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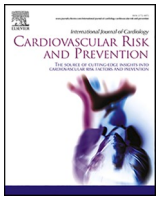

Sex-specific associations between prolonged serum uric acid levels and risk of major adverse cardiovascular events

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ABSTRACT

Background: While hyperuricemia has been correlated with cardiovascular (CV) diseases, further evidence is required to evaluate the implications of stable serum uric acid (sUA) levels, especially concerning low sUA. This study aimed to investigate prolonged stable sUA levels and CV events/mortality.
Methods: We conducted a retrospective cohort study at a medical center using electronic medical records linked with the national claims database. Patients with at least two sUA measurements, with intervals ranging from 6 months to 4 years, were included. The mean of the first two eligible sUA measurements were analyzed, stratified by sex. Outcomes of interest comprised major adverse cardiovascular events (MACE), heart failure hospitalization, CV and all-cause mortality.
Results: This study included 33,096 patients (follow-up: men 6.6 years, women 6.4 years). After multivariable adjustment, cubic spline models showed that long-term high sUA levels were consistently associated with a higher risk of MACE, heart failure hospitalization, CV and all-cause mortality. A U-shaped association was observed between sUA levels and all-cause mortality in both sexes and between sUA levels and CV mortality in women. The impact of sUA, especially lower levels, on CV events and mortality was more pronounced in women than in men.
Conclusion: Long-term high sUA levels are consistently associated with increased risk of CV events and mortality. A U-shaped association between sUA levels and all-cause mortality was observed in both men and women and was pronounced in women. The findings underscore the importance of considering sUA levels, especially in women, when assessing CV risk.

1. Introduction

Uric acid (UA) is the end product of human purine metabolism [1]. Hyperuricemia is generally defined as blood UA concentration exceeding 7.0 mg/dL in men and 6.0 mg/dL in women, which can result from either excessive production or reduced renal excretion of urate. Studies have demonstrated that hyperuricemia is associated with cardiovascular diseases (CVD) such as hypertension and coronary artery disease [2,3]. Hyperuricemia has also been linked to an elevated risk of heart failure (HF) [4,5]. Additionally, there is evidence suggesting that a high serum UA (sUA) level at discharge from HF hospitalization is a robust predictor of a combined outcome comprising all-cause mortality and HF rehospitalization [6].

Despite the known link between hyperuricemia and increased risk of CVD, the relationship between sUA levels and CVD risk may not be linear. Recent studies indicated a U-shaped association between sUA levels and all-cause mortality [7–11], CV mortality [9,10], and CV events [4]. This implies that both excessively high and excessively low sUA levels may elevate the risk of adverse outcomes. However, most of these studies have relied on a single sUA measurement to project the

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long-term risk of CVD [4,7,10,12,13], which could limit the ability to assess the effects of prolonged sUA exposure. Furthermore, the majority of previous studies focused on CV and all-cause mortality [7–11], with limited examination of major adverse cardiovascular events (MACE) and hospitalization due to HF [4,14]. To help fill the gaps in knowledge, our study aimed to conduct a comprehensive cohort analysis to evaluate the relationship between long-term stable sUA levels and the risk of MACE, HF hospitalization, CV mortality, and all-cause mortality.

2. Methods

2.1. Data source

This retrospective cohort study was conducted using the Integrated Medical Database of National Taiwan University Hospital (NTUH-iMD) and the National Health Insurance Research Database (NHIRD). The NTUH-iMD is a repository of electronic health records containing patient demographics, clinical diagnoses, physician orders, physical examination findings, pharmacy records, and laboratory test results. Our cohort consisted of individuals diagnosed with hypertension (ICD-9-CM: 401.x; ICD-10-CM: I10.x), diabetes (ICD-9-CM: 250.x; ICD-10-CM: E11), dyslipidemia (ICD-9-CM: 272.x; ICD-10-CM: E78.x), or any CVD (ICD-9-CM: 390.x-459.x; ICD-10-CM: I00.x-I99.x) at NTUH between January 1, 2006 and July 31, 2017. To augment the NTUH-iMD records and ensure longitudinal data completeness, we linked patient records to the NHIRD using unique personal identifiers. The NHIRD, in conjunction with the Cause of Death Registry, comprises a nationwide database covering 99.9 % of Taiwan's 23 million residents and includes data on outpatient visits, inpatient admissions, emergency department visits, pharmacy records, and causes of death. The study was approved by the Research Ethics Committee of NTUH (No. 201710009RINC). All databases utilized in this study were de-identified and adhered to pertinent guidelines and regulatory standards.

2.2. Study population and exposure

Our initial cohort was comprised of individuals with a minimum of two sUA assessments recorded between 2009 and 2014. To mitigate the influence of sUA fluctuations, we refined our cohort to include only individuals with stable sUA levels, defined as having at least two measurements taken 6 months to 4 years apart with a difference between the two sUA levels of less than 2 mg/dL. This interval was chosen in consideration of the available data period. The first two sUA measurements meeting these criteria were used to calculate the mean stable sUA value, and the date of the second sUA measurement was designated as the index date. Patients were excluded if they met any of the following criteria: (1) age below 20 years, (2) hospitalization for myocardial infarction (MI), ischemic stroke, or HF within 3 years prior to the index date, or (3) had a diagnosis of severe liver disease or cancer or had undergone regular dialysis or kidney/liver transplant within 3 years before the index date.

2.3. Outcomes and follow-up

The study assessed several outcomes, including MACE (a composite outcome comprising MI, ischemic stroke, and CV mortality), HF hospitalization, CV mortality, and all-cause mortality. MACE was specifically defined as hospitalization with a diagnosis of MI (ICD-9-CM codes: 410; ICD-10-CM codes: I21, I22), hospitalization with a diagnosis of ischemic stroke (ICD-9-CM codes: 433, 434; ICD-10-CM codes: I63, I65, I66), or CV mortality. HF hospitalization was defined as the occurrence of any inpatient diagnosis coded with ICD-9-CM 428 and ICD-10-CM I50. CV mortality and all-cause mortality were determined using data from the Cause of Death Registry, of which CV mortality was categorized as heart-related (ICD-10-CM codes: I01–I02, I05–I09, I20–I25, I27, I30–I52), cerebrovascular-related (I60–I69), or atherosclerosis-related (I70).

Eligible patients were followed up from the index date until the occurrence of the specified outcome, or they were censored at the end of the study (December 31, 2017) or in the case of death, specifically for analyses that did not focus on all-cause mortality as the study outcome.

2.4. Covariates

The following covariates were collected: body mass index (BMI), hemoglobin A1c (HbA1c), low-density lipoprotein cholesterol (LDL-C), estimated glomerular filtration rate (eGFR), smoking status, history of coronary revascularization, comorbidities (hypertension, diabetes mellitus, hyperlipidemia, HF, cardiomyopathy, ischemic heart disease, atrial fibrillation, valvular heart disease, previous ischemic stroke or transient ischemic attack, hemorrhagic stroke, venous thromboembolism, peripheral vascular disease, gout, thyroid disorders, renal disease, liver disease, chronic obstructive pulmonary disease), and comedications (nonsteroidal anti-inflammatory drugs, systemic corticosteroids, colchicine, allopurinol, uricosurics, α-blockers, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, diuretics, antiarrhythmic agents, digoxin, nitrate, anticoagulants, aspirin, other antiplatelets, statins, fibrates, oral antihyperglycemic agents, and insulins). BMI, HbA1c, LDL-C, and eGFR data were sourced from the hospital's electronic health records up to two years before the index date, with the last available data point utilized. Coronary revascularization was identified in the inpatient setting based on ICD procedure codes or NHI order codes within 3 years preceding the index date. Comorbidities were defined as having at least 2 outpatient diagnoses or 1 inpatient diagnosis within 3 years before the index date, and history of medications was determined within a 1-year timeframe before the index date.

2.5. Statistical analysis

Baseline characteristics are presented as count and percentage for categorical variables and as mean ± standard deviation for continuous variables. Differences among study groups were assessed using chi-square test or one-way ANOVA test. Rates of missing data in BMI, HbA1c, LDL-C, and eGFR data were reported and handled through multiple imputation techniques. We applied restricted cubic spline models to investigate the continuous relationship between sUA levels and the study outcomes. The reference levels were set as 5 mg/dL for men and 4 mg/dL for women.

Subgroup analyses were performed to assess the effects of sUA among different subpopulations based on history of hypertension, history of CVD (including HF, ischemic heart disease, cardiomyopathy, atrial fibrillation, valvular heart disease), and age (<65 years and ≥65 years). Additionally, a series of sensitivity analyses were conducted to ensure the consistency of the results. First, we restricted the definition of hospitalization outcomes to be based solely on the primary diagnosis. Second, we conducted the analyses without further adjustment for HbA1c, LDL-C, and eGFR to assess the robustness of the results. All data analyses were carried out using SAS, version 9.4 (SAS Institute, Cary, NC, USA). A two-sided *P* value less than 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

Among the 293,697 patients diagnosed with hypertension, diabetes, hyperlipidemia, or CVD identified in the NTUH-iMD database between January 2006 and July 2017, 59,485 patients had undergone two or more sUA measurements with intervals spanning from 6 months to 4 years. Among them, 33,096 patients (comprising 17,997 men and 15,099 women) were included in the analysis (Fig. 1).

Table 1 provides an overview of the baseline characteristics of these

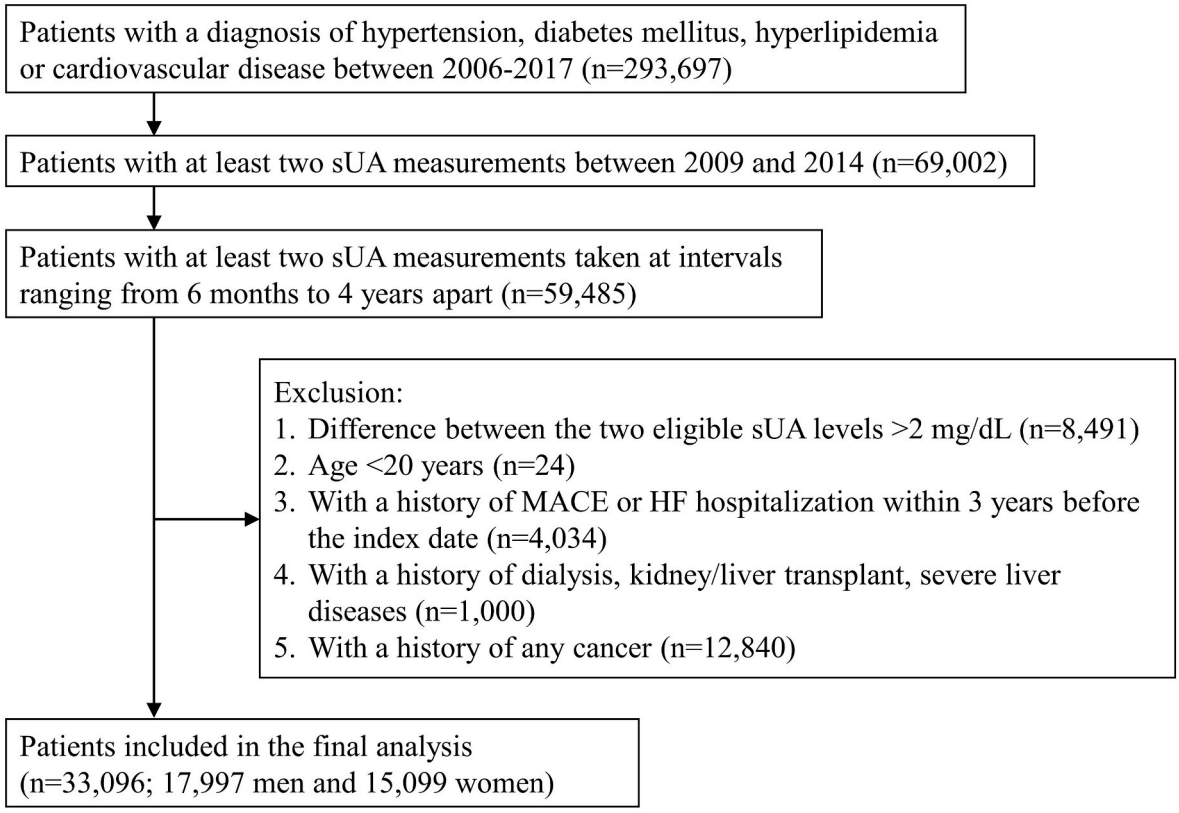

Fig. 1. Flowchart of patient selection Abbreviations: HF, heart failure; MACE, major adverse cardiovascular events (including myocardial infarction, ischemic stroke, and cardiovascular death); sUA, serum uric acid.

patients, stratified by sex. The mean age was 61.1 years for men and 64.0 years for women. Generally, men had higher sUA levels compared to women; for instance, men were more likely to have long-term sUA levels within the ranges of 6.0–7.0 mg/dL, 7.0–8.0 mg/dL, and >8 mg/dL. In men, the sUA levels at the 25th percentile, median (50th percentile), and 75th percentile were 5.65 mg/dL, 6.55 mg/dL, and 7.50 mg/dL, respectively. In women, the sUA levels at the 25th percentile, median (50th percentile), and 75th percentile were 4.70 mg/dL, 5.50 mg/dL, and 6.45 mg/dL, respectively. Additionally, a higher proportion of men in the study had gout and were treated with colchicine, allopurinol, or uricosurics. Male participants were also more likely to be current smokers and have a history of ischemic heart disease and coronary revascularization.

There was a significant proportion of missing data regarding BMI with 42.3 % of males and 43.1 % of females lacking this information. Additionally, 58.3 % of males and 59.8 % of females had missing HbA1c values. LDL-C levels were absent in 23.7 % of males and 22.8 % of females, while eGFR data was missing for 15.6 % of males and 14.9 % of females.

3.2. Associations between sUA and risk of CVD

Over a median follow-up period of 6.6 years, 1,954 men died among which 558 of these deaths were attributed to CVD. Among men, 1,553 MACE and 954 cases of HF hospitalization were recorded (Table 2). In women, 1,360 deaths occurred over a median follow-up period of 6.4 years among which 374 were attributed to CVD. Additionally, 955 MACE and 904 cases of HF hospitalization occurred in women. The rates of MACE and all-cause mortality were higher in men than in women.

Utilizing restricted cubic splines, we illustrated the relationship between continuous sUA levels and MACE, HF hospitalization, CV mortality, and all-cause mortality by sex (Fig. 2). After adjusting for age, smoking, BMI, LDL-C, HbA1c, eGFR, history of coronary revascularization, comorbidities, and comedications, a U-shaped association was revealed between sUA levels and all-cause mortality in both sexes (Fig. 2G and H) and between sUA levels and CV mortality in women (Fig. 2F). Notably, sUA had a more pronounced effect in women than in men, especially at low sUA levels. Furthermore, higher sUA levels were linked to an increased rate of MACE and HF hospitalization in both men and women.

3.3. Subgroup analyses and sensitivity analyses

Subgroup analyses and sensitivity analyses were performed to evaluate the effects of sUA within specific subpopulations and to ascertain the consistency of the findings. These results are detailed in the Supplementary Materials. As depicted in Supplementary Fig. S1, a more pronounced association was observed between low sUA levels and all-cause mortality in men under the age of 65 and without hypertension. Conversely, women aged 65 and above experienced a higher influence from low sUA levels compared to women below the age of 65 (Supplementary Fig. S2). The main findings remained consistent in the sensitivity analyses when the definition of hospitalization outcomes was restricted to the primary diagnosis (Supplementary Fig. S3) and when HbA1c, LDL-C, and eGFR were not adjusted (Supplementary Fig. S4).

4. Discussion

This study provides a comprehensive evaluation that reinforces the existing body of evidence regarding the relationship between long-term stable sUA levels and CVD. The findings of this study highlight a significant association between higher sUA levels and increased risk of MACE, HF hospitalization, CV mortality, and all-cause mortality. Additionally, we observed that patients with lower sUA levels were at a higher risk of all-cause mortality in both men and women as well as CV mortality in women, but not with other outcomes. Interestingly, the

Table 1
Baseline characteristics of patients stratified by sex.

Characteristics	Men (n = 17,997)	Women (n = 15,099)	*P*-value
Age, years	61.1 ± 13.8	64.0 ± 13.8	<0.0001
Serum uric acid (sUA), mg/dL	6.6 ± 1.4	5.7 ± 1.4	<0.0001
≤4 (%)	430 (2.4)	1369 (9.1)	
4.0–5.0(%)	1573 (8.7)	3758 (24.9)	
5.0–6.0 (%)	3976 (22.1)	4516 (29.9)	
6.0–7.0 (%)	5057 (28.1)	3002 (19.9)	
7.0–8.0 (%)	4052 (22.5)	1501 (9.9)	
>8 (%)	2909 (16.2)	953 (6.3)	
Body mass index (BMI), kg/m^{2}[a]	25.3 ± 3.5	24.7 ± 4.1	<0.0001
HbA1c, mg/dL[a]	6.7 ± 1.3	6.7 ± 1.2	0.50
LDL-C, mg/dL[a]	106.7 ± 31.7	110.6 ± 32.6	<0.0001
eGFR, ml/min/1.73m^{2}[a]	74.6 ± 22.8	74.2 ± 24.2	0.08
Current smoker (%)	3647 (20.3)	227 (1.5)	<0.0001
History of coronary revascularization (%)			
Percutaneous coronary intervention	1071 (6.0)	272 (1.8)	<0.0001
Coronary artery bypass grafting	224 (1.2)	47 (0.3)	<0.0001
Comorbidities (%)			
Atrial fibrillation	860 (4.8)	656 (4.3)	0.06
Cardiomyopathy	120 (0.7)	66 (0.4)	0.01
Chronic obstructive pulmonary disease	1344 (7.5)	734 (4.9)	<0.0001
Diabetes	6035 (33.5)	4642 (30.7)	<0.0001
Disorders of thyroid gland	629 (3.5)	1533 (10.2)	
Gout	3431 (19.1)	970 (6.4)	
Heart failure	641 (3,6)	613 (4.1)	0.02
Hemorrhagic stroke	218 (1.2)	101 (0.7)	<0.0001
Hyperlipidemia	9351 (52.0)	7792 (51.6)	0.52
Hypertension	12,303 (68.4)	10,418 (69.0)	0.21
Ischemic heart disease	6699 (37.2)	3963 (26.3)	<0.0001
Liver disease	2699 (14.5)	1708 (11.3)	<0.0001
Peripheral vascular disease	826 (4.6)	607 (4.0)	0.01
Prior ischemic stroke/transient ischemic attack	1396 (7.8)	1056 (7.0)	0.01
Renal disease	1277 (7.1)	780 (5.2)	<0.0001
Valvular heart disease	1092 (6.1)	1416 (9.4)	<0.0001
Venous thromboembolism	153 (0.9)	180 (1.2)	0.002
Medications (%)			
α blockers	2023 (11.2)	583 (3.9)	<0.0001
β blockers	7657 (42.6)	6321 (41.9)	0.21
ACEI/ARB	10,073 (56.0)	7787 (51.6)	<0.0001
Allopurinol	1496 (8.3)	417 (2.8)	<0.0001
Antiarrhythmic agents	1008 (5.6)	748 (5.0)	0.01
Anticoagulants	1466 (8.2)	819 (5.4)	<0.0001
Aspirin	7052 (39.2)	4141 (27.4)	<0.0001
Calcium channel blocker	8621 (47.9)	7399 (49.0)	0.046
Colchicine	1434 (8.0)	418 (2.8)	<0.0001
Digoxin	515 (2.9)	457 (3.0)	0.38
Diuretics	4087 (22.7)	4137 (27.4)	<0.0001
Fibrates	1341 (7.5)	761 (5.0)	<0.0001
Nitrate	3752 (20.9)	1924 (12.7)	<0.0001
Nonsteroidal anti-inflammatory drugs	10,339 (57.5)	9838 (65.2)	<0.0001
Insulins	860 (4.8)	860 (5.7)	0.55
Oral antihyperglycemic agents	5094 (28.3)	3908 (25.9)	<0.0001
Other antiplatelet agents	2561 (14.2)	1510 (10.0)	<0.0001
Statins	7054 (39.2)	5879 (38.9)	0.63
Systemic corticosteroids	3232 (18.0)	3232 (21.4)	<0.0001
Uricosurics	2103 (11.7)	571 (3.8)	<0.0001

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; LDL-C, low density lipoprotein-cholesterol.
[a] Calculated among participants with complete data for that variable.

Table 2
Risk of study outcomes during follow-up.

	Event number	Median follow-up in years	Incidence rate (standard error) per 1000 person-years
Men			
MACE	1,553	6.33	15.06 (0.38)
Myocardial infarction	510	6.25	4.86 (0.22)
Stroke	743	6.26	7.13 (0.26)
CV mortality	558	6.31	5.25 (0.22)
HF hospitalization	954	6.28	9.17 (0.30)
All-cause mortality	1,954	6.55	18.40 (0.42)
Women			
MACE	955	6.20	11.06 (0.36)
Myocardial infarction	214	6.14	2.44 (0.17)
Ischemic stroke	518	6.15	5.97 (0.26)
CV mortality	374	6.20	4.25 (0.22)
HF hospitalization	904	6.19	10.51 (0.35)
All-cause mortality	1,360	6.40	15.45 (0.42)

Abbreviations: CV, cardiovascular; HF, heart failure.; MACE, major adverse cardiovascular events (including myocardial infarction [MI], ischemic stroke, and cardiovascular death).

associations appeared to be more pronounced in women than in men. While previous studies primarily focused on the outcomes of CV mortality or all-cause mortality [7–11,15], only a limited number of studies delved into the impact of sUA levels on specific CV outcomes such as acute MI, HF hospitalization, and hypertension [4,6]. Prior studies have provided mixed results when exploring the potential link between lower sUA levels and an elevated risk of HF hospitalization. However, in our study, we observed that higher sUA levels were associated with a greater risk of HF hospitalization, whereas no such association was observed in individuals with lower sUA levels.

Several potential mechanisms support the findings indicating that elevated sUA levels are associated with an increased risk of MACE, HF hospitalization, CV mortality, and all-cause mortality [2,3,6]. Uric acid is produced during purine metabolism, and higher UA production signifies increased oxidant formation contributing to oxidative stress and tissue damage [16]. The excess of reactive oxygen species (ROS) and UA accumulation may reduce nitric oxide, in which may lead to endothelial dysfunction, atherosclerosis, hypertension, MI, and HF [17,18]. Elevated sUA levels may also induce a pro-oxidative and pro-inflammatory state which may predispose patients to atherosclerosis and CVD through crystal-dependent and crystal-independent renal injury [17].

In our study, we observed a U-shaped association between sUA levels and all-cause mortality in both men and women after adjusting for confounding factors. A U-shaped association was also revealed between sUA levels and CV mortality in women. To comprehensively examine the impact of sUA on CVD, we analyzed the sUA level as a continuous variable using restricted cubic splines rather than as categorical groups. This approach avoids the challenges associated with categorizing sUA levels into groups and provides a more flexible and nuanced exploration of its relationship with CVD. In prior research, higher all-cause and CV mortality rates were observed in patients with sUA levels lower than 4 mg/dL and higher than 8 mg/dL [4,7,10,11,13]. However, within our study population, only 2.4 % of men and 9.1 % of women had sUA levels less than or equal to 4 mg/dL. Similarly, only 16.2 % of men and 6.3 % of women had sUA levels exceeding 8 mg/dL. The limited number of individuals with extreme (low or high) sUA levels in our study may restrict our ability to assess the relationship across a wide range of sUA levels. Our cubic spline models revealed that sUA levels below 4 mg/dL and above 8 mg/dL were associated with higher all-cause mortality, which is consistent with the findings of previous studies. However, this U-shaped association was not observed for MACE and HF hospitalization.

The findings of the current and previous studies suggest that lower levels of sUA may increase the risk of all-cause mortality [15,19]. Specifically, the URRAH study identified sUA levels of 4.7 mg/dL and 5.6

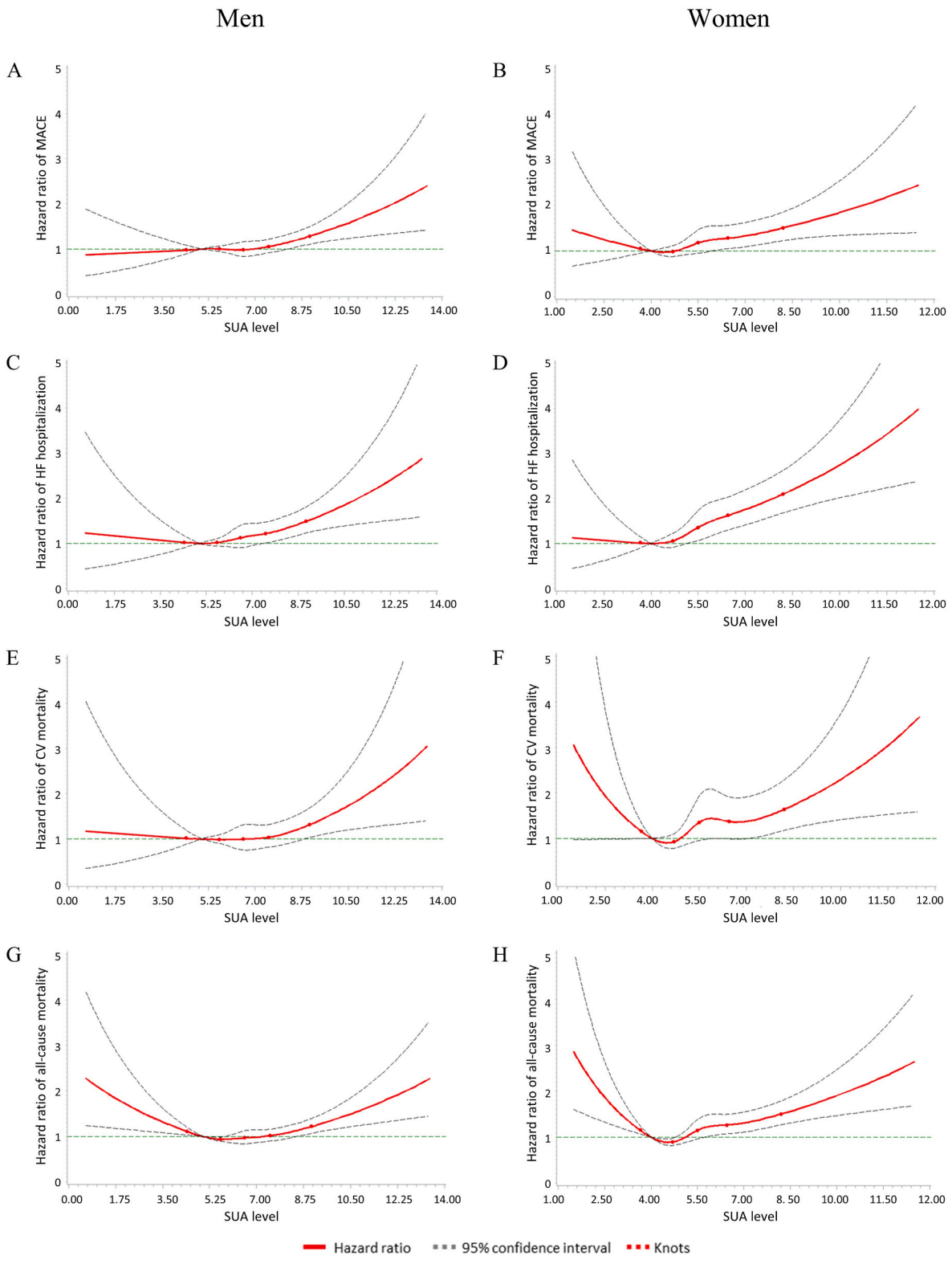

Fig. 2. Restricted cubic splines of hazard ratios for the risk of study outcomes according to continuous serum uric acid levels. These figures present the results of restricted cubic splines of hazard ratios associated with continuous sUA levels and the following outcomes: MACE (A, B), HF hospitalization (C, D), CV mortality (E, F), and all-cause mortality (G, H), stratified by sex. The hazard ratios were adjusted for age, smoking, BMI, LDL-C, HbA1c, eGFR, history of coronary revascularization, comorbidities, and comedications. The knots on the restricted cubic splines represent the 5th, 25th, 50th, 75th, and 95th percentiles, from left to right. Abbreviations: BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HF, heart failure; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events (including myocardial infarction, ischemic stroke, and cardiovascular death); sUA, serum uric acid.

mg/dL as discriminators for total mortality and CV mortality, respectively [20]. While this may seem counterintuitive, considering that UA metabolism generates pro-inflammatory ROS, it is important to acknowledge sUA's role as an antioxidant that protects against oxidative stress-induced organ damage [21]. UA functions as an oxygen radical scavenger, which prevents peroxynitrite-induced protein nitrosylation, lipid and protein peroxidation, and tetrahydrobiopterin inactivation. These actions collectively reduce ROS-induced CV damage [21]. Consequently, these underlying mechanisms could explain the observed non-linear relationship between sUA and all-cause mortality.

Furthermore, we observed a stronger association between sUA and outcomes in women compared to men, as well as more pronounced U-shape associations for mortality. Previous studies have demonstrated a sex-dependent relationship between sUA and CVD risk, with women generally having lower cutoff points for increased risk of CV mortality compared to men [11,22,23]. One study also demonstrated that sUA is an independent risk factor for fatal MI, especially in women [24]. Several factors may contribute to this sex difference. First, women may be more susceptible to vascular damage caused by sUA, including increased arterial stiffness, compared to men [25]. Second, our female patients are slightly older than men, and age could be a crucial factor associated with mortality, which might also account for the observed difference [26]. Additionally, estrogen has been shown to facilitate renal excretion of uric acid in women by inhibiting its reabsorption in proximal tubules [27]. Given that the majority of female participants in our study were postmenopausal, the absence of estrogen protection may partially explain the observed sex differences in the effects of UA. We recommend that future studies stratify women by menopausal status to elucidate its impact on the relationship between UA levels and CV outcomes.

Our study possesses several notable strengths. First, it leveraged a large sample size, allowing us to robustly explore the relationship between long-term stable sUA levels and the risk of CVD and mortality. In contrast to prior studies that often relied on single sUA measurements for each patient to infer long-term risk [4,7,10–12,14], our approach ensured that analysis was based on long-term stable sUA levels. While sUA levels typically exhibit limited variation over the course of a year [13], short-term fluctuations in UA levels can occur due to acute conditions such as acute kidney injury or tumor lysis syndrome. Second, we conducted further analyses by adjusting for LDL-C, HbA1c, and medication history. Although LDL-C and HbA1c are independently associated with an increased risk of CVD outcomes [28,29], many studies have overlooked the potential confounding effect of these variables [4,19,30]. To minimize residual confounding, we adjusted for BMI, LDL-C, HbA1c, and smoking status, in addition to patient demographics, comorbidities, and comedications. Importantly, even after implementing these comprehensive adjustments, our study still found a significant U-shaped association between sUA levels and all-cause mortality. Furthermore, our study utilized the extensive data resources of the electronic health records linked to the national claims database, ensuring the comprehensiveness of information used in our analysis. Additionally, our cohort study benefits from a long follow-up period without loss to follow-up, facilitated by the nationwide claims database and death registry to fully capture the events under investigation.

This study is subject to several limitations. First, elevated blood pressure is widely recognized as one of the strongest risk factors for CVD [31]; however, due to limitations in the available data, our analysis could only account for the diagnosis of hypertension, rather than specific blood pressure levels. Second, it is important to acknowledge that despite our efforts to minimize potential confounding, some degree of residual confounding and unmeasured confounders could still persist in our analysis. Third, our study cohort was composed of patients with a diagnosis of hypertension, diabetes, hyperlipidemia, or CVD during the study period. Consequently, the generalizability of our findings to the broader population may be limited. Lastly, our study did not establish a specific target sUA level for reducing the risk of CVD or mortality. As such, further research is required to corroborate the findings and provide additional evidence to inform strategies for disease management and prevention.

5. Conclusion

Our study revealed that consistently high sUA levels is associated with increased risk of MACE, HF hospitalization, and mortality. In both men and women, a U-shaped association was observed between sUA levels and all-cause mortality. Furthermore, among women, a U-shaped association was noted between sUA levels and CV mortality. Compared to men, sUA appears to exert a more marked influence on CV events and mortality in women, especially at low sUA levels. Special attention to sUA levels, especially in women, is vital for assessing CV risk.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and the supplementary files. Additional details can be provided by the corresponding author upon a reasonable request.

CRediT authorship contribution statement

Hsiu-Ting Chien: Writing – original draft, Investigation. **Yu-Wen Lin:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Li-Jiuan Shen:** Writing – review & editing, Investigation, Conceptualization. **Song-Chou Hsieh:** Writing – review & editing, Investigation, Conceptualization. **Lian-Yu Lin:** Writing – review & editing, Investigation, Conceptualization. **Yi-An Chen:** Writing – review & editing, Methodology, Formal analysis. **Fang-Ju Lin:** Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2024.200302.

References

[1] J. Maiuolo, F. Oppedisano, S. Gratteri, C. Muscoli, V. Mollace, Regulation of uric acid metabolism and excretion, Int. J. Cardiol. 213 (2016) 8–14. https://doi:10.1016/j.ijcard.2015.08.109.

[2] K.R. Tuttle, R.A. Short, R.J. Johnson, Sex differences in uric acid and risk factors for coronary artery disease, Am. J. Cardiol. 87 (12) (2001) 1411–1414. https://doi:10.1016/s0002-9149(01)01566-1.
[3] N.F. Chu, D.J. Wang, S.H. Liou, S.M. Shieh, Relationship between hyperuricemia and other cardiovascular disease risk factors among adult males in Taiwan, Eur. J. Epidemiol. 16 (1) (2000) 13–17. https://doi:10.1023/a:1007654507054.
[4] M.N. Essex, M. Hopps, E.J. Bienen, M. Udall, J. Mardekian, G.T. Makinson, Evaluation of the relationship between serum uric acid levels and cardiovascular events in patients with gout: a retrospective analysis using electronic medical record data, J. Clin. Rheumatol. 23 (3) (2017) 160–166. https://doi:10.1097/rhu.0000000000000496.
[5] O.J. Ekundayo, L.J. Dell'Italia, P.W. Sanders, et al., Association between hyperuricemia and incident heart failure among older adults: a propensity-matched study, Int. J. Cardiol. 142 (3) (2010) 279–287. https://doi:10.1016/j.ijcard.2009.01.010.
[6] S. Coiro, E. Carluccio, P. Biagioli, et al., Elevated serum uric acid concentration at discharge confers additive prognostic value in elderly patients with acute heart failure, Nutr. Metabol. Cardiovasc. Dis. 28 (4) (2018) 361–368. https://doi:10.1016/j.numecd.2017.12.009.
[7] E. Kang, S.S. Hwang, D.K. Kim, et al., Sex-specific relationship of serum uric acid with all-cause mortality in adults with normal kidney function: an observational study, J. Rheumatol. 44 (3) (2017) 380–387. https://doi:10.3899/jrheum.160792.
[8] P.W. De Leeuw, L. Thijs, W.H. Birkenhäger, et al., Prognostic significance of renal function in elderly patients with isolated systolic hypertension: results from the Syst-Eur trial, J. Am. Soc. Nephrol. 13 (9) (2002) 2213–2222. https://doi:10.1097/01.asn.0000027871.86296.92.
[9] C.-F. Kuo, L.-C. See, K.-H. Yu, I.-J. Chou, M.-J. Chiou, S.-F. Luo, Significance of serum uric acid levels on the risk of all-cause and cardiovascular mortality, Rheumatology 52 (1) (2012) 127–134. https://doi:10.1093/rheumatology/kes223.
[10] W.C. Tseng, Y.T. Chen, S.M. Ou, C.J. Shih, D.C. Tarng, U-shaped association between serum uric acid levels with cardiovascular and all-cause mortality in the elderly: the role of malnourishment, J. Am. Heart Assoc. 7 (4) (2018). https://doi:10.1161/jaha.117.007523.
[11] S.K. Cho, Y. Chang, I. Kim, S. Ryu, U-shaped association between serum uric acid level and risk of mortality: a cohort Study, Arthritis Rheumatol. 70 (7) (2018) 1122–1132. https://doi:10.1002/art.40472.
[12] G. Shen, J.Y. Huang, Y.L. Yu, et al., J-shaped association between serum uric acid and acute coronary syndrome in patients with essential hypertension, Postgrad. Med. 96 (1132) (2020) 73–78. https://doi:10.1136/postgradmedj-2019-136650.
[13] C.F. Kuo, L.C. See, K.H. Yu, I.J. Chou, M.J. Chiou, S.F. Luo, Significance of serum uric acid levels on the risk of all-cause and cardiovascular mortality, Rheumatology 52 (1) (2013) 127–134. https://doi:10.1093/rheumatology/kes223.
[14] H.B. Gwag, J.H. Yang, T.K. Park, et al., Uric acid level has a U-shaped association with clinical outcomes in patients with vasospastic angina, J. Kor. Med. Sci. 32 (8) (2017) 1275–1280. https://doi:10.3346/jkms.2017.32.8.1275.
[15] Y. Zheng, J. Ou, D. Huang, et al., The U-shaped relationship between serum uric acid and long-term all-cause mortality in coronary artery disease patients: a cohort study of 33,034 patients, Front Cardiovasc Med 9 (2022) 858889. https://doi:10.3389/fcvm.2022.858889.
[16] M.G. Battelli, L. Polito, M. Bortolotti, A. Bolognesi, Xanthine oxidoreductase-derived reactive species: physiological and pathological effects, Oxid. Med. Cell. Longev. 2016 (2016) 3527579. https://doi:10.1155/2016/3527579.
[17] Sharaf El Din Uaa, M.M. Salem, D.O. Abdulazim, Uric acid in the pathogenesis of metabolic, renal, and cardiovascular diseases: a review, J. Adv. Res. 8 (5) (2017) 537–548. https://doi:10.1016/j.jare.2016.11.004.
[18] Y. Higashi, K. Noma, M. Yoshizumi, Y. Kihara, Endothelial function and oxidative stress in cardiovascular diseases, Circ. J. 73 (3) (2009) 411–418. https://doi:10.1253/circj.cj-08-1102.
[19] Y. Cang, S. Xu, J. Zhang, et al., Serum uric acid revealed a U-shaped relationship with all-cause mortality and cardiovascular mortality in high atherosclerosis risk patients: the ASSURE study, Front Cardiovasc Med 8 (2021) 641513. https://doi:10.3389/fcvm.2021.641513.
[20] A. Virdis, S. Masi, E. Casiglia, et al., Identification of the uric acid thresholds predicting an increased total and cardiovascular mortality over 20 years, Hypertension 75 (2) (Feb 2020) 302–308. https://doi:10.1161/hypertensionaha.119.13643.
[21]] D.H. Kang, S.K. Ha, Uric Acid Puzzle: Dual Role as Anti-oxidantand Pro-oxidant, Electrolyte Blood Press, 2014, pp. 1–6, 12(1), https://doi:10.5049/EBP.2014.12.1.1.
[22] W. Zhang, H. Iso, Y. Murakami, et al., Serum uric acid and mortality form cardiovascular disease: EPOCH-Japan study, J. Atherosclerosis Thromb. 23 (6) (Jun 1 2016) 692–703. https://doi:10.5551/jat.31591.
[23] S. Zhang, L. Liu, Y.Q. Huang, K. Lo, Y.Q. Feng, A U-shaped association between serum uric acid with all-cause mortality in normal-weight population, Postgrad. Med. (2020) 1–7. https://doi:10.1080/00325481.2020.1730610.
[24] E. Casiglia, V. Tikhonoff, A. Virdis, et al., Serum uric acid and fatal myocardial infarction: detection of prognostic cut-off values: the URRAH (Uric Acid Right for Heart Health) study, J. Hypertens. 38 (3) (2020) 412–419. https://doi:10.1097/hjh.0000000000002287.
[25] J.A. Cipolli, M.C. Ferreira-Sae, R.P. Martins, et al., Relationship between serum uric acid and internal carotid resistive index in hypertensive women: a cross-sectional study, BMC Cardiovasc. Disord. 12 (2012) 52. https://doi:10.1186/1471-2261-12-52.
[26] E. Martelli, M. Zamboni, G. Sotgiu, et al., Sex-related differences and factors associated with peri-procedural and 1 year mortality in chronic limb-threatening ischemia patients from the CLIMATE Italian Registry, J. Personalized Med. 13 (2) (2023). https://doi:10.3390/jpm13020316.
[27] F.M. Anton, J. Garcia Puig, T. Ramos, P. Gonzalez, J. Ordas, Sex differences in uric acid metabolism in adults: evidence for a lack of influence of estradiol-17 beta (E2) on the renal handling of urate, Metabolism 35 (4) (1986) 343–348. https://doi:10.1016/0026-0495(86)90152-6.
[28] M.G. Silverman, B.A. Ference, K. Im, et al., Association between lowering LDL-C and cardiovascular risk Reduction among different therapeutic interventions: a systematic review and meta-analysis, JAMA 316 (12) (2016) 1289–1297. https://doi:10.1001/jama.2016.13985.
[29] I. Cavero-Redondo, B. Peleteiro, C. Álvarez-Bueno, F. Rodriguez-Artalejo, V. Martínez-Vizcaíno, Glycated haemoglobin A1c as a risk factor of cardiovascular outcomes and all-cause mortality in diabetic and non-diabetic populations: a systematic review and meta-analysis, BMJ Open 7 (7) (2017) e015949. https://doi:10.1136/bmjopen-2017-015949.
[30] S. Zhang, L. Liu, Y.Q. Huang, K. Lo, Y.Q. Feng, A U-shaped association between serum uric acid with all-cause mortality in normal-weight population, Postgrad. Med. 132 (4) (2020) 391–397. https://doi:10.1080/00325481.2020.1730610.
[31] F.D. Fuchs, P.K. Whelton, High blood pressure and cardiovascular disease, Hypertension 75 (2) (2020) 285–292. https://doi:10.1161/hypertensionaha.119.14240.