

Hyperuricemia is associated with all-cause mortality among males and females: Findings from a study on Japanese community-dwelling individuals

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ABSTRACT

Background: Serum uric acid (SUA) is a key determinant of cardiovascular diseases (CVDs). Studies have also shown that SUA independently impacts age-related health outcomes, although their findings differ between males and females. Furthermore, predictive data on all-cause mortality remain limited, particularly for the Japanese population. Thus, this study examined the association between SUA and survival prognosis among males and females based on a follow-up period of 7 or 19 years.

Methods: The study was based on 1,573 male (63 ± 14 years) and 1,980 female (65 ± 12 years) participants who participated in a Nomura Cohort Study in 2002 (Cohort 1) and 2014 (Cohort 2), and continued throughout the follow-up period. A basic resident register was referenced to derive the adjusted relative risk estimates for all-cause mortality. Finally, a Cox proportional hazards model analysis was conducted and was adjusted for possible confounders to estimate hazard ratios (HRs). 95% confidence intervals (CIs) were computed separately for male and female participants.

Results: Of the total 3,553 participants, 905 (25.5%) were deceased. Of these, 473 were male (30.1% of all males) and 432 were female (21.8% of all females). Hyperuricemia was defined in males with SUA levels of 8.5 mg/dL or higher, and in females with SUA levels of 7.5 mg/dL or higher, and was associated with a significantly increased HR for all-cause mortality (males: 1.67; 95% CI: 1.06–2.63; females: 2.17; 95% CI: 1.20–3.94). The data were further stratified based on age (< 65 years or ≥ 65 years), body mass index (BMI) (< 25.0 kg/m² or ≥ 25.0 kg/m²), History of cardiovascular disease, estimated glomerular filtration rate (< 60 mL/min/1.73 m² or ≥ 60 mL/min/1.73 m²), and presence of SUA-lowering medication. All stratified groups demonstrated a similar trend. The hyperuricemia group in particular reported a significant increase in HR. On the other hand, a U-shaped increase in HR was observed in those with BMI greater than 25 kg/m² and SUA-lowering medication, but interaction effect was not significant.

Conclusions: Hyperuricemia is a key risk indicator for all-cause mortality in male and female community-dwelling individuals in Japan.

1. Introduction

Uric acid (UA) is the end metabolite of endogenous purine catabolism in humans and plays a critical role in free radical damage [1]. The enzymes involved in UA production significantly contribute to oxidative stress [1]. Hyperuricemia is mainly caused by increased production or decreased excretion of UA, or both. Numerous experimental and epidemiological studies have shown that increased serum uric acid

(SUA) in humans is associated with systemic inflammation [2], endothelial dysfunction [3], hypertension [4], and diabetes [5]. Moreover, several researchers highlighted hyperuricemia as a key factor associated with cardiovascular disease (CVD) [6–13], renal dysfunction (e.g., acute kidney injury [14]), and chronic kidney disease [15].

SUA levels are strongly correlated with age, sex, renal function, obesity, and metabolic abnormalities. The causal role of SUA in all-cause mortality remains controversial. Studies reported a relationship

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between hyperuricemia and all-cause mortality. However, these results have been inconsistent, especially when considering the results across both sexes. For example, studies have reported that the relationship between SUA and all-cause mortality is observed only in males [7,8,16], females [6,11,17], and/or both [12,18,19]. Some studies indicated that the association between SUA levels and mortality is J-shaped for males [12] and U-shaped for females [20–22], rather than being a linear relationship. A long-term cohort study with an adequate number of events and various sex-specific correction factors is needed to address such inconsistencies.

Thus, this study aimed to investigate whether hyperuricemia is related to all-cause mortality based on a 7- or 19-year follow-up on male and female community-dwelling individuals in Japan.

2. Materials and methods

2.1. Study design and participants

This prospective cohort analysis is part of the Nomura Study conducted in 2002 (first cohort) and 2014 (second cohort). Participants were primarily rural residents of Ehime Prefecture who underwent a community-based annual health checkup. A total of 3,164 participants were in the first cohort and 1,832 participants were in the second cohort. Participants' age ranged between 22 and 95 years. In the first cohort, 2,775 patients were followed, excluding 389 with missing data, of which 268 were lost to follow-up and 2,507 were ultimately included in the study. In the second cohort, 1074 cases were followed excluding 758 cases with missing data and duplicates, of which 28 were lost to follow-up during the period, and 1,046 cases were finally included in the study.

This study used data on participants' habits, medical history, current condition, and medication usage from self-administered questionnaires. A flowchart for enrollment and exclusion criteria is available in a previous study [23]. Follow-up surveys were administered at 19-year intervals for the first cohort and at 7-year intervals for the second cohort. Survival status was ascertained from the Japanese Basic Resident Register. This study analyzed assessment data from both cohorts (N = 3, 553). The Institutional Review Board (RIB) of Ehime University Hospital (1903018) reviewed and approved this study. All participants provided written informed consent.

2.2. Evaluation of risk factors

Weight and height were measured as baseline anthropometric indices. Body mass index (BMI) was calculated by dividing weight (kg) by height (m²). Smoking status (in pack-years) was estimated by multiplying the number of years as a smoker by the average number of packs per day. Participants were categorized as non-smokers, ex-smokers, light smokers (< 20 pack-years), and heavy smokers (≥ 20 pack-years). Daily alcohol intake was estimated in units equivalent to one bottle of sake (22.9 g ethanol). Participants were categorized as non-drinkers, occasional drinkers (< 1 unit/day), light daily drinkers (1–2 units/day), and heavy daily drinkers (2–3 units/day). No participant consumed more than 3 units/day. An automated sphygmomanometer was used to measure systolic blood pressure (SBP) and diastolic blood pressure (DBP). Participants were asked to rest for at least 5 min in a seated position before an appropriately sized cuff was placed on their right upper arm. All participants were asked to fast overnight prior to measuring their triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), SUA, blood glucose (BG), alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was modified with a Japanese coefficient as follows to estimate the glomerular filtration ratio (eGFR) in males: Cr ≤ 0.9 mg/dL, $141 \times (\text{Cr}/0.9)^{-0.411} \times 0.993^{\text{age}} \times 0.813$; Cr > 0.9 mg/dL, $141 \times (\text{Cr}/0.9)^{-1.209} \times 0.993^{\text{age}} \times 0.813$; and in females: Cr ≤ 0.7 mg/dL, $144 \times (\text{Cr}/0.7)^{-0.329} \times 0.993^{\text{age}} \times 0.813$; Cr > 0.7 mg/dL, $144 \times$

$(\text{Cr}/0.7)^{-1.209} \times 0.993^{\text{age}} \times 0.813$ [24].

Participants who reported a SBP of 140 mmHg or higher, a DBP of 90 mmHg or higher, or were on antihypertensive medication were considered to have hypertension. In addition, participants were classified as having hypertriglyceridemia if their TG levels were 150 mg/dL or higher; as having low HDL cholesterolemia if their HDL-C levels were 39 mg/dL or lower; and as having high LDL-cholesterolemia if their LDL-C levels were 140 mg/dL or higher, or if they were taking antidyslipidemic medication. Those with BG of 126 mg/dL or higher and those on anti-diabetic medication were considered diabetic. Males with SUA 8.5 mg/dL or higher and females with SUA 7.5 mg/dL or higher were classified as hyperuricemic [22,25–27]. Those with AST of 40 IU/L or higher or ALT of 45 IU/L or higher were defined as liver dysfunction. eGFR less than 60 mL/min/1.73 m² or was considered an indicator of CKD. Ischemic heart disease, ischemic stroke, and peripheral vascular disease were all classified as types of CVD.

2.3. Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics (version 28.0; SPSS Inc., Chicago, IL, United States). Continuous variables of a normal distribution were expressed as mean ± standard deviation (SD), and median and interquartile range were reported for variables showing a non-normal distribution (e.g., TG, BG, AST, and ALT). In all analyses, log-transformed values were used for non-normally distributed parameters. Categorical variables were compared by conducting a chi-square analysis, and continuous variables were compared by performing a student's *t*-test on normally distributed variables. Cox proportional hazards regression was used to examine factors related to all-cause mortality and to model relationships between SUA and all-cause mortality while adjusting for baseline characteristics and using age as the time scale. Adjustments were performed for possible confounding factors: age, BMI, smoking habits, drinking habits, history of CVD, hypertension, hypertriglyceridemia, low HDL-cholesterolemia, high LDL-cholesterolemia, diabetes, liver dysfunction, and CKD. The reference group comprised those with the lowest hazard ratio (HR) for mortality. The observed association between baseline SUA and all-cause mortality was confirmed by performing a sensitivity analysis in groups stratified by age (< 65 years and ≥ 65 years), BMI (< 25 kg/m² and ≥ 25 kg/m²), CVD (presence and absence), eGFR (< 60 mL/min/1.73 m² and ≥ 60 mL/min/1.73 m²), SUA-lowering medication (presence and absence), and time to death. The effect variable and all significant confounding variables other than the effect variable were adjusted for in interaction tests. All *p*-values were two-sided, and *p* < 0.05 was considered significant.

3. Results

3.1. Baseline characteristics of participants by sex and baseline SUA categories

Of the 3,553 subjects, 1,573 (44.3%) were male. The mean age of the male participants was 63 ± 14 years and the mean age of the female participants was 65 ± 12 years. Table 1a (male) and Table 1b (female) report the baseline characteristics of the participants by their SUA categories. The results indicate that antihypertensive and SUA-lowering medication; higher values of BMI, TG, and SUA; and lower eGFR were associated with higher SUA levels in both males and females. Male subjects with higher SUA levels were younger and had a higher prevalence of CKD, while female subjects were older and had a higher prevalence of CKD.

3.2. Kaplan-Meier survival curves for relationships between baseline SUA categories and all-cause mortality by sex

The median (interquartile range) follow-up period was 6,391

Table 1a

Baseline characteristics of male participants by baseline serum uric acid categories.

Men Characteristics N = 1,573	SUA < 3.5 mg/dL N = 46	3.5 ≤ SUA < 8.5 mg/ dL N = 1,475	SUA ≥ 8.5 mg/dL N = 52	p- value *
Age (years)	68 ± 11	63 ± 13	60 ± 16	0.008
Obesity, n (%)	5 (10.9)	404(27.4)	19 (36.5)	0.014
Body mass index (kg/m ²)	22.4 ± 2.3	23.4 ± 3.0	24.7 ± 3.6	0.001
Smoking habits (non = 1, ex = 2, light = 3, heavy = 4) (%)	41.3/ 15.2	35.7/48.0/ 4.9/11.5	30.8/ 7.7	0.491
Alcohol habits (non = 1, occasional = 2, light = 3, heavy = 4) (%)	34.8/ 21.7/ 23.9/19.6	22.7/31.6/ 26.3/19.4	15.4/ 21.2/ 28.8/34.6	0.038
History of cardiovascular disease, n (%)	4 (8.7)	145 (9.8)	7 (13.5)	0.664
Hypertension, n (%)	26 (56.5)	851 (57.7)	39 (75.0)	0.044
Systolic blood pressure (mmHg)	137 ± 20	138 ± 20	142 ± 19	0.227
Diastolic blood pressure (mmHg)	80 ± 11	82 ± 11	87 ± 12	0.003
Antihypertensive medication, n (%)	11 (23.9)	462 (31.3)	24 (46.2)	0.041
Hypertriglyceridemia, n (%)	7 (15.2)	317 (21.5)	19 (36.5)	0.019
Triglyceride (mg/dL)	79 (63–105)	96 (72–138)	117 (83–186)	0.001
Low HDL-cholesterolemia, n (%)	3 (6.5)	122 (8.3)	9 (17.3)	0.064
HDL cholesterol (mg/dL)	63 ± 17	60 ± 16	57 ± 16	0.133
High LDL-cholesterolemia, n (%)	10 (21.7)	341 (23.1)	13 (25.0)	0.927
LDL cholesterol (mg/dL)	114 ± 31	110 ± 31	110 ± 36	0.730
Lipid-lowering medication, n (%)	0 (0)	104 (7.1)	4 (7.7)	0.172
Diabetes, n (%)	11 (23.9)	228 (15.5)	8 (15.4)	0.299
Blood glucose (mg/dL)	99 (91–121)	103 (93–117)	103 (94–114)	0.195
Antidiabetic medication, n (%)	8 (17.4)	176 (11.9)	6 (11.5)	0.531
Liver dysfunction, n (%)	4 (8.7)	155 (10.5)	11 (21.2)	0.047
Alanine aminotransferase (IU/L)	19 (14–24)	20 (15–27)	23 (15–38)	0.016
Aspartate aminotransferase (IU/L)	24 (19–30)	24 (20–30)	26 (21–36)	0.206
Chronic kidney disease, n (%)	1 (2.2)	170 (11.5)	16 (30.8)	< 0.001
eGFR (mL/min/1.73 m ²)	83.9 ± 13.9	77.8 ± 16.2	67.5 ± 19.1	< 0.001
Serum uric acid (mg/dL)	2.7 ± 0.8	5.9 ± 1.1	9.2 ± 0.8	< 0.001
SUA-lowering medication, n (%)	2 (4.3)	110 (7.5)	26 (50.0)	< 0.001

Data presented as mean ± standard deviation. Data for triglycerides, blood glucose, alanine aminotransferase, and aspartate aminotransferase were skewed and are thus presented as median (interquartile range) values and were log-transformed for analysis. *P-values are from the Student's *t*-test for continuous variables or from the χ^2 -test for categorical variables. Significant values ($p < 0.05$) are presented in bold.

(2,694–6,991) days. The follow-up revealed 905 deaths (25.5%), of which 473 were male (30.1% of all males) and 432 were female (21.8% of all females). Kaplan-Meier survival curves were created for survival days and cumulative survival rates to identify patterns in the relationships between the SUA categories and all-cause mortality by sex (Fig. 1).

The cumulative survival rate was significantly lower in female subject with hyperuricemia (females: ≥ 7.5 mg/dL) compared with the reference group (SUA ≥ 3.0 and SUA < 7.5 mg/dL) (log-rank $p < 0.001$). In male subject, on the other hand, hypouricemia group (SUA ≤ 3.5 mg/dL) showed lower cumulative survival rate compared to reference group (SUA ≥ 3.5 and SUA < 8.5 mg/dL) (log-rank $P = 0.034$).

Table 1b

Baseline characteristics of female participants by baseline serum uric acid categories.

Women Characteristics N = 1,980	SUA < 3.0 mg/dL N = 105	3.0 ≤ SUA < 7.5 mg/ dL N = 1857	SUA ≥ 7.5 mg/dL N = 18	p- value *
Age (years)	64 ± 12	64 ± 12	74 ± 6	0.002
Obesity, n (%)	13 (12.4)	508 (27.4)	10 (55.6)	< 0.001
Body mass index (kg/m ²)	21.4 ± 2.9	23.2 ± 3.3	24.7 ± 3.8	< 0.001
Smoking habits (non = 1, ex = 2, light = 3, heavy = 4) (%)	93.3/5.7/ 1.0/0.0	90.2/7.9/ 1.3/0.6	72.2/ 27.8/0.0/ 0.0	0.075
Alcohol habits (non = 1, occasional = 2, light = 3, heavy = 4) (%)	77.1/ 21.9/1.0/ 0.0	74.3/21.4/ 3.9/0.4	50.0/ 44.4/5.6/ 0.0	0.181
History of cardiovascular disease, n (%)	4 (3.8)	121 (6.5)	2 (11.1)	0.391
Hypertension, n (%)	51 (48.6)	1,036 (55.8)	14 (77.8)	0.057
Systolic blood pressure (mmHg)	135 ± 23	137 ± 22	144 ± 23	0.232
Diastolic blood pressure (mmHg)	77 ± 12	79 ± 11	81 ± 14	0.178
Antihypertensive medication, n (%)	19 (18.1)	585 (31.5)	10 (55.6)	0.001
Hypertriglyceridemia, n (%)	10 (9.5)	288 (15.5)	3 (16.7)	0.248
Triglyceride (mg/dL)	82 (57–115)	90 (68–126)	107 (91–138)	0.006
Low HDL-cholesterolemia, n (%)	2 (1.9)	59 (3.2)	0	0.572
HDL cholesterol (mg/dL)	66 ± 14	65 ± 16	57 ± 12	0.072
High LDL-cholesterolemia, n (%)	24 (22.9)	727 (39.1)	8 (44.4)	0.003
LDL cholesterol (mg/dL)	114 ± 29	125 ± 29	133 ± 27	< 0.001
Lipid-lowering medication, n (%)	10 (9.5)	227 (12.2)	2 (11.1)	0.705
Diabetes, n (%)	9 (8.6)	193 (10.4)	3 (16.7)	0.567
Blood glucose (mg/dL)	97 (88–115)	98 (90–114)	106 (94–126)	0.399
Antidiabetic medication, n (%)	7 (6.7)	117 (6.3)	2 (11.1)	0.701
Liver dysfunction, n (%)	3 (2.9)	81 (4.4)	1 (5.6)	0.734
Alanine aminotransferase (IU/L)	14 (11–19)	16 (13–20)	14 (13–17)	0.037
Aspartate aminotransferase (IU/L)	21 (18–26)	21 (19–26)	21 (18–23)	0.482
Chronic kidney disease, n (%)	2 (1.9)	156 (8.4)	12 (66.7)	< 0.001
eGFR (mL/min/1.73 m ²)	85.4 ± 16.9	78.1 ± 15.6	51.6 ± 15.6	< 0.001
Serum uric acid (mg/dL)	2.5 ± 0.4	4.6 ± 1.0	8.2 ± 0.8	< 0.001
SUA-lowering medication, n (%)	0	14 (0.8)	2 (11.1)	< 0.001

Data presented as mean ± standard deviation. Data for triglycerides, blood glucose, alanine aminotransferase, and aspartate aminotransferase were skewed and are thus presented as median (interquartile range) values and were log-transformed for analysis. *P-values are from the Student's *t*-test for continuous variables or from the χ^2 -test for categorical variables. Significant values ($p < 0.05$) are presented in bold.

3.3. Hazard ratios for all-cause mortality per 1.0 mg/dL increase in baseline SUA levels by sex

Table 2 reports the relationship between a 1.0 mg/dL increase in baseline SUA levels and all-cause mortality. As per the unadjusted and multivariable-adjusted model, for each 1.0 mg/dL increase in SUA level, the table shows the HR for all-cause mortality in both males with baseline SUA of ≥ 6.0 mg/dL (HR: 1.25; 95% CI: 1.07–1.47) and females with baseline SUA of ≥ 5.0 mg/dL (HR: 1.27; 95% CI: 1.03–1.58).

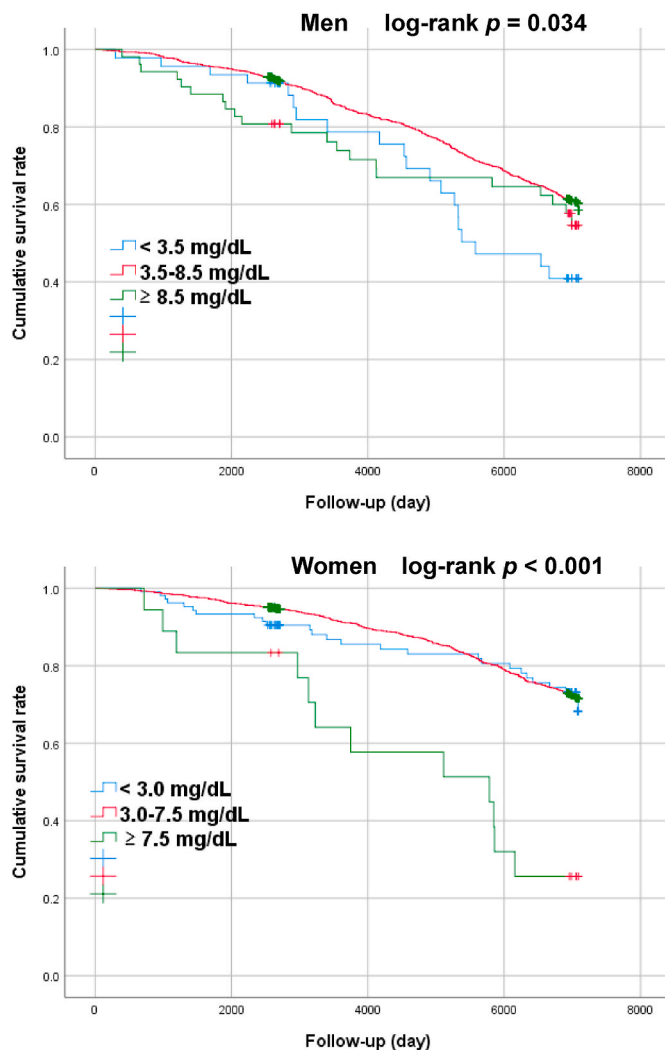


Fig. 1. Analysis on association between SUA categories and all-cause mortality by sex during the follow-up period using a survival function. P -values were obtained through a log-rank test of equality across various strata.

3.4. Relationship between baseline SUA categories and all-cause mortality by sex

Table 3 shows the results for the unadjusted model. The hyperuricemia group for female and the hypouricemia group for male subjects reported a higher HR for all-cause mortality when compared with the reference group. In the multivariate model, however, the hyperuricemia group for both male and female subjects showed a higher HR for all-cause mortality than reference group. The results also show that adjusted HR for all-cause mortality significantly increased in male subjects reporting a SUA ≥ 8.5 mg/dL (HR: 1.67; 95% CI: 1.06–2.63) and in female subjects reporting a SUA ≥ 7.5 mg/dL (HR: 2.17; 95% CI: 1.20–3.94).

3.5. Relationship between baseline SUA categories and all-cause mortality by sub-analysis

Finally, Table 4 reports the results for participants stratified by age (< 65 years and ≥ 65 years), BMI (< 25 and ≥ 25 kg/m²), History of CVD, CKD (eGFR < 60 mL/min/1.73 m² and eGFR ≥ 60 mL/min/1.73 m²), SUA-lowering medication (presence and absence), and time to death. The findings confirmed a significant association between hyperuricemia and all-cause mortality in the group that survived for more

Table 2

Hazard ratios for all-cause mortality per 1.0 mg/dL increase in baseline serum uric acid levels by sex.

Men	SUA < 6.0 mg/dL N = 823	p -value	SUA ≥ 6.0 mg/dL N = 750	p -value
Characteristics N = 1,573				
Unadjusted HR (95% CI)	0.90 (0.79–1.02)	0.108	1.28 (1.10–1.49)	0.002
Age-adjusted HR (95% CI)	1.07 (0.93–1.23)	0.379	1.27 (1.09–1.48)	0.002
Multivariable-adjusted HR * (95% CI)	1.00 (0.87–1.16)	0.960	1.25 (1.07–1.47)	0.007
Women	SUA < 5.0 mg/dL N = 1,353	p -value	SUA ≥ 5.0 mg/dL N = 627	p -value
Characteristics N = 1,980				
Unadjusted HR (95% CI)	1.06 (0.89–1.27)	0.509	1.53 (1.27–1.85)	<
Age-adjusted HR (95% CI)	1.04 (0.88–1.24)	0.636	1.23 (1.01–1.50)	0.040
Multivariable-adjusted HR * (95% CI)	1.03 (0.86–1.24)	0.769	1.27 (1.03–1.58)	0.028

HR, hazard ratio; CI, confidence interval. * Multivariable-adjusted for age, obesity, smoking habits, drinking habits, history of cardiovascular disease, hypertension, hypertriglyceridemia, low HDL-cholesterolemia, high LDL-cholesterolemia, diabetes, liver dysfunction, and chronic kidney disease.

than three years. This association was present, regardless of the presence of CKD or SUA-lowering medication. The findings also showed the association between hypouricemia with SUA-lowering medication and all-cause mortality. There was no interaction between hypo-/hyper-uricemia and these factors.

4. Discussion

This study presented a long-term prospective cohort study on the relationship between baseline SUA and all-cause mortality risk among a population-based sample. Drawing on findings from the median 17.5-year follow-up, this cohort study mainly highlighted that a significant and independent predictor of all-cause mortality is baseline hyperuricemia (males: SUA ≥ 8.5 mg/dL; females: SUA ≥ 7.5 mg/dL) after adjusting for confounders in community-dwelling individuals. The sensitivity analysis showed a similar trend, although there was a U-shaped relationship between baseline SUA levels and all-cause mortality in the group comprising subjects with SUA-lowering medication who had been determined to be in need of treatment.

To the best of the authors' knowledge, few studies have reported SUA levels associated with optimal patient survival. This study is the first to show a critical association between increased SUA levels and reduced survival and the first to establish a significant reduction in survival associated with values above a defined threshold range [17,27]. However, it remains yet to be proven if SUA is an independent risk factor for mortality and whether there exists a specific threshold associated with increased risk.

In Japan, hyperuricemia is generally defined as SUA > 7.0 mg/dL, irrespective of sex [28]. This study showed that baseline SUA levels of ≥ 8.5 mg/dL for males and ≥ 7.5 mg/dL for females were associated with increased mortality risks, only after adjustment for confounding risk factors. Viridis et al. [29] recently reported a linear association between SUA and mortality for a sample of 22,714 Italian subjects. The thresholds were 321 μ mol/L (5.4 mg/dL) for males and 279 μ mol/L (4.7 mg/dL) for females, and these values were significantly lower than those reported in this study. Further to this, a large-scale cohort study comprising 500,511 Japanese subjects (40–74 years) noted a significant increase in HR for all-cause mortality in males with SUA levels ≥ 7.0 mg/dL and in females with SUA levels ≥ 5.0 mg/dL [27]. By contrast, reports have shown differences in the relationship between SUA and all-cause mortality across both sexes, with some indicating a

Table 3
Hazard ratios of baseline serum uric acid categories for all-cause mortality by sex.

Men Characteristics N = 1,573	SUA < 3.5 mg/dL N = 46	p-value	3.5 ≤ SUA < 8.5 mg/dL N = 1,475	SUA ≥ 8.5 mg/dL N = 52	p-value	p for trend
Unadjusted HR (95% CI)	1.70 (1.09–2.67)	0.020	Reference	1.31 (0.85–2.04)	0.222	0.036
Age-adjusted HR (95% CI)	1.17 (0.75–1.84)	0.491	Reference	1.82 (1.18–2.83)	0.007	0.023
Multivariable HR * (95% CI)	1.22 (0.78–1.93)	0.388	Reference	1.67 (1.06–2.63)	0.026	0.061
Women Characteristics N = 1,980	SUA < 3.0 mg/dL N = 105	p-value	3.0 ≤ SUA < 7.5 mg/dL N = 1,857	SUA ≥ 7.5 mg/dL N = 18	p-value	p for trend
Unadjusted HR (95% CI)	1.07 (0.72–1.61)	0.739	Reference	4.24 (2.39–7.53)	< 0.001	< 0.001
Age-adjusted HR (95% CI)	1.03 (0.68–1.54)	0.901	Reference	2.27 (1.28–4.04)	0.005	0.020
Multivariable HR * (95% CI)	1.00 (0.66–1.51)	0.998	Reference	2.17 (1.20–3.94)	0.010	0.038
Total Men Women Characteristics N = 3,553	SUA < 3.5 mg/dL SUA < 3.0 mg/dL N = 151	p-value	3.5 ≤ SUA < 8.5 mg/dL 3.0 ≤ SUA < 7.5 mg/dL N = 3,332	SUA ≥ 8.5 mg/dL SUA ≥ 7.5 mg/dL N = 70	p-value	p for trend
Unadjusted HR (95% CI)	1.19 (0.88–1.61)	0.249	Reference	2.03 (1.43–2.87)	< 0.001	< 0.001
Age-adjusted HR (95% CI)	1.03 (0.76–1.39)	0.859	Reference	2.19 (1.54–3.10)	< 0.001	< 0.001
Multivariable HR ** (95% CI)	1.11 (0.82–1.50)	0.515	Reference	1.87 (1.31–2.67)	0.001	0.002

HR, hazard ratio; CI, confidence interval. * All-adjusted for age, obesity, smoking habits, drinking habits, history of cardiovascular disease, hypertension, hypertriglyceridemia, low HDL-cholesterolemia, hyper LDL-cholesterolemia, diabetes, liver dysfunction, and chronic kidney disease. ** All-adjusted for sex, age, body mass index, smoking habits, drinking habits, history of cardiovascular disease, hypertension, hypertriglyceridemia, low HDL-cholesterolemia, high LDL-cholesterolemia, diabetes, liver dysfunction, and chronic kidney disease. Significant values ($p < 0.05$) are presented in bold.

Table 4
Hazard ratios of baseline serum uric acid for all-cause mortality by sub-analysis.

Total Men Women Characteristics N = 3,553	SUA < 3.5 mg/dL SUA < 3.0 mg/dL N = 151	p-value	3.5 ≤ SUA < 8.5 mg/dL 3.0 ≤ SUA < 7.5 mg/dL N = 3,332	SUA ≥ 8.5 mg/dL SUA ≥ 7.5 mg/dL N = 70	p-value	p for interaction
	HR (95% CI)			HR (95% CI)		
Age						
< 65 years (N = 1,522)	1.51 (0.69–3.31)	0.299	Reference	2.46 (1.01–6.00)	0.048	0.559
≥ 65 years (N = 2,031)	1.07 (0.77–1.48)	0.699	Reference	1.81 (1.22–2.69)	0.003	
Body mass index						
< 25.0 kg/m ² (N = 2,594)	1.00 (0.72–1.40)	0.983	Reference	2.21 (1.41–3.46)	0.001	0.099
≥ 25.0 kg/m ² (N = 959)	2.19 (1.01–4.73)	0.047	Reference	1.48 (0.79–2.79)	0.223	
History of cardiovascular disease						
No (N = 3270)	1.10 (0.79–1.53)	0.566	Reference	2.07 (1.38–3.11)	< 0.001	0.278
Yes (N = 283)	1.31 (0.56–3.06)	0.535	Reference	1.09 (0.45–2.60)	0.855	
CKD (eGFR)						
< 60 mL/min/1.73 m ² (N = 357)	2.41 (0.72–8.00)	0.152	Reference	2.09 (1.16–3.77)	0.014	0.229
≥ 60 mL/min/1.73 m ² (N = 3,196)	1.06 (0.77–1.45)	0.725	Reference	1.81 (1.14–2.89)	0.012	
Serum uric acid-lowering medication						
No (N = 3,399)	1.08 (0.79–1.47)	0.628	Reference	1.86 (1.17–2.95)	0.009	0.511
Yes (N = 154)	7.61 (1.12–51.6)	0.038	Reference	2.18 (1.13–4.22)	0.021	
Time to death						
< 1,095 days (N = 73)	–	–	–	–	–	–
≥ 1,095 days (N = 3,480)	1.04 (0.75–1.44)	0.810	Reference	1.73 (1.18–2.55)	0.005	

HR, hazard ratio; CI, confidence interval. Multivariable-adjusted for sex, age, obesity, smoking habits, drinking habits, history of cardiovascular disease, hypertension, hypertriglyceridemia, low HDL-cholesterolemia, high LDL-cholesterolemia, diabetes, liver dysfunction, and chronic kidney disease. Significant values ($p < 0.05$) are presented in bold.

relationship only in men [7,8,16] or women [11,17,30]. The present study defined hyperuricemia as SUA ≥ 8.5 mg/dL for males and SUA ≥ 7.5 mg/dL for females. The results revealed that hyperuricemia was associated with an increased risk in all-cause mortality in both Japanese males and females. Furthermore, for each 1 mg/dL increase in SUA level, a significant increase in the HR for all-cause mortality in males with baseline SUA ≥ 6.0 mg/dL and in females with baseline SUA ≥ 5.0 mg/dL was reported. The differences in SUA thresholds for all-cause mortality reported in this study may reflect inherent differences in the populations of interest and the different degrees of adjustment for confounding factors [22].

Previous studies on the relationship between SUA and all-cause mortality have yielded conflicting results, sparking debate over whether low or high levels of SUA have a negative health impact [20–22, 31]. A retrospective cohort study performed on 26,525 Irish participants showed that the trend for the association between SUA and mortality

differed between men and women. That is, mortality risk significantly increased in men at extreme thresholds of SUA < 304 μmol/L (3.1 mg/dL) and SUA > 454 μmol/L (7.6 mg/dL), and this relationship was U-shaped. On the other hand, mortality risk increased for women with SUA > 409 μmol/L (6.8 mg/dL), and this association was J-shaped [22]. Hu et al. [31] used data from the National Health and Nutrition Examination Survey involving 9,118 adults in the United States and demonstrated a U-shaped association for both sexes. The inflection point for SUA was 6 mg/dL in males and 4 mg/dL in females. Cho et al.'s [19] study was based on 375,163 males and females in South Korea. Compared with the sex-specific reference category, they reported that the multivariable-adjusted HRs for all-cause mortality in the lowest SUA categories (< 3.5 mg/dl for males and < 2.5 mg/dl for females) were 1.58 (95% CI: 1.18–2.10) and 1.80 (95% CI: 1.10–2.93) for males and females, respectively. Corresponding HRs in the highest SUA categories (males: ≥ 9.5 mg/dL; females: ≥ 8.5 mg/dL) were 2.39 (95% CI:

1.57–3.66) and 3.77 (95% CI: 1.17–12.17) for males and females, respectively.

The mechanisms behind an increased all-cause mortality in individuals with hyperuricemia are yet to be fully understood. This may be explained by the relative contribution of the antioxidant effects of UA and its role in endothelial dysfunction. To this effect, studies have reported an association between elevated SUA levels and increased antioxidant capacity [32]. However, the protective antioxidant effect may be lost if it is overwhelmed by other detrimental effects that increase in association with higher UA levels. SUA alters the proliferation and migration of human vascular smooth muscle cells, as well as their release of nitric oxide (NO), via the expression of C-reactive protein (CRP) [33,34], stimulating cell proliferation, angiotensin II production, and oxidative stress via the tissue renin-angiotensin system [35]. NO increases blood flow to skeletal muscles, promotes glucose uptake, and is strongly associated with the action of insulin [36]. Thus, hyperuricemia induces endothelial dysfunction. This may allude to the pathogenic mechanism through which SUA induces vascular disease [37]. In a previous study, SUA was shown to be an independent determinant of insulin resistance and that a combined assessment of SUA and high-sensitivity CRP levels provides additional information on the risk stratification of community-dwelling females with metabolic syndrome [38]. Therefore, high SUA levels may contribute to high mortality. Recent studies suggested that pre-menopausal women reported lower SUA levels than post-menopausal women because estrogenic compounds increased renal UA clearance [39] and were strongly associated with other cardiovascular risk factors such as age, sex, BMI, SBP, DBP, total cholesterol, TG, and BG [32]. Thus, the association between SUA and all-cause mortality largely reflects the predominance of metabolic risk factors such as aging, insulin resistance, dyslipidemia, and renal dysfunction, which may exclude the effect of SUA on males exhibiting the aforementioned factors.

4.1. Limitation of the study

The key strengths of this study include its accuracy, which was only possible through a long-term follow-up study with a given number of subjects, as well as its adjustment for many possible confounders. However, this study is not free from limitations. Firstly, the sample focused on relatively healthy middle-aged and older adults (mean age: 64 ± 13 years) who participated in a health checkup and who lived in rural Japan, a country with a significant aging population. The sample cannot be considered representative of the general population. Secondly, the survey covered those whose deaths were registered in the Basic Resident Ledger. It did not account for those who moved away from the region during the survey period. Thirdly, the possible effects of medication (e.g., antihypertensive, lipid-lowering, antidiabetic, and SUA-lowering medication), underlying disease, metabolic syndrome, and lifestyle modification (e.g., dietary practice that may play an important role in SUA production) at baseline and during follow-up cannot be overlooked. Fourthly, renal function assessment was performed only by eGFR without urinary albumin data. Fifth, the threshold for the low SUA group may have been too low to evaluate the U-shaped relationship between SUA levels and all-cause mortality. Finally, it is possible that the relatively low number of participants and deaths could have weakened the causal relationship between SUA levels and all-cause mortality.

5. Conclusions

The follow-up study on subjects aged 22 years and above found a strong association between hyperuricemia (male: SUA ≥ 8.5 mg/dL; female: SUA ≥ 7.5 mg/dL) and increased all-cause mortality on Japanese community-dwelling individuals, after adjusting for potential confounders such as body composition index and metabolic factors.

Ethics approval

The study was approved by the Ethics Committee of the Ehime University Graduate School of Medicine (IRB: no. 1903018). Informed consent was obtained from all participating subjects in the study.

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Declaration of conflicting interests

The authors declare that they have no competing interests.

Authors' contributions

AK and RK participated in the study design, performed the statistical analysis, and drafted the manuscript. AK, RK, DN, and TK contributed to data acquisition and interpretation. AK and RK contributed to the conception and design of the statistical analysis. RK conceived the study, participated in its design, coordinated and helped with drafting the manuscript. All authors have read and approved the manuscript.

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List of abbreviations

SUA	serum uric acid
CVD	cardiovascular diseases
IRB	Institutional Review Board
HR	hazard ratio
CI	confidence interval
BMI	body mass index
UA	uric acid
SBP	systolic blood pressure
DBP	diastolic blood pressure
TG	triglyceride
HDL-C	high-density lipoprotein cholesterol
LDL-C	low-density lipoprotein cholesterol
BG	blood glucose
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
eGFR	estimate the glomerular filtration ratio
SD	standard deviation
NO	nitric oxide
CRP	C-reactive protein

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