 (0.37-3.77)	0.775	1.50 (0.43-5.28)	0.518

* CKD was defined as estimated glomerular filtration rate less than 60 mL/min/1.73 m^2; ** estimated in NHANES 1999-2006. Hazard ratio (95% confidence interval) was estimated via weighted cox regression analysis after adjustment for age (years, continuous), sex (female or male), race/ethnicity (non-Hispanic white, black, Hispanic-Mexican, or other), poverty to income ratio (<1.3, 1.3-3.5, ≥3.5, or missing), body mass index (<18.5, 18.5-25, 25-30, or ≥30 kg/m^2), smoking status, alcohol intake (no, <5, 5-30, ≥30g/d, or missing), physical activity (inactive, moderate, or vigorous), TG, total cholesterol (mmol/L, continuous), high-density lipoprotein cholesterol (mmol/L, continuous), cardiovascular diseases (no/yes), diabetes (no/yes), chronic obstructive pulmonary disease (no/yes), cancer (no/yes), lowing lipid agents (no/yes), antiplatelet treatment (no/yes), ACEI/ARBs (no/yes), β-blocker (no/yes), CCB (no/yes), diuretics (no/yes) and other antihypertensive drugs (no/yes).

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Supplementary Table 3. Stratification analysis by race/ethnicity.

Uric acid, mg/dl	White (n=7,378)	p Value	Non-white (n=7,781)	p Value
	HR (95% CI)		HR (95% CI)	
All-cause mortality				
≤3.5	1.82 (1.25-2.65)	0.002	0.69 (0.47-1.02)	0.064
3.5-5.0	1.19 (1.03-1.37)	0.018	0.89 (0.71-1.12)	0.316
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	1.11 (0.94-1.31)	0.204	1.03 (0.85-1.24)	0.798
>7.5	1.42 (1.17-1.72)	0.000	1.17 (0.90-1.5)	0.237
CVD mortality*				
≤3.5	2.91 (1.62-5.22)	0.001	0.53 (0.16-1.77)	0.296
3.5-5.0	1.53 (1.02-2.28)	0.039	0.58 (0.32-1.08)	0.083
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	1.24 (0.88-1.74)	0.216	0.94 (0.56-1.57)	0.814
>7.5	1.63 (1.08-2.47)	0.022	0.72 (0.37-1.38)	0.317
Heart-related mortality				
≤3.5	2.01 (1.07-3.77)	0.029	0.32 (0.11-0.90)	0.031
3.5-5.0	1.41 (0.97-2.06)	0.072	0.59 (0.33-1.07)	0.080
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	1.19 (0.86-1.67)	0.294	1.06 (0.67-1.68)	0.810
>7.5	1.65 (1.16-2.34)	0.006	0.95 (0.56-1.61)	0.847
Stroke mortality*				
≤3.5	5.53 (1.79-17.1)	0.004	2.01 (0.42-9.75)	0.379
3.5-5.0	1.44 (0.75-2.78)	0.268	0.95 (0.21-4.35)	0.945
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	1.7 (0.76-3.79)	0.191	0.67 (0.17-2.58)	0.554
>7.5	1.6 (0.55-4.72)	0.383	0.78 (0.17-3.58)	0.747
Cancer mortality				
≤3.5	1.76 (0.84-3.68)	0.133	1.62 (0.86-3.06)	0.136
3.5-5.0	1.04 (0.71-1.52)	0.842	1.07 (0.71-1.60)	0.753
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	1.17 (0.81-1.69)	0.412	1.00 (0.63-1.59)	0.999
>7.5	1.30 (0.80-2.13)	0.284	1.23 (0.77-1.99)	0.381

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Supplementary Table 4. Stratification analysis by BMI.

Uric acid, mg/dl	BMI <30 (n=8,396)	p Value	BMI ≥30 (n=7,150)	p Value
	HR (95% CI)		HR (95% CI)	
All-cause mortality				
≤3.5	1.41 (1.02-1.94)	0.035	2.05 (1.29-3.26)	0.003
3.5-5.0	1.08 (0.94-1.24)	0.280	1.22 (0.94-1.58)	0.129
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	1.13 (0.96-1.33)	0.152	1.01 (0.81-1.25)	0.948
>7.5	1.43 (1.20-1.70)	0.000	1.23 (0.93-1.63)	0.142
CVD mortality*	1 (ref.)		1 (ref.)	
≤3.5	2.42 (1.25-4.66)	0.009	1.37 (0.30-6.32)	0.682
3.5-5.0	1.29 (0.86-1.95)	0.213	1.46 (0.79-2.68)	0.220
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	1.34 (0.92-1.94)	0.123	0.94 (0.62-1.43)	0.768
>7.5	1.24 (0.75-2.05)	0.397	1.51 (0.80-2.84)	0.197
Heart-related mortality	1 (ref.)		1 (ref.)	
≤3.5	1.67 (0.90-3.09)	0.105	1.57 (0.46-5.35)	0.467
3.5-5.0	1.22 (0.85-1.73)	0.275	1.43 (0.77-2.68)	0.259
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	1.32 (0.94-1.86)	0.112	0.97 (0.66-1.44)	0.896
>7.5	1.17 (0.74-1.84)	0.494	1.74 (1.02-2.99)	0.044
Stroke mortality*	1 (ref.)		1 (ref.)	
≤3.5	4.24 (1.46-12.34)	0.009	5.74 (0.60-54.82)	0.126
3.5-5.0	1.28 (0.62-2.63)	0.498	0.77 (0.27-2.22)	0.620
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	1.17 (0.51-2.67)	0.706	1.07 (0.38-2.95)	0.901
>7.5	1.71 (0.58-5.06)	0.326	0.99 (0.25-3.84)	0.985
Cancer mortality	1 (ref.)		1 (ref.)	
≤3.5	1.48 (0.71-3.12)	0.295	2.88 (1.41-5.86)	0.004
3.5-5.0	1.06 (0.75-1.49)	0.736	1.06 (0.66-1.70)	0.810
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	1.09 (0.79-1.50)	0.611	1.10 (0.64-1.89)	0.721
>7.5	1.45 (0.96-2.20)	0.076	1.01 (0.57-1.78)	0.972

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Supplementary Table 5. Stratification analysis by age groups.

Uric acid, mg/dl	Age <65y (n=8,716)	p Value	Age ≥65y (n=6,443)	p Value
	HR (95% CI)		HR (95% CI)	
All-cause mortality				
≤3.5	1.32 (0.75-2.31)	0.333	1.55 (1.07-2.26)	0.021
3.5-5.0	0.90 (0.67-1.22)	0.502	1.27 (1.08-1.49)	0.003
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	0.90 (0.70-1.16)	0.422	1.17 (0.99-1.39)	0.071
>7.5	1.27 (0.91-1.78)	0.165	1.30 (1.10-1.54)	0.003
CVD mortality*				
≤3.5	1.70 (0.41-7.05)	0.456	2.01 (0.98-4.11)	0.056
3.5-5.0	0.98 (0.45-2.12)	0.959	1.44 (0.92-2.24)	0.107
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	0.94 (0.53-1.66)	0.822	1.31 (0.93-1.84)	0.124
>7.5	1.64 (0.73-3.67)	0.225	1.15 (0.80-1.64)	0.453
Heart-related mortality				
≤3.5	0.88 (0.13-5.86)	0.893	1.46 (0.74-2.89)	0.275
3.5-5.0	1.32 (0.65-2.66)	0.436	1.16 (0.78-1.73)	0.455
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	1.41 (0.81-2.46)	0.221	1.15 (0.82-1.61)	0.422
>7.5	2.43 (1.15-5.14)	0.020	1.21 (0.85-1.73)	0.293
Stroke mortality*				
≤3.5	11.2 (1.80-69.68)	0.010	3.69 (1.34-10.21)	0.013
3.5-5.0	1.03 (0.12-8.58)	0.976	1.50 (0.84-2.70)	0.167
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	0.37 (0.06-2.37)	0.286	1.52 (0.73-3.19)	0.262
>7.5	0.93 (0.14-6.42)	0.943	1.12 (0.39-3.18)	0.836
Cancer mortality				
≤3.5	2.47 (1.23-4.98)	0.012	1.07 (0.46-2.51)	0.877
3.5-5.0	0.96 (0.52-1.77)	0.897	1.11 (0.79-1.55)	0.549
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	1.06 (0.61-1.85)	0.835	1.08 (0.81-1.44)	0.596
>7.5	1.19 (0.64-2.20)	0.575	1.13 (0.73-1.74)	0.586

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Supplementary Table 6. Stratification analysis by anti-hypertension medications.

Uric acid, mg/dl	Non-antihypertension agents (n=5,671)	p Value	Anti-hypertension (n=9,488)	p Value
	HR (95% CI)		HR (95% CI)	
All-cause mortality				
≤3.5	0.90 (0.53-1.53)	0.688	1.91 (1.38-2.62)	0.000
3.5-5.0	0.85 (0.68-1.07)	0.163	1.26 (1.08-1.47)	0.004
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	0.9 (0.68-1.18)	0.427	1.17 (1.01-1.34)	0.031
>7.5	1.19 (0.85-1.66)	0.314	1.41 (1.18-1.69)	0.000
CVD mortality*	1 (ref.)		1 (ref.)	
≤3.5	0.85 (0.32-2.24)	0.734	2.87 (1.47-5.58)	0.002
3.5-5.0	0.65 (0.38-1.13)	0.126	1.60 (1.05-2.44)	0.029
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	0.71 (0.38-1.31)	0.265	1.41 (1.00-1.99)	0.047
>7.5	1.40 (0.61-3.2)	0.417	1.52 (1.01-2.31)	0.046
Heart-related mortality	1 (ref.)		1 (ref.)	
≤3.5	1.40 (0.57-3.45)	0.461	1.17 (0.55-2.51)	0.675
3.5-5.0	0.79 (0.41-1.52)	0.484	1.28 (0.88-1.87)	0.191
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	1.10 (0.62-1.97)	0.738	1.23 (0.90-1.69)	0.194
>7.5	1.62 (0.6-4.34)	0.337	1.56 (1.10-2.23)	0.014
Stroke mortality*	1 (ref.)		1 (ref.)	
≤3.5	0.38 (0.04-4.06)	0.419	15.92 (5.41-46.88)	0.000
3.5-5.0	0.38 (0.11-1.35)	0.131	3.50 (1.60-7.65)	0.002
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	0.21 (0.06-0.68)	0.011	3.54 (1.58-7.96)	0.003
>7.5	0.91 (0.20-4.08)	0.903	2.70 (1.02-7.10)	0.045
Cancer mortality	1 (ref.)		1 (ref.)	
≤3.5	1.51 (0.59-3.89)	0.39	1.85 (0.87-3.90)	0.107
3.5-5.0	1.17 (0.71-1.94)	0.54	0.94 (0.61-1.46)	0.796
5.0-6.0	1 (ref.)		1 (ref.)	
6.0-7.5	1.05 (0.61-1.82)	0.851	1.13 (0.79-1.62)	0.506
>7.5	0.71 (0.28-1.81)	0.471	1.39 (0.87-2.20)	0.163

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Supplementary Table 7. Repeated analysis after adjustment for C-reactive protein in NHANES 1999-2006.

Uric acid, mg/dl	HR (95% CI)	p Value
All-cause mortality		
≤3.5	1.51 (0.99-2.31)	0.055
3.5-5.0	1.17 (0.99-1.38)	0.064
5.0-6.0	1.00 (ref.)	
6.0-7.5	1.17 (0.99-1.39)	0.057
>7.5	1.42 (1.16-1.74)	0.001
Heart-related mortality		
≤3.5	1.18 (0.54-2.56)	0.676
3.5-5.0	1.24 (0.82-1.86)	0.306
5.0-6.0	1.00 (ref.)	
6.0-7.5	1.16 (0.85-1.57)	0.343
>7.5	1.38 (0.97-1.96)	0.071
Cancer mortality		
≤3.5	2.15 (1.07-4.34)	0.033
3.5-5.0	1.14 (0.81-1.61)	0.451
5.0-6.0	1.00 (ref.)	
6.0-7.5	1.3 (0.90-1.89)	0.158
>7.5	1.41 (0.87-2.28)	0.165
CVD mortality**		
≤3.5	1.93 (1.08-3.44)	0.027
3.5-5.0	1.26 (0.88-1.81)	0.204
5.0-6.0	1.00 (ref.)	
6.0-7.5	1.19 (0.91-1.54)	0.193
>7.5	1.36 (0.98-1.87)	0.062
Stroke mortality**		
≤3.5	4.31 (1.64-11.31)	0.004
3.5-5.0	1.29 (0.70-2.38)	0.413
5.0-6.0	1.00 (ref.)	
6.0-7.5	1.31 (0.67-2.55)	0.426
>7.5	1.25 (0.53-2.96)	0.599

** Estimated in NHANES 1999-2006. Hazard ratio (95% confidence interval) was estimated via weighted cox regression analysis after adjustment for age (years, continuous), sex (female or male), race/ethnicity (non-Hispanic white, black, Hispanic-Mexican, or other), poverty to income ratio (<1.3, 1.3-3.5, ≥3.5, or missing), body mass index (<18.5, 18.5-25, 25-30, or ≥30 kg/m^2), smoking status, alcohol intake (no, <5, 5-30, ≥30 g/d, or missing), physical activity (inactive, moderate, or vigorous), TG, total cholesterol (mmol/L, continuous), high-density lipoprotein cholesterol (mmol/L, continuous), C-reactive protein (mg/dL, continuous), estimated glomerular filtration rate (mL/min/1.73 m^2, continuous), cardiovascular diseases (no/yes), diabetes (no/yes), chronic obstructive pulmonary disease (no/yes), cancer (no/yes), lowing lipid agents (no/yes), antiplatelet treatment (no/yes), ACEI/ARBs (no/yes), β-blocker (no/yes), CCB (no/yes), diuretics (no/yes) and other antihypertensive drugs (no/yes).

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