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FULL RESEARCH PAPER
Cardiovascular disease

Associations of uric acid with the risk of cardiovascular disease and all-cause mortality among individuals with chronic kidney disease: the Kailuan Study

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Aims

The relationship between uric acid (UA) concentrations and the risk of cardiovascular disease (CVD), especially for subtypes of CVD among individuals with chronic kidney disease (CKD), is not well understood. This study aimed to investigate whether UA concentration was associated with subtypes of CVD and all-cause mortality among individuals with CKD.

Methods and results

A total of 27 707 individuals with CKD, free of CVD at recruitment from the Kailuan Study, were included. Cox proportional hazards regression models were used to compute hazard ratios (HRs) and 95% confidence intervals (CIs). Over a median follow-up of 11–12 years, we documented 674 myocardial infarctions, 1197 heart failures, 2406 strokes, and 5676 total deaths. Among participants with CKD, compared with those in the lowest tertile of UA, the HRs (95% CIs) of participants in the highest UA tertile were 1.38 (1.13–1.67) for myocardial infarction, 1.60 (1.38–1.85) for heart failure, 1.01 (0.91–1.12) for stroke, and 1.29 (1.21–1.38) for all-cause mortality. Subgroup analyses showed that the associations between UA and heart failure and all-cause mortality were stronger in individuals with estimated glomerular filtration rate <45 mL/min/1.73 m^2 compared to their counterparts ($P_{interaction} < 0.05$). Additionally, the association between UA and all-cause mortality was stronger among individuals without diabetes than those with diabetes ($P_{interaction} < 0.05$).

Conclusion

In individuals with CKD, a higher concentration of UA was associated with a higher risk of myocardial infarction, heart failure, and all-cause mortality, following a dose–response relationship. Our data underscore the importance of UA screening among individuals with CKD for CVD and premature death prevention.

Lay summary

This study investigated the relationship between uric acid (UA) concentrations and the risk of cardiovascular disease and all-cause mortality in individuals with chronic kidney disease (CKD) using the Kailuan Study.

- A higher concentration of UA was associated with a higher risk of myocardial infarction, heart failure, and all-cause mortality among individuals with CKD, following a dose–response manner.
- The associations between concentrations of UA and the risk of heart failure and all-cause mortality were more pronounced in individuals with severe kidney impairment (estimated glomerular filtration rate <45 mL/min/1.73 m^2). Furthermore, the association between UA and all-cause mortality was stronger among individuals without diabetes compared to those with the condition.

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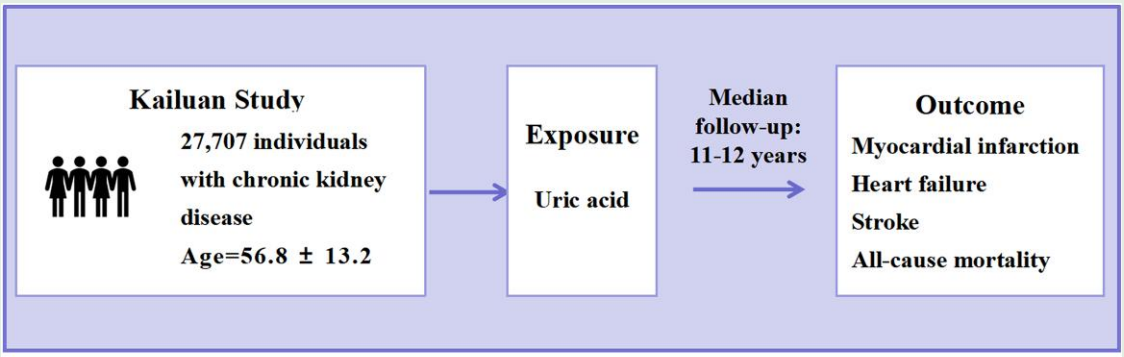
Graphical Abstract



Main Findings

	Events/person-years	Incidence per 1000 person-years	Hazard ratio (95% confidence interval)
Myocardial infarction			
Tertile 1	176/115,270	1.5	Ref.
Tertile 2	214/112,277	1.9	1.14 (0.93-1.39)
Tertile 3	284/105,961	2.7	1.38 (1.13-1.67)
Heart failure			
Tertile 1	294/107,293	2.7	Ref.
Tertile 2	363/104,633	3.5	1.13 (0.97-1.32)
Tertile 3	540/98,000	5.5	1.60 (1.38-1.85)
Stroke			
Tertile 1	761/120,735	6.3	Ref.
Tertile 2	762/119,993	6.4	0.93 (0.84-1.02)
Tertile 3	883/115,240	7.7	1.01 (0.91-1.12)
All-cause mortality			
Tertile 1	1,546/116,241	13.3	Ref.
Tertile 2	1,921/113,490	16.9	1.11 (1.04-1.19)
Tertile 3	2,209/107,407	20.6	1.29 (1.21-1.38)

Keywords Uric acid • Chronic kidney disease • Cardiovascular disease • All-cause mortality • Kailuan Study

Introduction

Chronic kidney disease (CKD) is an increasing global public health concern, with an estimated global prevalence ranging from 9.1 to 13.4%, imposing substantial medical and financial burdens on societies and healthcare systems.[1–3] In addition, individuals with CKD are at higher risks for cardiovascular disease (CVD) and mortality.[4] Notably, CVD is the leading cause of death in this population, often occurring before the advancement to end-stage kidney disease[5]; hence, CVD prevention among CKD is paramount. However, managing traditional cardiovascular risk factors such as hypertension, diabetes, and dyslipidaemia does not fully mitigate the cardiovascular risks associated with CKD,[6] underscoring the need for further investigation into additional risk factors. Therefore, it becomes imperative to delve deeper into additional risk factors that could facilitate the identification and management of individuals with CKD at high risk for CVD and mortality, thereby tailoring more effective prevention and intervention strategies.

In recent decades, epidemiological studies have linked uric acid (UA) to the risk of CVD and premature death in the general population.[7–9] However, the association of UA with CVD and mortality among individuals with CKD, a group commonly affected by hyperuricaemia,[10] has not been thoroughly explored. Although some studies found that higher concentrations of UA were associated with a higher risk of all-cause and CVD mortality among individuals with CKD,[11,12] the specific nature of the relationship between UA concentrations and CVD risk within this group is not well understood. This uncertainty regarding the effects of UA on various subtypes of CVD underscores a critical gap in our current medical knowledge. Clarifying these relationships is essential not only for filling this gap but also for its substantial public health and clinical implications. Specifically, a deeper understanding could lead to more effective strategies for managing high-risk patients and reducing complications associated with CKD. Enhanced insights could inform targeted therapies and prevention programmes, potentially reducing the CVD events in CKD populations, thereby improving patient outcomes, and reducing healthcare burdens.

To address the research gaps, we examined the associations of UA with subsequent risks of myocardial infarction, heart failure, stroke, and all-cause mortality among individuals with CKD leveraging data from the Kailuan Study.

Methods

Study population

The Kailuan Study (registration number: ChiCTR-TNC-11001489) is a large prospective cohort study conducted in Tangshan City, China, which aimed to investigate the risk factors of cardiovascular and other non-communicable chronic diseases. The design of the study has been described previously.[13] Briefly, a total of 101 510 community-dwelling adults (aged 18–98 years, 81 110 men, and 20 400 women) were recruited and completed the baseline survey between June 2006 and October 2007. Follow-up examinations were carried out biennially, in which all participants underwent questionnaires, laboratory tests, and physical examinations. Meanwhile, the incidence of CVD and all-cause mortality is documented via electronic health records every year. The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Kailuan Hospital. All participants gave written informed consent.

The present study included participants who underwent at least one health examination from 2006 to 2012. A total of 27 707 individuals with CKD at baseline were enrolled in the final analyses after excluding participants who had no data on UA at baseline ($n = 262$), those who had a history of CVD ($n = 2189$), and those who were on dialysis or had a history of renal transplantation ($n = 129$; *Figure 1*). Participants with estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 or proteinuria ≥2+ (≥300 mg/dL) were considered as CKD.

Assessment of exposure

After an overnight fasting period (at least 8 h), blood samples were collected in the morning and transfused into EDTA-containing vacuum tubes. The concentration of UA was examined with a commercial kit (Ke Hua Biological Engineering Corporation, Shanghai, China) using an automatic biochemical analyser (Hitachi 747, Tokyo, Japan) according to the manufacturer's instructions. Uric acid was detected by the oxidase method, with an intra- and interassay coefficient of variation ≤6%.[14] Uric acid concentrations vary between men and women, necessitating the calculation of distinct tertile cut-offs for each sex: 257.0 and 336.0 μmol/L for men and 224.3 and 284.0 μmol/L for women. To accommodate these differences, individuals were initially categorized into three groups according to sex-specific UA tertiles. Subsequently, these groups were consolidated into broader categories: Tertile 1 ($n = 9235$), Tertile 2 ($n = 9257$), and Tertile 3 ($n = 9215$).

Assessment of the covariates

All blood samples were analysed using an automatic analyser (Hitachi 747, Tokyo, Japan). The biochemical markers included creatinine, high-sensitivity C-reactive protein, fasting blood glucose (FBG), triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), and high-density lipoprotein cholesterol (HDL-c). Serum creatinine was assessed using the sarcosine oxidase assay method (creatinine kit; Biosino Bio-technology and Science Inc., Beijing, China), with a lower limit detection of 22 μmol/L and an upper limit detection of 3000 μmol/L (linear correlation coefficient ≥0.99). Within-laboratory intra- and interassay variable coefficients for serum creatinine were ≤5 and ≤6%, respectively.[15] The eGFR was calculated according to the formula of the Chronic Kidney Disease Epidemiology Cooperation.[16]

A single random midstream morning urine sample was collected from each participant during their interview, and all the urine samples were measured using a urine analyser (N-600; Changchun Dirui Medical Technology Co., Ltd) at the central laboratory of the Kailuan General Hospital. The results of semiquantitative proteinuria were recorded as negative (<15 mg/dL), trace (15–29 mg/dL), 1+ (30–300 mg/dL), 2+ (300–1000 mg/dL), or 3+ (>1000 mg/dL).[15]

Demographic and clinical characteristics, including age, sex, education concentration, smoking, drinking, physical exercise, and medical history (hypertension, diabetes, dyslipidaemia, etc.) were collected for all Kailuan participants at every clinical follow-up visit. Medication information was obtained from the outpatient records. Height, weight, and blood pressure were evaluated by trained staff during the survey interview. The blood pressure measurements were administered by trained physicians and nurses. Blood pressure was measured in the left upper arm using a calibrated mercury sphygmomanometer with the participant in a sitting position. At least two measurements were taken after 5 min of rest, and the average of the readings was used for the analyses. The body mass index (BMI) was calculated by body weight (kg) divided by height squared (m^2). Hypertension was defined as a self-reported history of hypertension, current treatment with an antihypertensive agent, or a measured systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg. Diabetes was defined as a self-reported history of diabetes, current treatment with a hypoglycaemic agent, or FBG ≥7.0 mmol/L. Dyslipidaemia was defined as having a self-reported history of dyslipidaemia, use of lipid-lowering drugs, or meeting any of the following criteria: TC ≥5.2 mmol/L, TG ≥1.7 mmol/L, LDL-c ≥ 3.4 mmol/L, or HDL-c < 1.0 mmol/L. Current drinker was defined as individuals who consumed alcohol at least once a day in the past year, and current smoker referred to those who smoked at least one cigarette a day on average during the past year. Physical activity was defined as an exercise frequency ≥3 times/week and duration ≥30 min/time.

Follow-up and outcomes

The outcomes of the study were the occurrence of all-cause mortality and incident CVD, including both fatal and nonfatal cases of myocardial infarction, heart failure, and stroke. The types of CVD were all confirmed by professional physicians in the hospitalization medical records. An expert panel collected and reviewed annual discharge records from 11 local hospitals to identify patients who were suspected of CVD. Myocardial infarction refers to the global definition of myocardial infarction in 2018.[17] The definition of heart failure was revised according to the diagnostic criteria outlined in the Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2018.[18] Stroke was diagnosed according to the World Health Organization.[19] All-cause death was defined as death caused by any cause during follow-up. The death event information was obtained through the Kailuan Social Security Information System every year. Each participant's person-years were calculated from the date of attending the initial physical examination at the time of established CKD until the date reported for diagnosis of CVD events, death, or end of the follow-up. For incident CVD events, follow-up was censored on the date of CVD event diagnosis, death, or end of the follow-up (31 December 2020), whichever occurred first, and for mortality outcomes, follow-up was censored on the date of death or end of the follow-up if that occurred earlier.

Statistical analysis

Baseline characteristics were compared using analysis of variance (ANOVA) or Kruskal–Wallis test according to distribution, and categorical variables were compared using χ^2 test. To adjust for multiple comparisons, we used the Benjamini–Hochberg false discovery rate (FDR) method, setting the threshold for statistical significance at 0.05. Kaplan–Meier curves were performed to estimate the cumulative incidence of different outcomes, and the differences in curves were compared with the log-rank test.

Cox proportional hazards regression models were constructed to compute the hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of UA and subsequent risks of myocardial infarction, heart failure, stroke, and all-cause mortality. We tested the proportional hazards assumption of the Cox models using Schoenfeld residuals method. Although some covariates violated the proportional hazards assumption, the primary exposure (UA) did not. Model 1 was adjusted for age and sex. Model 2 was further adjusted for smoking status (current or non-current smokers), drinking status (current or non-current drinkers), physical activity (inactive or active), education (below high school or high school and above), BMI (kg/m^2, continuous), high-sensitivity C-reactive protein (mg/L, continuous), eGFR (mL/min/1.73 m^2, continuous), proteinuria (yes or no), hypertension (yes or no), diabetes (yes or no), dyslipidaemia (yes or no), gout (yes or no), and family history of CVD (yes or no). To robustly evaluate the dose–response relationship between UA levels and the outcomes among individuals with CKD, we employed a restricted cubic spline (RCS) analysis with three knots positioned at the 5th, 50th, and 95th percentiles. Restricted cubic spline is a type of cubic spline with an additional constraint of linearity before the first and after the last knot.[20] We also stratified the analyses by age (<55, ≥55 years), sex (men, women), smoking (current or non-current smokers), drinking (current or non-current drinkers), BMI (<24 or ≥24 kg/m^2), eGFR (<45, ≥45 mL/min/1.73 m^2), hypertension (yes, no), and diabetes (yes, no) and tested for interactions by

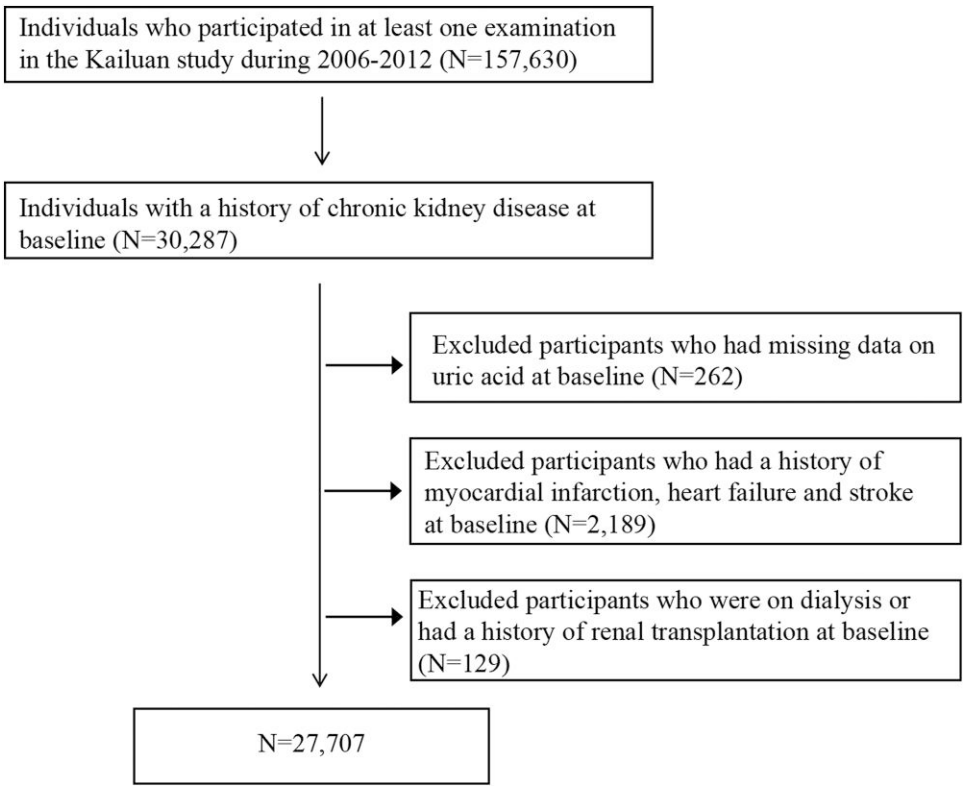


Figure 1 Flowchart of the study population.

including the multiplicative interactions between UA levels and the stratified factors for the outcomes of interest in Model 2.

To test the robustness of our findings, several sensitivity analyses were conducted. First, we repeated the main analyses after excluding the individuals with <3 years of follow-up to minimize the effect of subclinical conditions on the observed associations. Second, considering the potential impact of the UA-lowering drugs, we excluded individuals with a history of gout from the analysis. Third, to exclude the potential cases with nephrotic syndrome, we excluded individuals with CKD diagnosed based on proteinuria only. Fourth, to mitigate the potential influence of patients with terminal CKD on our results, we excluded participants with eGFR <15 mL/min/1.73 m^2. Fifth, considering that a portion of the medical history regarding hypertension, diabetes, and dyslipidaemia may rely on self-reporting, potentially impacting the accuracy of our results, we conducted a sensitivity analysis by adjusting for SBP, DBP, FBG, LDL-c, TG, and HDL-c instead of histories of hypertension, diabetes, and dyslipidaemia in Model 2. Additionally, the model was further adjusted for use of antidiabetic agents, antihypertensive agents, and lipid-lowering agents. Sixth, as antihypertensive agents such as renin–angiotensin blockers are also commonly used in the management of CKD, we conducted a sensitivity analysis by excluding individuals using these agents from the analysis. Seventh, to address the potential impact of the extreme values, we have conducted another sensitivity analysis by excluding UA values beyond the 99th percentile. Eighth, we repeated the main analyses by regrouping the overall study population without differentiating UA concentrations based on sex. Ninth, we conducted a sensitivity analysis using a time-dependent Cox model to adjust for time-dependent covariates. Finally, to account for competing risks of death, we assessed the associations of UA with risks of myocardial infarction, heart failure, and stroke using Fine–Gray subdistribution hazards models.

All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). Statistical significance was set as a two-sided $P < 0.05$.

Results

The characteristics of participants according to sex-specific UA tertiles are presented in *Table 1*. Of 27 707 participants with CKD, the mean age was 56.8 ± 13.2 years and 75.8% were men. Compared with those in the lowest tertile of UA, participants in the highest tertile were more likely to be older, current drinkers, current smokers, physically active, and highly educated. They also had higher levels of BMI, SBP, DBP, TG, and high-sensitivity C-reactive protein, but a lower level of HDL-c. Moreover, they had a higher prevalence of proteinuria, hypertension, history of dyslipidaemia, gout, and family history of CVD (all $Ps < 0.05$).

The median (interquartile range) follow-up time for myocardial infarction, heart failure, stroke, and all-cause mortality was 12.0 years (10.2–15.0), 11.2 years (9.5–14.0), 12.8 years (11.4–15.1), and 12.2 years (10.5–15.0), respectively. Over the follow-up period, 674 participants had incident myocardial infarction, 1197 had heart failure, 2406 had stroke, and 5676 died. Incidence rates of all outcomes were substantially higher among participants in the highest UA tertile compared with those in the lowest UA tertile (log-rank $P < 0.05$; Supplementary material online, *Figure S1*; *Table 2*).

After adjusting for potential confounders, we observed that the concentration of UA was positively associated with the risk of myocardial infarction, heart failure, and all-cause mortality in a dose–response manner ($P_{trend} < 0.001$) among individuals with CKD (*Table 2*). Compared with those in the lowest tertile of UA, participants in the highest UA tertile had higher HRs of myocardial infarction, heart failure, and all-cause mortality, and the corresponding HRs (95% CI) were 1.38 (1.13–1.67), 1.60 (1.38–1.85), and 1.29 (1.21–1.38) in the multivariable-adjusted Model 2. However, the association between UA and stroke is

Table 1 Baseline characteristics of the study population according to the tertiles of uric acid levels in individuals with chronic kidney disease

Characteristics	Total	UA, μmol/L			*P*-value	
		Tertile 1 (men <257.0, women <224.3)	Tertile 2 (men 257.0–336.0, women 224.3–284.0)	Tertile 3 (men ≥336.0, women ≥284.0)		FDR-adjusted *P*-value
No. of participants	27 707	9235	9257	9215		
UA, μmol/L	297.4 ± 92.9	208.7 ± 34.9	285.5 ± 27.7	398.3 ± 75.8	<0.001	<0.001[a]
Age, years	56.8 ± 13.2	54.1 ± 12.6	57.1 ± 13.0	59.2 ± 13.5	<0.001	<0.001[a]
Men	21 013 (75.8)	7004 (75.8)	7035 (76.0)	6974 (75.7)	0.88	0.88[b]
Current drinker	8505 (30.7)	2540 (27.5)	2717 (29.4)	3248 (35.3)	<0.001	<0.001[b]
Current smoker	8923 (32.2)	2736 (29.6)	2845 (30.7)	3342 (36.3)	<0.001	<0.001[b]
Physical activity	5080 (18.3)	1347 (14.5)	1741 (18.8)	1999 (21.7)	<0.001	<0.001[b]
High school and above	4770 (17.2)	1498 (16.2)	1447 (15.6)	1825 (19.8)	<0.001	<0.001[b]
BMI, kg/m^2	25.4 ± 3.5	24.9 ± 3.3	25.3 ± 3.4	26.1 ± 3.6	<0.001	<0.001[a]
SBP, mmHg	137.2 ± 22.0	134.9 ± 21.2	137.0 ± 22.1	139.6 ± 22.5	<0.001	<0.001[a]
DBP, mmHg	86.0 ± 12.0	85.4 ± 11.6	85.7 ± 11.9	86.9 ± 12.6	<0.001	<0.001[a]
FBG, mmol/L	5.85 ± 2.05	5.91 ± 2.24	5.81 ± 2.03	5.81 ± 1.86	<0.001	<0.001[a]
TC, mmol/L	4.97 ± 1.20	4.81 ± 1.22	4.92 ± 1.17	5.19 ± 1.19	<0.001	<0.001[a]
LDL-c, mmol/L	2.63 ± 0.85	2.59 ± 0.75	2.62 ± 0.83	2.67 ± 0.96	0.03	0.04[a]
HDL-c, mmol/L	1.52 ± 0.40	1.54 ± 0.37	1.54 ± 0.40	1.48 ± 0.42	<0.001	<0.001[a]
TG, mmol/L	1.38 (1.02, 2.13)	1.31 (1.01, 1.88)	1.31 (0.99, 1.99)	1.60 (1.11, 2.50)	<0.001	<0.001[a]
High-sensitivity C-reactive protein, mg/L	1.20 (0.45, 2.84)	0.91 (0.32, 2.27)	1.10 (0.41, 2.60)	1.52 (0.66, 3.60)	<0.001	<0.001[a]
eGFR, mL/min/1.73 m^2	57.4 ± 16.9	57.0 ± 16.9	57.9 ± 16.5	57.2 ± 17.3	<0.001	<0.001[a]
Proteinuria ≥300 mg/dL	5783 (20.9)	1837 (19.9)	1902 (20.6)	2044 (22.2)	<0.001	<0.001[b]
History of hypertension	17 429 (62.9)	5498 (59.5)	5678 (61.3)	6253 (67.9)	<0.001	<0.001[b]
History of diabetes	4496 (16.2)	1538 (16.7)	1446 (15.6)	1512 (16.4)	0.14	0.14[b]
History of dyslipidaemia	16675 (60.2)	4783 (51.8)	5332 (57.6)	6560 (71.2)	<0.001	<0.001[b]
Family history of CVD	2260 (8.2)	693 (7.5)	682 (7.4)	885 (9.6)	<0.001	<0.001[b]
History of gout	1665 (0.6)	42 (0.5)	33 (0.4)	90 (1.0)	<0.001	<0.001[b]

Data are presented as mean ± SD, median (interquartile range), or *n* (%). *P*-values were obtained using ANOVA for continuous variables (age, UA, BMI, SBP, DBP, FBG, TC, LDL-c, HDL-c, and eGFR), Kruskal–Wallis for continuous variables (TG and high-sensitivity C-reactive protein), and χ^2 tests for categorical variables (sex, smoking status, drinking status, physical activity, education, proteinuria, history of hypertension, history of diabetes, history of dyslipidaemia, family history of CVD, and history of gout).

BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; FDR, false discovery rate; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol; TG, triglycerides; UA, uric acid.

[a]Indicates comparisons following ANOVA or Kruskal–Wallis tests using the Bonferroni correction for continuous variables.

[b]Indicates χ^2 tests with the Bonferroni correction for categorical variables.

not significant. With per SD increase in UA, the HRs (95% CIs) of myocardial infarction, heart failure, and all-cause mortality were 1.14 (1.06–1.23), 1.23 (1.17–1.30), and 1.13 (1.10–1.16). Further, the RCS model showed a linear positive association between UA concentrations and the risks of myocardial infarction, heart failure, and all-cause mortality in individuals with CKD ($P_{overall} < 0.05$; $P_{nonlinearity} > 0.05$; *Figure 2*).

The results of subgroup analyses are shown in *Figure 3* and Supplementary material online, *Figure S2*. A stronger association between UA and heart failure and all-cause mortality was found in patients with eGFR <45 mL/min/1.73 m^2 compared to their counterparts ($P_{interaction} < 0.05$). Additionally, the association between UA and the risk of all-cause mortality was stronger among individuals without a history of diabetes than those with a history of diabetes ($P_{interaction} < 0.05$). However, we did not find significant heterogeneity in the risk estimates between any other stratified factors and UA for risks of outcomes ($P_{interaction} > 0.05$). Additionally, our primary finding persisted in all sensitivity analyses (see Supplementary material online, *Table S1*).

Discussion

In this large prospective cohort study of individuals with CKD, the main findings of this study indicated that a higher concentration of UA was associated with a higher risk of myocardial infarction, heart failure, and all-cause mortality, following a dose–response manner. Moreover, the associations between UA concentrations and both heart failure and all-cause mortality were stronger in individuals with eGFR <45 mL/min/1.73 m^2 than those with eGFR ≥45 mL/min/1.73 m^2, and the association between UA concentrations and all-cause mortality was more pronounced in participants without diabetes than those with diabetes.

Table 2 Associations of uric acid levels with risks of myocardial infarction, heart failure, stroke, and all-cause mortality among individuals with chronic kidney disease

	UA, μmol/L, HR (95%CI)			P_{trend}	Per SD (92.9 μmol/L)
	Tertile 1	Tertile 2	Tertile 3		
Myocardial infarction					
Events/person-years	176/115 270	214/112 277	284/105 961		
Incidence per 1000 person-years	1.5	1.9	2.7		
Model 1	Ref.	1.11 (0.91–1.35)	1.47 (1.22–1.78)	<0.001	1.20 (1.12–1.29)
Model 2	Ref.	1.14 (0.93–1.39)	1.38 (1.13–1.67)	<0.001	1.14 (1.06–1.23)
Heart failure					
Events/person-years	294/107 293	363/104 633	540/98 000		
Incidence per 1000 person-years	2.7	3.5	5.5		
Model 1	Ref.	1.09 (0.93–1.27)	1.61 (1.40–1.86)	<0.001	1.26 (1.19–1.32)
Model 2	Ref.	1.13 (0.97–1.32)	1.60 (1.38–1.85)	<0.001	1.23 (1.17–1.30)
Stroke					
Events/person-years	761/120 735	762/119 993	883/115 240		
Incidence per 1000 person-years	6.3	6.4	7.7		
Model 1	Ref.	0.93 (0.84–1.03)	1.09 (0.98–1.20)	0.08	1.04 (1.00–1.08)
Model 2	Ref.	0.93 (0.84–1.02)	1.01 (0.91–1.12)	0.82	1.00 (0.96–1.04)
All-cause mortality					
Events/person-years	1546/116 241	1921/113 490	2209/107 407		
Incidence per 1000 person-years	13.3	16.9	20.6		
Model 1	Ref.	1.05 (0.98–1.13)	1.19 (1.11–1.27)	<0.001	1.10 (1.07–1.12)
Model 2	Ref.	1.11 (1.04–1.19)	1.29 (1.21–1.38)	<0.001	1.13 (1.10–1.16)

Model 1: age and sex. Model 2: Model 1 + smoking status, drinking status, physical activity, education, BMI, high-sensitivity C-reactive protein, eGFR, proteinuria, hypertension, diabetes, dyslipidaemia, gout, and family history of cardiovascular disease.
BMI, body mass index; CKD, chronic kidney disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; SD, standard deviation; UA, uric acid.

Our results corroborate prior work suggesting that UA is a risk factor for CVD in general populations and extend these findings to patients with CKD. Holme *et al.*[21] reported that there was a gradual increase in the risk of myocardial infarction and heart failure by increasing UA concentrations in middle-aged adults without prior CVD. Further, a cohort study using the UK Biobank showed that compared to individuals who were free of hyperuricaemia/gout, patients with hyperuricaemia had a 1.33-fold increased risk of CVD. Meanwhile, Mendelian randomization analysis provided support that the observed association was causal.[22] A meta-analysis, pooling data from five studies, demonstrated that hyperuricaemia was associated with a 1.65-fold higher risk of heart failure.[23] In addition, we observed a linear positive relationship between UA concentrations and the risk of all-cause mortality in individuals with CKD. This finding contrasts with earlier studies focusing on patients with kidney failure, which reported a J-shaped association between UA concentrations and all-cause mortality.[24,25] The divergence in findings may be attributed to the differences in the studied populations. Specifically, previous research largely targeted patients receiving haemodialysis, a treatment known to directly influence UA clearance, potentially explaining the variation in the observed associations.

Our study extended the previous findings to patients with CKD, which may have significant clinical relevance and public health implications for the prevention and management of CVD, specifically myocardial infarction, and heart failure, among patients with CKD. Hyperuricaemia is notably prevalent in CKD due to increased reabsorption and decreased secretion of UA in the proximal tubules.[26] By providing detailed insights into the relationship between UA concentrations and various subtypes of cardiovascular risk, our research sheds light on the intricacies of cardiovascular health in CKD patients. This emphasizes the importance of recognizing hyperuricaemia not only as a common condition among those with CKD but also as a significant factor that exacerbates their risk for developing cardiovascular complications. Therefore, integrating the management of hyperuricaemia into the comprehensive care of CKD patients could play a crucial role in mitigating their overall cardiovascular risk and improving health outcomes.

We also demonstrated that the risk for both heart failure and all-cause mortality related to UA was stronger in individuals with eGFR <45 mL/min/1.73 m^2 compared to their counterparts. Uric acid elimination primarily occurs through the kidneys, involving processes such as glomerular filtration, presecretory reabsorption, secretion, and postsecretory reabsorption. As renal function declines, UA concentrations tend to rise, indicating an association between reduced eGFR and an increased incidence of hyperuricaemia.[27] The observed interaction among patients with lower eGFR can be attributed to several potential mechanisms. First, elevated UA concentrations in the context of reduced kidney function may lead to increased oxidative stress and inflammation,[28,29] both of which are recognized pathways for cardiovascular damage. Additionally, hyperuricaemia has been associated with endothelial dysfunction, a precursor to atherosclerosis, further elevating the risk of CVD.[30] Moreover, the accumulation of UA might exacerbate hypertension,[28] a well-known risk factor for both heart failure and CKD progression. Elevated UA concentrations can induce renal vasoconstriction, reducing nephron perfusion and leading to activation of the renin–angiotensin–aldosterone system, thereby contributing to blood pressure elevation and subsequent cardiovascular strain.[31,32] Our data suggest implementing primordial prevention of cardiovascular health is of particular importance among patients with CKD, especially in individuals with eGFR <45 mL/min/1.73 m^2, to effectively reduce the risk of heart failure and premature death.

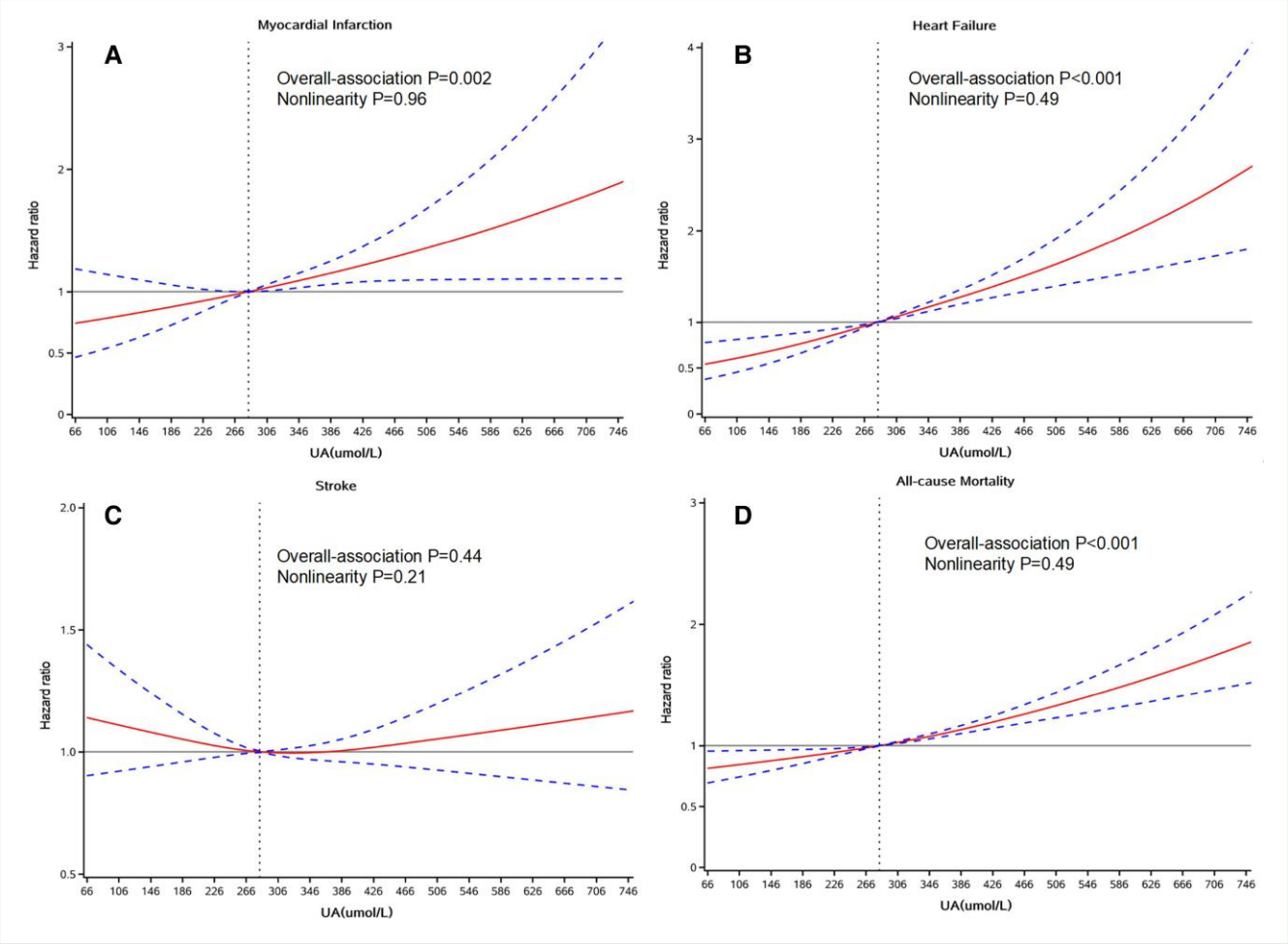


Figure 2 Hazard ratios and 95% confidence intervals for uric acid with the risks of myocardial infarction (*A*), heart failure (*B*), stroke (*C*), and all-cause mortality (*D*) among individuals with chronic kidney disease by using restricted cubic spline regression. Hazard ratios were adjusted for age, sex, smoking status, drinking status, physical activity, education, body mass index, high-sensitivity C-reactive protein, estimated glomerular filtration rate, proteinuria, hypertension, diabetes, dyslipidaemia, gout, and family history of cardiovascular disease. UA, uric acid.

In addition, we also found that diabetes modified the association between UA and all-cause mortality risk among individuals with CKD, and individuals without diabetes exhibited a high risk of all-cause mortality. Kuo *et al.*[33] found that in non-diabetic individuals, concentrations of UA increased with the 2-h postload glucose (2hPG), and interestingly, concentrations of UA were inversely associated with both fasting plasma glucose and 2hPG in patients with diabetes. It has been shown that patients with diabetes experiencing glycosuria exhibit a negligible prevalence of hyperuricaemia and higher UA excretion in urine compared to those without glycosuria. Moreover, in diabetes treatment, the use of sodium–glucose cotransporter-2 inhibition, such as empagliflozin, could effectively reduce the concentrations of UA.[34] However, further research is warranted to elucidate the underlying mechanisms driving these observed differences.

The biological mechanisms underlying the association of UA with the risk of CVD and all-cause mortality in individuals with CKD mainly included oxidative stress, endothelial dysfunction systematic, activation of the renin–angiotensin–aldosterone system, and inflammation caused by long-term high UA concentrations.[31,35,36] Furthermore, UA is closely associated with almost all known cardiovascular risk factors,[37] insulin resistance,[38] metabolic syndrome,[39] and obesity.[40] Elevated UA concentrations may be interpreted either as a direct indicator of CVD or a marker reflecting the presence of co-existing cardio-metabolic risk factors.

Strengths and limitations

The strengths of our study include its large sample size, prospective study design, and long follow-up period. However, some limitations must be acknowledged to aid in the interpretation of our results. First, given that this was an observational study, the causal relationship between UA and the risks of CVD and all-cause mortality in patients with CKD cannot be established. Second, the use of serum creatinine to evaluate GFR offers an incomplete picture, and it is recognized that more accurate methods like insulin clearance could enhance the characterization of kidney function in our research. In addition, our diagnosis of CKD was based on a single measurement of eGFR and a one-time dipstick test, without follow-up assessments after 3 months, which could potentially lead to an overdiagnosis of CKD. Nonetheless, these methods are not feasible in a community-based study setting. Third, while the influence of diet on UA concentrations is an important factor in the study of kidney function, data on specific dietary variables

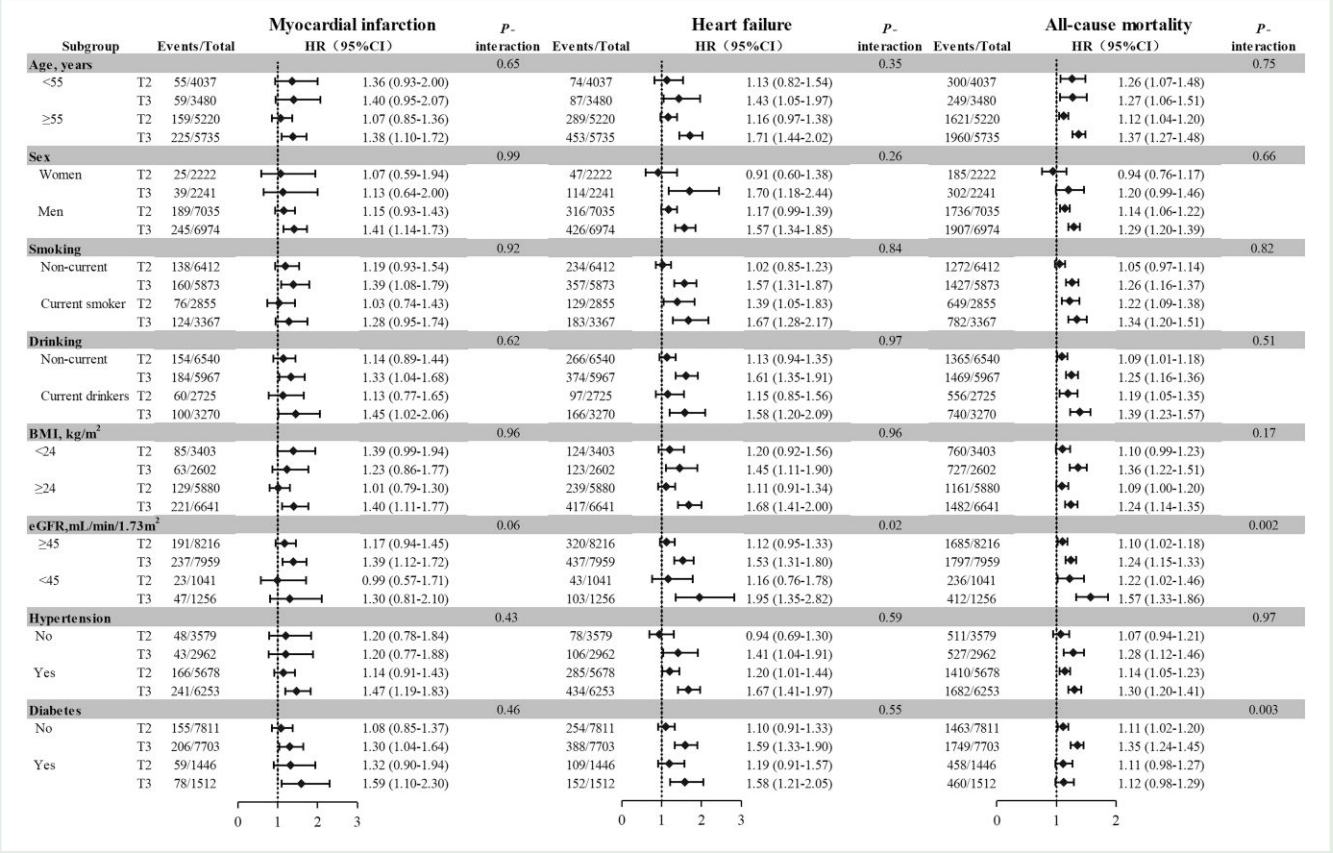


Figure 3 Subgroup analyses of uric acid levels with the risks of subsequent myocardial infarction, heart failure, and all-cause mortality among individuals with chronic kidney disease. Hazard ratios were adjusted for age, sex, smoking status, drinking status, physical activity, education, body mass index, high-sensitivity C-reactive protein, estimated glomerular filtration rate, proteinuria, hypertension, diabetes, dyslipidaemia, gout, and family history of cardiovascular disease. BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

were not available at baseline in the Kailuan Study. Fourth, a considerable limitation of our study is that over 70% of the participants were Chinese men from the Kailuan community, which could restrict the generalizability of our results to populations with different sex compositions. Fifth, we had challenges in differentiating subtypes of heart failure in our current analysis due to a lack of information, which hindered our ability to uncover a more detailed association between UA and different heart failure classifications in CKD. Sixth, while we lack specific data on the use of UA-lowering drugs such as allopurinol and febuxostat, the sensitivity analysis showed consistent results after excluding patients with a history of gout. Furthermore, we consider the potential influence on our results to be limited as the prescription of these drugs is typically exclusively to patients diagnosed with gout. Finally, the participants were mainly Chinese adults from the Kailuan community, which might limit the generalizability of our findings to other racial/ethnic or socioeconomic groups. However, the homogeneity of socioeconomic status in the study population helps reduce potential confounding related to socioeconomic status or cultural practices.

In conclusion, a higher concentration of UA was associated with a higher risk of myocardial infarction, heart failure, and all-cause mortality among individuals with CKD. Regular monitoring of UA in CKD patients may serve as a useful tool to identify individuals at high risk, thereby implementing potential intervention strategies aimed at enhancing disease prevention.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Author contribution

T.G., S.W., X.G., and N.L. contributed to the conception or design of the work. N.L., L.C., and T.G. contributed to the acquisition, analysis, or interpretation of data for the work. N.L. and T.G. drafted the manuscript with critical input from all authors. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Ethical approval

The study was performed according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the Kailuan General Hospital (approval number: 2006–05). Written informed consent was obtained from all participants.

Conflict of interest: none declared.

Data availability

Data described in the manuscript can be made available upon request, pending application and approval by the chair of the steering committee for the cohort.

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