

Serum uric acid and incident sepsis risk: sex-specific nonlinear associations modified by kidney function in the UK Biobank

Zongjun Hu

Chongqing University Three Gorges Hospital

Yaping Su

Chongqing University Cancer Hospital

Xia Huang

huangxia2008@cqu.edu.cn

Chongqing University Three Gorges Hospital

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Abstract

Background

Serum uric acid (SUA), the end product of purine metabolism, has opposing biological effects: it acts as an antioxidant at physiological concentrations but contributes to inflammation and endothelial dysfunction at elevated concentrations. Whether these effects translate into a concentration-dependent association with incident sepsis remains uncertain.

Methods

We included 466,753 UK Biobank participants. Sex-specific associations were examined using restricted cubic splines, two-piecewise Cox regression models, and multivariable Cox models. A three-way interaction among sex, SUA, and eGFR was tested to assess whether baseline eGFR modified the SUA-sepsis association differently by sex.

Results

During a mean follow-up of 13.5 years, 17,249 incident sepsis cases occurred. In males, SUA showed a U-shaped association with incident sepsis, with an inflection point at 5.69 mg/dL. Below this point, each 1-mg/dL increase in SUA was associated with lower sepsis risk (HR, 0.85; 95% CI, 0.81–0.89); above this point, higher SUA was associated with increased risk (HR, 1.05; 95% CI, 1.02–1.08). Males in the lowest and highest SUA sextiles had a higher risk than those in the reference sextile (Q1: HR, 1.26; 95% CI, 1.18–1.36; Q6: HR, 1.15; 95% CI, 1.08–1.24). In females, the association was modified by baseline eGFR: a U-shaped pattern was observed among those with eGFR < 90 mL/min/1.73 m², whereas among those with eGFR ≥ 90 mL/min/1.73 m², risk was elevated mainly at higher SUA concentrations.

Conclusions

Baseline SUA is associated with incident sepsis in a nonlinear, sex-specific, and kidney function-dependent manner. In males, both low and high SUA concentrations confer increased risk. In females, baseline eGFR modifies the association, with a U-shaped pattern among those with reduced kidney function and increased risk confined to higher SUA concentrations among those with preserved kidney function.

Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection[1]. It remains one of the leading causes of morbidity and mortality worldwide, with an estimated 166 million incident cases and 21.4 million sepsis-related deaths reported in 2021, accounting for 31.5% of total global deaths[2]. The burden extends well beyond the acute episode. Survivors frequently experience prolonged physical disability, cognitive impairment, and psychological disturbance, collectively termed post-sepsis syndrome, which can persist for months to years after hospital

discharge[3, 4]. Despite substantial advances in critical care medicine, clinical deterioration can progress rapidly once infection transitions to sepsis, leaving a narrow window for effective intervention[5]. For these reasons, circulating biomarkers that are measurable before illness onset could help characterize baseline host susceptibility and enable population-level risk stratification before the acute event[6].

Serum uric acid (SUA), the end product of purine metabolism in humans, is produced by xanthine oxidoreductase-mediated purine catabolism and contributes directly to redox homeostasis[7]. Physiologically, extracellular uric acid acts as an endogenous antioxidant, neutralizing reactive oxygen species and peroxynitrite[8]. Low SUA may therefore indicate diminished circulating antioxidant capacity, which could compromise host defense against infection[9]. In contrast, hyperuricemia has been implicated in oxidative stress, endothelial dysfunction, and innate immune activation through NADPH oxidase activity, impaired nitric oxide bioavailability, and inflammasome signaling[10–13]. Experimental evidence from endotoxemia and bacterial sepsis models further suggests that elevated SUA can amplify inflammatory responses and impair neutrophil-mediated bacterial clearance[14]. These opposing biological effects motivate investigating the association between baseline SUA and sepsis risk.

Despite this biological rationale, evidence regarding pre-illness SUA as a predictor of sepsis remains scarce. Existing studies have largely focused on SUA measured after sepsis onset, which may reflect acute pathophysiological changes rather than baseline susceptibility[15–17]. Concentrations during acute illness are susceptible to metabolic stress, tissue hypoxia, renal dysfunction, organ injury, fluid management, and other features of critical illness, and therefore may not capture pre-illness risk. Moreover, sex-specific differences in SUA distribution, purine metabolism, and renal urate handling have received limited attention in this context[18]. Whether baseline kidney function, a principal determinant of circulating SUA, modifies the association between SUA and sepsis has also not been systematically evaluated.

Using the UK Biobank cohort, we aimed to evaluate the association between baseline SUA and incident sepsis. Specifically, we sought to characterize potential nonlinear dose-response relationships, assess sex-specific differences, and determine whether baseline kidney function modifies the association between SUA and incident sepsis.

Methods

Data source and study population

This prospective cohort study used data from the UK Biobank, which recruited approximately 500,000 participants aged 40–69 years from assessment centres across the United Kingdom between 2006 and 2010. At baseline, participants completed standardized touchscreen questionnaires and underwent physical examinations and biological sample collection, providing information on sociodemographic characteristics, lifestyle factors, medical history, anthropometric measurements, circulating biomarkers, and genetic data[19, 20]. All participants provided written informed consent, and the UK Biobank was

approved by the North West Multi-centre Research Ethics Committee. The present analysis was conducted under UK Biobank application number 1092882.

A total of 501,936 participants were initially considered. After excluding 158 participants who had withdrawn from the UK Biobank, 501,778 participants remained eligible. Participants with prevalent sepsis recorded before the baseline assessment date were further excluded to allow assessment of incident sepsis ($n = 1,794$). Among the remaining 499,984 participants, 33,231 were excluded because baseline SUA, the primary exposure, was missing. The final analytic cohort included 466,753 participants (Fig. 1).

Assessment of serum uric acid

SUA was measured at baseline in $\mu\text{mol/L}$ using an enzymatic assay on the Beckman Coulter AU5800 analyzer. Standardized calibration and internal quality control procedures were implemented by the UK Biobank to ensure analytical reliability. The analytical measurement range for SUA was 89–1785 $\mu\text{mol/L}$, and the coefficients of variation ranged from 1.21% to 1.54%[21]. For the present analysis, SUA values were converted from $\mu\text{mol/L}$ to mg/dL using the standard conversion factor: $\text{mg/dL} = \mu\text{mol/L} / 59.48$.

Ascertainment of incident sepsis

Incident sepsis was the primary outcome. Cases were identified from linked hospital inpatient records, death registry records, and UK Biobank first-occurrence fields using International Classification of Diseases, Tenth Revision (ICD-10) codes consistent with those used in previous research[22]. The codes are listed in Supplementary Table 1. For participants with more than one qualifying record, the earliest recorded date was used as the date of incident sepsis. Follow-up was calculated from the baseline assessment date until incident sepsis, death, loss to follow-up, or administrative censoring, whichever occurred first. Administrative censoring dates were October 31, 2022, for England; August 31, 2022, for Scotland; and May 31, 2022, for Wales.

Assessment of covariates

Covariates were selected a priori based on clinical relevance, prior evidence, and the conceptual framework shown in the directed acyclic graph (DAG; Supplementary Fig. 1).

Demographic and socioeconomic covariates were obtained from baseline assessment data and included age at recruitment, sex, ethnicity, educational attainment, employment status, and the Townsend deprivation index. Ethnicity was categorized as White or non-White. Educational attainment was classified as college or university degree versus no college or university degree. Employment status was categorized as employed, retired, or other. Lifestyle-related covariates were obtained from baseline touchscreen questionnaires and included smoking status and alcohol consumption status, categorized

as never, previous, or current. For questionnaire-based covariates, responses of “Do not know,” “Prefer not to answer,” or “None of the above” were coded as missing values, where applicable. Body mass index (BMI) was calculated from measured weight and height.

Clinical covariates included prevalent cardiovascular disease (CVD), hypertension, diabetes, and eGFR. eGFR was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine-cystatin C equation[23]. Detailed definitions of prevalent chronic diseases are provided in Supplementary Table 2. Baseline biomarkers included albumin, C-reactive protein (CRP), glycated hemoglobin, hemoglobin, platelet count, neutrophil count, and lymphocyte count.

Statistical analysis

Continuous variables are presented as means $\pm$ standard deviations or medians with interquartile ranges, depending on distribution; categorical variables are presented as counts and percentages. Differences between males and females were assessed using independent-samples t-tests or Mann-Whitney U tests for continuous variables and chi-square tests for categorical variables. For descriptive analyses, participants were grouped according to sextiles of SUA. Differences across SUA sextile groups were evaluated using one-way analysis of variance or Kruskal-Wallis tests for continuous variables and chi-square tests for categorical variables.

The number and percentage of participants with missing covariate data are shown in Supplementary Table 3. Missing covariate data were imputed using multiple imputation by chained equations under a missing-at-random assumption[24]. The imputation model included all covariates used in the analytic models. A total of 50 imputed datasets were generated, and model estimates were combined using Rubin’s rules[25].

Cox proportional hazards regression models, with time since baseline as the underlying time scale, were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for incident sepsis. Model 1 adjusted for age at recruitment, Townsend deprivation index, employment status, educational attainment, ethnicity, smoking status, alcohol consumption status, and BMI. Model 2 additionally adjusted for diabetes, hypertension, CVD, and eGFR and was the fully adjusted model unless otherwise specified. Sex was excluded from sex-specific models. Interaction analyses were conducted using Model 2, with specific interaction terms added only where relevant.

Given the marked differences in SUA distribution between females and males, along with sex-specific variations in purine metabolism and renal urate handling, we first assessed whether sex modified the association between SUA and incident sepsis. Effect modification by sex was tested using sex-by-SUA interaction terms in Model 2, with SUA modeled using restricted cubic splines. The overall sex-by-SUA interaction was evaluated using a likelihood ratio test comparing models with and without interaction terms. Dose-response analyses were subsequently performed separately in females and males, with sex omitted from the covariates.

Within each sex, SUA was analyzed as a continuous variable to characterize the dose-response association with incident sepsis. Restricted cubic spline analyses were performed using Model 2 to assess potential nonlinearity. Knots were placed at the 5th, 35th, 65th, and 95th percentiles of the sex-specific SUA distribution. Overall and nonlinear associations were assessed by testing the spline terms in Model 2.

Sex-specific two-piecewise Cox regression models were fitted to assess piecewise associations. Candidate cutpoints were selected based on dose-response patterns observed in the restricted cubic spline analyses and model fit comparisons. HRs and 95% CIs were estimated separately for SUA values below and above the identified inflection points. HRs were expressed per 1-mg/dL increase in SUA. Likelihood ratio tests were used to compare two-piecewise models with standard Cox models containing a single linear term for SUA.

SUA was also analyzed categorically using sex-specific sextiles to provide clinically interpretable risk estimates. Sextile cutpoints were defined at the 16.7th, 33.3rd, 50.0th, 66.7th, and 83.3rd percentiles within each sex. For males, Q4 was used as the reference category; for females, Q3 was used as the reference category. Categorical Cox models were used to estimate HRs and 95% CIs across SUA sextiles in Model 1 and Model 2.

Subgroup analyses were conducted within sex-specific SUA ranges defined by the identified inflection points. HRs and 95% CIs were estimated per 1-mg/dL increase in SUA within the lower and higher SUA ranges. Prespecified subgroup variables included age, BMI, hypertension, diabetes, and CVD. Clinically relevant cutpoints are shown in Fig. 3. The stratification variable was excluded from its corresponding model. Effect modification was assessed by adding multiplicative interaction terms between SUA and each subgroup variable to Model 2.

We evaluated a three-way interaction among sex, SUA, and eGFR in the overall cohort to test whether baseline eGFR modified the SUA-sepsis association differently by sex. SUA and eGFR were modeled as continuous variables using restricted cubic splines. The three-way interaction was tested using a likelihood ratio test comparing models with and without interaction terms. Following a significant three-way interaction, sex-specific restricted cubic spline Cox models were used to assess SUA-eGFR interactions separately in males and females using Model 2. Two-dimensional contour plots were generated to visualize the joint associations of continuous SUA and continuous eGFR with incident sepsis separately for each sex. HRs were referenced to the sex-specific SUA inflection point combined with eGFR = 90 mL/min/1.73 m²: SUA = 5.69 mg/dL in males and 4.47 mg/dL in females.

Participants were stratified by sex and baseline eGFR (< 90 vs. ≥90 mL/min/1.73 m²). Within each stratum, restricted cubic spline Cox models were fitted to examine nonlinear associations between SUA and incident sepsis. Sex- and eGFR-stratified two-piecewise Cox regression models were fitted using the sex-specific SUA inflection points, with HRs and 95% CIs estimated below and above the thresholds. Models were adjusted for Model 2 covariates, excluding eGFR.

We performed a descriptive standardized difference analysis to characterize clinical profiles at the extremes of the SUA distribution. Within each sex, the lowest and highest SUA sextiles were compared with the sex-specific reference sextile used in the categorical Cox models: Q4 in males and Q3 in females. Standardized differences were calculated for 11 selected baseline variables, including BMI, eGFR, albumin, CRP, HbA1c, hemoglobin, neutrophil count, lymphocyte count, CVD, hypertension, and diabetes, and visualized using a heatmap.

Sensitivity analyses were performed to assess the robustness of the findings. Complete-case analyses excluded participants with missing covariate data. Additional analyses excluded participants with gout, hyperuricemia, severe liver disease, HIV, prevalent CVD, diabetes, hypertension, eGFR < 60 mL/min/1.73 m², baseline CRP > 10 mg/L, hypoalbuminemia (< 35 g/L), low hemoglobin (< 12 g/dL in females and < 13 g/dL in males), or BMI < 18.5 kg/m², both individually and in composite exclusions. Further sensitivity models additionally adjusted for baseline albumin, hemoglobin, and CRP. Analyses excluding sepsis events occurring within the first 1, 2, or 3 years of follow-up were conducted to mitigate potential reverse causation. Competing-risk analyses were performed using Fine-Gray subdistribution hazard models, with all-cause mortality treated as the competing event. Sensitivity analyses were conducted by sex, comparing the lowest and highest SUA sextiles with the sex-specific reference categories (Q3 in females and Q4 in males). All sensitivity models used Model 2, except when the excluded covariate corresponded to the condition under analysis.

All statistical analyses were performed using R version 4.3.2. Two-sided P values < 0.05 were considered statistically significant.

Results

Baseline characteristics

A total of 466,753 participants were included, comprising 213,619 males and 253,134 females. The mean age was 56.53 years, and 94.7% were White (Table 1). Compared with females, males had higher BMI (27.83 vs. 27.07 kg/m²), serum uric acid (SUA; 5.96 vs. 4.56 mg/dL), hemoglobin (14.97 vs. 13.50 g/dL), and prevalence of cardiovascular disease (12.4% vs. 6.5%), hypertension (31.5% vs. 24.5%), and diabetes (7.1% vs. 3.6%); eGFR was slightly lower in males (94.41 vs. 95.28 mL/min/1.73 m²). During a mean follow-up of 13.5 years, incident sepsis occurred in 4.6% of males and 2.9% of females. Across sex-specific SUA sextiles, higher SUA was accompanied by higher BMI, CRP, HbA1c, and neutrophil count and lower eGFR. In the highest SUA sextile, the prevalences of hypertension, cardiovascular disease, diabetes, and incident sepsis were 45.6%, 16.5%, 7.5%, and 6.1%, respectively, in males and 46.4%, 10.9%, 8.0%, and 4.9%, respectively, in females. In males, the lowest SUA sextile had higher diabetes prevalence and sepsis incidence than several intermediate sextiles (Supplementary Tables 5 and 6).

Table 1
Characteristics of study participants according to sex

Characteristics	Total	Male	Female	P-value
N	466,753	213,619	253,134	
Age, years	56.53 (8.09)	56.73 (8.20)	56.36 (8.00)	< 0.001
White ethnicity (%)	442,016 (94.7)	202,197 (94.7)	239,819 (94.7)	0.189
Townsend deprivation index	-1.31 (3.08)	-1.27 (3.14)	-1.35 (3.03)	< 0.001
College or university degree (%)	152,174 (32.6)	72,687 (34.0)	79,487 (31.4)	< 0.001
Employment status (%)				< 0.001
Employed	271,092 (58.1)	130,773 (61.2)	140,319 (55.4)	
Retired	156,491 (33.5)	67,105 (31.4)	89,386 (35.3)	
Other	39,170 (8.4)	15,741 (7.4)	23,429 (9.3)	
Smoking status (%)				< 0.001
Never	255,763 (54.8)	104,827 (49.1)	150,936 (59.6)	
Previous	161,863 (34.7)	82,200 (38.5)	79,663 (31.5)	
Current	49,127 (10.5)	26,592 (12.4)	22,535 (8.9)	
Alcohol consumption status (%)				< 0.001
Never	20,574 (4.4)	5,906 (2.8)	14,668 (5.8)	
Previous	16,733 (3.6)	7,527 (3.5)	9,206 (3.6)	
Current	429,446 (92.0)	200,186 (93.7)	229,260 (90.6)	
BMI, kg/m ²	27.42 (4.77)	27.83 (4.23)	27.07 (5.17)	< 0.001
Serum uric acid, mg/dL	5.20 (1.35)	5.96 (1.21)	4.56 (1.11)	< 0.001
eGFR, mL/min/1.73 m ²	94.88 (14.53)	94.41 (14.42)	95.28 (14.61)	< 0.001
Albumin, g/L	45.21 (2.55)	45.53 (2.55)	44.94 (2.52)	< 0.001
Continuous variables are presented as mean (standard deviation [SD]) or median (interquartile range [IQR]), as appropriate. Categorical variables are presented as number (percentage). <i>P</i> values were calculated using independent-samples <i>t</i> tests or Mann–Whitney <i>U</i> tests for continuous variables and chi-square tests for categorical variables.				
Abbreviations: BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; SUA, serum uric acid.				

Characteristics	Total	Male	Female	P-value
CRP, mg/L	1.33 (0.66–2.76)	1.28 (0.66–2.55)	1.38 (0.65–2.98)	< 0.001
HbA1c, mmol/mol	35.20 (32.90–37.90)	35.30 (32.90–38.10)	35.20 (32.80–37.70)	< 0.001
Hemoglobin, g/dL	14.17 (1.23)	14.97 (1.03)	13.50 (0.96)	< 0.001
Platelet count, ×10 ⁹ /L	248.20 (214.00–286.50)	234.20 (202.40–269.00)	260.70 (226.20–299.40)	< 0.001
Neutrophil count, ×10 ⁹ /L	4.02 (3.29–4.95)	4.07 (3.30–5.00)	4.00 (3.26–4.90)	< 0.001
Lymphocyte count, ×10 ⁹ /L	1.89 (1.52–2.29)	1.80 (1.49–2.20)	1.91 (1.59–2.33)	< 0.001
CVD (%)	43,027 (9.2)	26,470 (12.4)	16,557 (6.5)	< 0.001
Hypertension (%)	129,296 (27.7)	67,220 (31.5)	62,076 (24.5)	< 0.001
Diabetes (%)	24,276 (5.2)	15,076 (7.1)	9,200 (3.6)	< 0.001
Incident sepsis (%)	17,249 (3.7)	9,885 (4.6)	7,364 (2.9)	< 0.001
Follow-up time, years	13.50 (2.22)	13.33 (2.46)	13.63 (1.99)	< 0.001
Continuous variables are presented as mean (standard deviation [SD]) or median (interquartile range [IQR]), as appropriate. Categorical variables are presented as number (percentage). <i>P</i> values were calculated using independent-samples <i>t</i> tests or Mann–Whitney <i>U</i> tests for continuous variables and chi-square tests for categorical variables.				
Abbreviations: BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; SUA, serum uric acid.				

Association of serum uric acid with incident sepsis

A significant interaction between sex and SUA was observed in the fully adjusted restricted cubic spline Cox model (*P* for overall interaction < 0.001; Supplementary Fig. 2). All subsequent analyses were sex-stratified. Restricted cubic spline analyses showed U-shaped associations between SUA and incident sepsis in both sexes (Fig. 2; *P* for overall association < 0.001 and *P* for nonlinearity < 0.001 in both males and females). Risk decreased at lower and increased at higher SUA concentrations, with sex-specific inflection patterns.

Two-piecewise Cox proportional hazards regression models identified sex-specific inflection points (Table 2). Among females, the inflection point was 4.47 mg/dL (266.5 µmol/L). Below this point, each 1-mg/dL increase in SUA was associated with a lower risk of incident sepsis (HR, 0.91; 95% CI, 0.84–0.97; *P* = 0.008), whereas above this point, each 1-mg/dL increase was associated with a higher risk (HR, 1.10; 95% CI, 1.06–1.14; *P* < 0.001). Among males, the inflection point was 5.69 mg/dL (338.0 µmol/L). Below this point, each 1-mg/dL increase in SUA was associated with a lower risk (HR, 0.85; 95% CI, 0.81–0.89;

P < 0.001), whereas above this point, each 1-mg/dL increase was associated with a higher risk (HR, 1.05; 95% CI, 1.02–1.08; P < 0.001). Likelihood ratio tests indicated better fit for the two-piecewise models than for standard Cox models with a single linear SUA term (P < 0.001 for both sexes).

Table 2
Sex-specific threshold effects of serum uric acid on the risk of incident sepsis

Serum uric acid range (mg/dL)	HR (95% CI)	P value
Male		
< 5.69	0.85 (0.81, 0.89)	< 0.001
≥ 5.69	1.05 (1.02, 1.08)	< 0.001
Likelihood ratio test		< 0.001
Female		
< 4.47	0.91 (0.84, 0.97)	0.008
≥ 4.47	1.10 (1.06, 1.14)	< 0.001
Likelihood ratio test		< 0.001
Threshold effect analyses were performed using sex-specific two-piecewise Cox proportional hazards regression models. HRs represent the risk of incident sepsis per 1-mg/dL increase in serum uric acid below or above the sex-specific inflection point. Inflection points were 5.69 mg/dL (338.0 μmol/L) in males and 4.47 mg/dL (266.5 μmol/L) in females. Models were adjusted for age at recruitment, Townsend deprivation index, employment status, educational attainment, ethnicity, smoking status, alcohol consumption status, BMI, diabetes, hypertension, CVD, and eGFR. The likelihood ratio test compared the two-piecewise Cox model with a Cox model including serum uric acid as a single linear term.		

In sex-specific sextile analyses (Table 3; Supplementary Table 4), females in the lowest SUA sextile had a higher risk of incident sepsis than those in the reference sextile, Q3 (Q1: HR, 1.11; 95% CI, 1.01–1.21; P = 0.032). Risk was also higher in the highest sextile (Q6: HR, 1.11; 95% CI, 1.02–1.21; P = 0.011). Among males, Q4 was the reference sextile. Risk was higher in both the lowest sextile (Q1: HR, 1.26; 95% CI, 1.18–1.36; P < 0.001) and the highest sextile (Q6: HR, 1.15; 95% CI, 1.08–1.24; P < 0.001). Among males, risk was also higher in Q2 (HR, 1.12; 95% CI, 1.04–1.20; P = 0.003) and Q3 (HR, 1.10; 95% CI, 1.03–1.19; P = 0.007), whereas Q5 was not significantly associated with incident sepsis (HR, 1.04; 95% CI, 0.97–1.12; P = 0.235). In females, Q2, Q4, and Q5 were not significantly associated with incident sepsis (all P ≥ 0.375).

Table 3
Risk of incident sepsis across sex-specific serum uric acid sextiles

Groups	Crude Model		Model 1		Model 2	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Male						
Q1 (1.51–4.82)	1.15 (1.07, 1.23)	< 0.001	1.20 (1.11, 1.28)	< 0.001	1.26 (1.18, 1.36)	< 0.001
Q2 (> 4.82–5.39)	1.01 (0.94, 1.09)	0.694	1.07 (1.00, 1.15)	0.065	1.12 (1.04, 1.20)	0.003
Q3 (> 5.39–5.88)	1.05 (0.98, 1.13)	0.191	1.08 (1.01, 1.16)	0.036	1.10 (1.03, 1.19)	0.007
Q4 (> 5.88–6.40)	1.00 (Reference)	—	1.00 (Reference)	—	1.00 (Reference)	—
Q5 (> 6.40–7.09)	1.14 (1.06, 1.22)	< 0.001	1.08 (1.01, 1.16)	0.028	1.04 (0.97, 1.12)	0.235
Q6 (> 7.09–17.95)	1.53 (1.44, 1.64)	< 0.001	1.32 (1.24, 1.42)	< 0.001	1.15 (1.08, 1.24)	< 0.001
Female						
Q1 (1.50–3.52)	0.87 (0.79, 0.95)	0.002	1.03 (0.94, 1.13)	0.556	1.11 (1.01, 1.21)	0.032
Q2 (> 3.52–4.01)	0.90 (0.83, 0.99)	0.027	0.98 (0.89, 1.07)	0.601	1.01 (0.92, 1.10)	0.836
Q3 (> 4.01–4.44)	1.00 (Reference)	—	1.00 (Reference)	—	1.00 (Reference)	—
Serum uric acid categories (Q1–Q6) were defined using sex-specific sextiles and are shown in mg/dL. For males, Q4 served as the reference category; for females, Q3 served as the reference category. The crude model was unadjusted. Model 1 was adjusted for age at recruitment, Townsend deprivation index, employment status, educational attainment, ethnicity, smoking status, alcohol consumption status, and BMI. Model 2 was further adjusted for diabetes, hypertension, CVD, and eGFR.						
Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; SUA, serum uric acid.						

Groups	Crude Model		Model 1		Model 2	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Male						
Q4 (> 4.44–4.91)	1.18 (1.09, 1.29)	< 0.001	1.08 (0.99, 1.17)	0.081	1.04 (0.96, 1.13)	0.375
Q5 (> 4.91–5.57)	1.29 (1.19, 1.40)	< 0.001	1.06 (0.98, 1.15)	0.160	0.97 (0.89, 1.06)	0.490
Q6 (> 5.57–12.93)	2.12 (1.97, 2.28)	< 0.001	1.42 (1.31, 1.53)	< 0.001	1.11 (1.02, 1.21)	0.011
Serum uric acid categories (Q1–Q6) were defined using sex-specific sextiles and are shown in mg/dL. For males, Q4 served as the reference category; for females, Q3 served as the reference category. The crude model was unadjusted. Model 1 was adjusted for age at recruitment, Townsend deprivation index, employment status, educational attainment, ethnicity, smoking status, alcohol consumption status, and BMI. Model 2 was further adjusted for diabetes, hypertension, CVD, and eGFR.						
Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; SUA, serum uric acid.						

Subgroup analyses

Subgroup analyses were conducted within sex-specific lower and higher SUA strata defined by the identified inflection points (Fig. 3). In males with SUA < 5.69 mg/dL, the inverse association between SUA and incident sepsis was consistent across strata of age, BMI, hypertension, diabetes, and CVD, with a significant interaction only for age (P for interaction = 0.021) (Fig. 3A). In males with SUA ≥ 5.69 mg/dL, the association was consistent across the prespecified subgroups, with no statistically significant interactions (all P ≥ 0.314) (Fig. 3B). In females with SUA < 4.47 mg/dL, the association between SUA and incident sepsis was consistent across subgroups defined by age, BMI, hypertension, diabetes, and CVD (all P ≥ 0.082) (Fig. 3C). In females with SUA ≥ 4.47 mg/dL, a significant interaction was observed for BMI (P for interaction = 0.003), whereas no statistically significant interactions were observed for the other subgroup variables (all P ≥ 0.107) (Fig. 3D). The association between SUA and incident sepsis was consistent across most clinically defined subgroups. Statistically significant heterogeneity was observed only for age among males in the lower SUA stratum and for BMI among females in the higher SUA stratum (Fig. 3).

SUA-eGFR interaction analyses

The joint association of SUA and eGFR with incident sepsis differed by sex. The spline-based sex-SUA-eGFR interaction was statistically significant (P for three-way interaction < 0.001). In sex-specific

analyses, the SUA-eGFR interaction was not statistically significant in males (P for interaction = 0.248; Fig. 4A), whereas it was significant in females (P for interaction < 0.001; Fig. 4B). In males, eGFR-stratified restricted cubic spline curves showed U-shaped associations between SUA and incident sepsis in both eGFR strata, with significant threshold effects below and above 5.69 mg/dL in both strata (all P < 0.001). In females, the association differed by eGFR strata: a U-shaped pattern was observed among those with eGFR < 90 mL/min/1.73 m², whereas among those with eGFR ≥ 90 mL/min/1.73 m², SUA below 4.47 mg/dL was not associated with risk (HR, 1.01; 95% CI, 0.94–1.08), whereas SUA above 4.47 mg/dL was positively associated with risk (HR, 1.12; 95% CI, 1.06–1.19) (Supplementary Fig. 3; Supplementary Table 8).

Clinical profiles of participants in extreme SUA sextiles

Standardized-difference analyses showed distinct baseline profiles at the extremes of the SUA distribution (Supplementary Fig. 4). Across both sexes, the lowest SUA groups were characterized by lower BMI, higher eGFR, and lower hemoglobin compared with the sex-specific reference sextile. The highest SUA groups had higher BMI, lower eGFR, higher CRP and neutrophil count, and higher HbA1c, hypertension, and CVD.

Sensitivity analyses

Associations for the lowest and highest SUA sextiles in males and for the highest SUA sextile in females were consistent across sensitivity analyses (Supplementary Table 7). For the lowest SUA sextile in females, 95% CIs included unity in several analyses.

Discussion

In this prospective cohort of 466,753 participants followed for a mean of 13.5 years, baseline SUA was associated with incident sepsis in a nonlinear, sex-specific, and kidney function-dependent manner. In males, the association was U-shaped, with elevated risk at both ends of the concentration spectrum. Compared with the reference sextile, males in the lowest and highest SUA sextiles had a 26% and 15% higher risk of incident sepsis, respectively. The inflection point identified by threshold analysis was 5.69 mg/dL. In females, baseline eGFR modified the association. Among those with eGFR below 90 mL/min/1.73 m², a U-shaped pattern was observed; among those with eGFR at or above 90 mL/min/1.73 m², excess risk was confined to higher concentrations. These findings were independent of demographic, lifestyle, and clinical confounders, and remained robust across sensitivity analyses.

Previous epidemiological studies have consistently reported that both low and high SUA concentrations are associated with increased all-cause and cardiovascular mortality, suggesting a U-shaped or J-shaped relationship across diverse populations, including the general population[26, 27] and patients with osteoarthritis[28]. In the context of infectious diseases, the evidence base has largely focused on SUA measured after disease onset. In critically ill patients with established sepsis, hyperuricemia at ICU admission was associated with higher short-term mortality[15], and hyperuricemia within 24 hours of

admission was associated with a higher incidence of acute kidney injury (76.7% vs. 42.3%)[16]. Among patients with sepsis-associated acute kidney injury, elevated SUA was linked to increased in-hospital mortality[17]. Beyond sepsis, hyperuricemia has also been associated with disease severity and adverse outcomes in patients hospitalized with COVID-19[29]. These studies show that SUA carries prognostic information among patients who already have infection or sepsis. In contrast, the present study shifts the focus from acute prognostication to pre-illness risk prediction and shows that baseline SUA is associated with the subsequent development of sepsis in a nonlinear, sex-specific, and kidney function-dependent manner.

The U-shaped association between SUA and sepsis is consistent with the opposing biological effects of uric acid. At low concentrations, the antioxidant role of uric acid may be insufficient to support host defense; experimental evidence indicates that lowering circulating uric acid can reduce systemic antioxidant capacity and increase oxidative stress markers[30]. At high concentrations, the pro-inflammatory and endothelial effects of hyperuricemia may predominate, including oxidative injury, endothelial dysfunction, and inflammasome activation[10–13].

The clinical profile of participants in the lowest SUA sextiles may help identify individuals at elevated sepsis risk. Compared with reference groups, these participants had lower BMI and hemoglobin, together with higher eGFR. Lower BMI could reflect nutritional vulnerability or reduced metabolic reserve, while lower hemoglobin may indicate subclinical anemia or diminished oxygen-carrying capacity, both of which could compromise host defense during infection. Higher eGFR may indicate increased renal urate clearance, resulting in chronically low circulating SUA. This phenotype, characterized by lower body mass, lower hemoglobin, and higher glomerular filtration, has not been extensively studied in the context of infection susceptibility and needs further characterization in other cohorts.

The sex-specific findings are notable. The estimated risk nadir was higher in males than in females. This pattern may reflect known sex differences in SUA distribution, purine metabolism, renal urate handling, and urate transporter expression[18]. Females generally have lower SUA concentrations than males, and the inverse association below the inflection point appeared stronger in males, whereas the positive association above the threshold was numerically steeper in females. Estrogen affects renal urate reabsorption and secretion, and the loss of estrogen during menopause may alter the relationship between kidney function and SUA levels[31]. Reduced kidney function is also associated with chronic inflammation and immune dysfunction, which may amplify the effects of both low and high SUA on sepsis risk. The modification by eGFR, observed only in females, suggests that kidney function influences the balance between the opposing effects of SUA. Among those with reduced kidney function, the U-shaped pattern resembles that in males, whereas among those with preserved function, excess risk is confined to higher concentrations. This observation is consistent with evidence linking reduced kidney function to higher risks of infection-related hospitalization, bloodstream infection, and infection-related mortality[32–35].

SUA is inexpensive, widely available, and routinely measured. The present findings suggest that SUA may help identify individuals at elevated sepsis risk, particularly at the extremes of the concentration spectrum. Future studies should evaluate whether incorporating SUA into sex- and kidney function-specific risk profiles can improve sepsis prediction beyond established clinical factors.

Several limitations should be acknowledged. First, this observational study cannot establish causality, and residual confounding remains possible. Unmeasured or incompletely captured factors, including diet, urate-lowering therapy, diuretics, and other medications, prior infection history, immune status, frailty, and chronic inflammatory conditions, may have influenced both SUA and sepsis risk. Second, SUA was measured only at baseline, and longitudinal changes in SUA, kidney function, comorbidities, and medication exposure during follow-up could not be fully assessed. Third, incident sepsis was identified using routinely collected health records and ICD-10 codes, which may have introduced outcome misclassification and did not allow detailed characterization of infection source, pathogen, organ dysfunction severity, community- versus hospital-acquired sepsis, or acute treatment. Fourth, although eGFR was estimated using a creatinine-cystatin C equation, albuminuria was not included in the main analyses, and kidney-related risk may therefore have been incompletely captured. Fifth, the UK Biobank cohort is healthier and less socioeconomically deprived than the general UK population and consists predominantly of White participants, which may limit generalizability to more diverse or higher-risk populations[36].

Conclusion

In this large prospective cohort, baseline SUA was associated with incident sepsis in nonlinear, sex-specific, and kidney function-dependent patterns. In males, both low and high SUA concentrations were associated with higher sepsis risk, whereas in females, baseline eGFR modified the SUA-sepsis association. These findings suggest that SUA may reflect baseline host susceptibility to sepsis in a manner that depends on sex and kidney function. Further studies are needed to confirm these findings in diverse populations and to evaluate whether SUA can improve sepsis risk stratification.

Abbreviations

BMI Body mass index

CI Confidence interval

CRP C-reactive protein

CVD Cardiovascular disease

DAG Directed acyclic graph

eGFR Estimated glomerular filtration rate

HbA1c Glycated hemoglobin

HIV Human immunodeficiency virus

HR Hazard ratio

ICD-10 International Classification of Diseases, Tenth Revision

SUA Serum uric acid

Declarations

Human Ethics and Consent to Participate declarations

The UK Biobank study was conducted in accordance with the principles of the Declaration of Helsinki. UK Biobank has received full ethical approval from the North West Multi-Centre Research Ethics Committee (approval number 16/NW/0274). All participants provided written informed consent before enrollment.

Clinical trial number

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The UK Biobank Resource holds the data used in this article. Data can be accessed by application to the UK Biobank (www.ukbiobank.ac.uk/register-apply).

Competing interests

The authors declare no competing interests.

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Authors' contributions

Data curation, methodology, formal analysis, and visualization were performed by Zongjun Hu and Yaping Su. The original draft was written by Zongjun Hu and Yaping Su. Writing, review, and editing were performed by Xia Huang, Zongjun Hu, and Yaping Su. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Figures

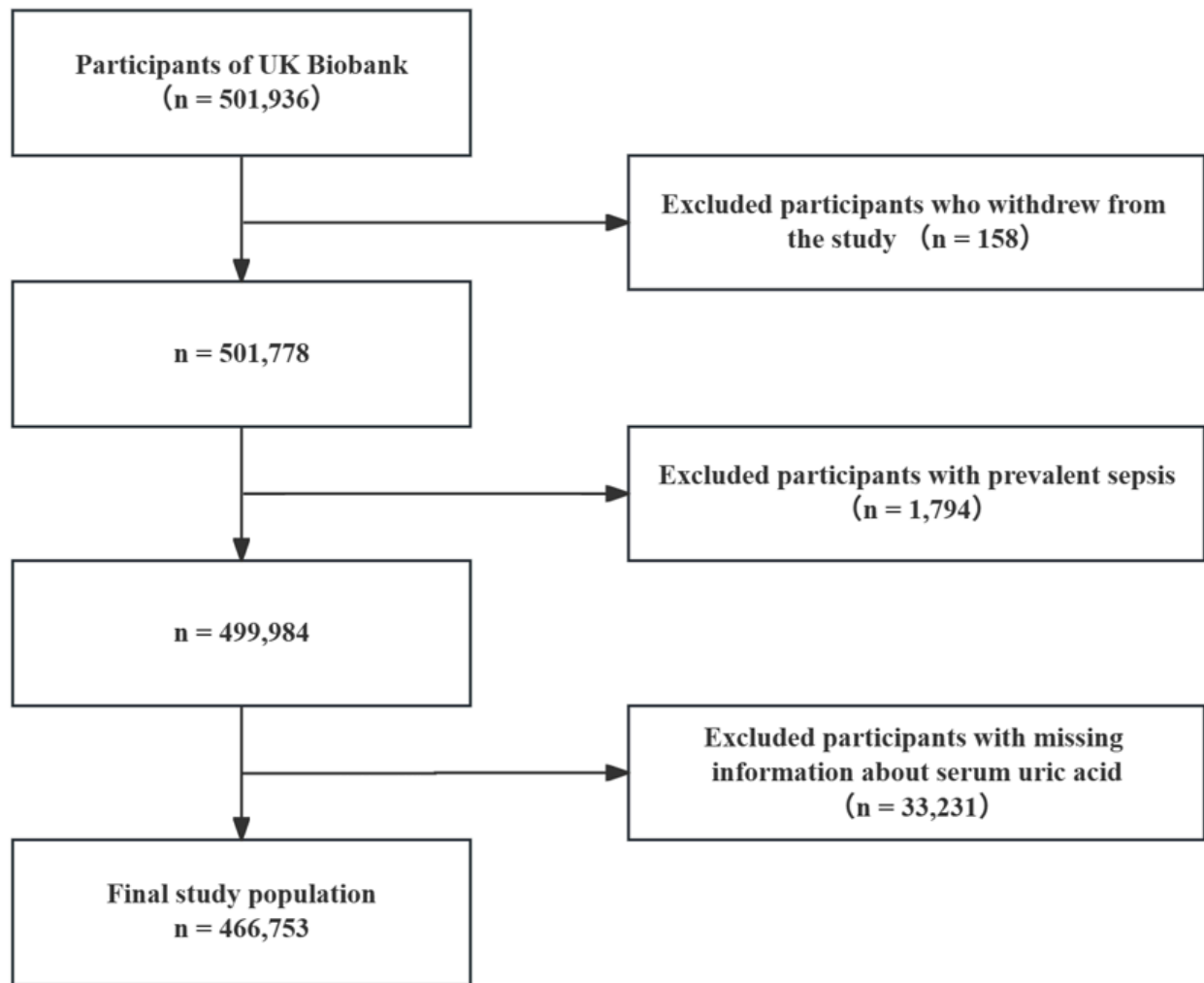


Figure 1

Flow chart of the study

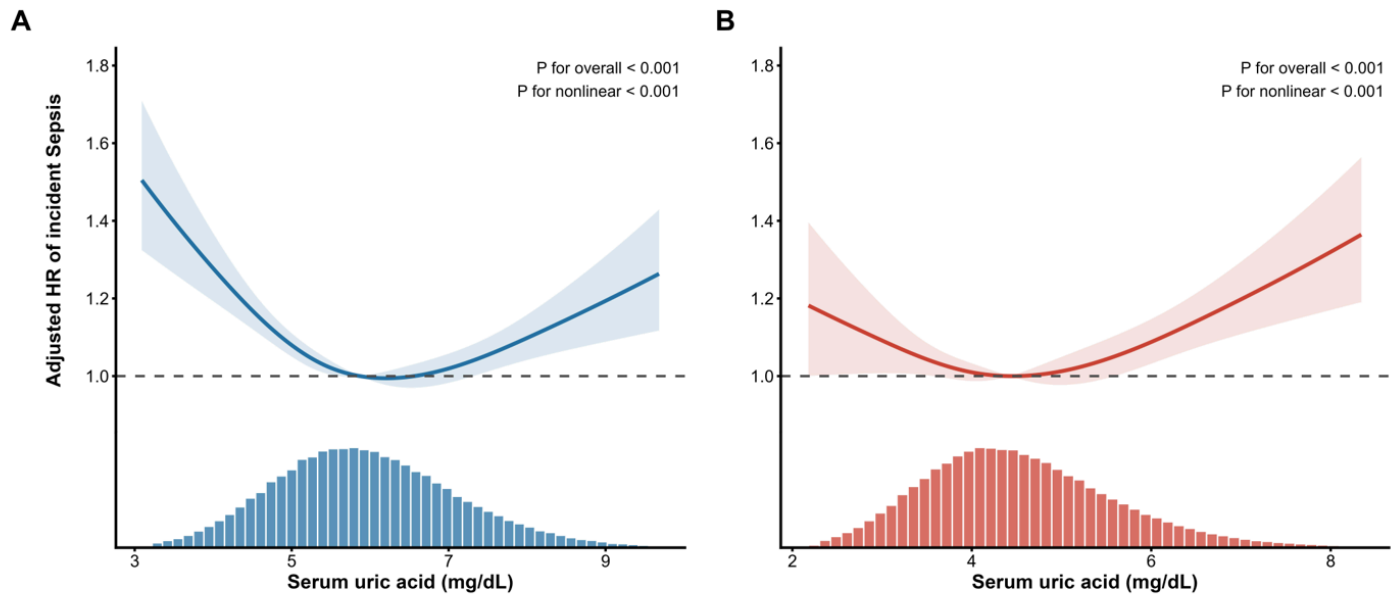


Figure 2

Restricted cubic spline analysis of the association between serum uric acid levels and incident sepsis risk by sex

Restricted cubic spline curves show the association between SUA and incident sepsis in males (A) and females (B). Solid lines indicate adjusted HRs; shaded areas indicate 95% CIs. Models were adjusted for age, Townsend deprivation index, employment status, educational attainment, ethnicity, smoking status, alcohol consumption status, BMI, diabetes, hypertension, CVD, and eGFR.

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

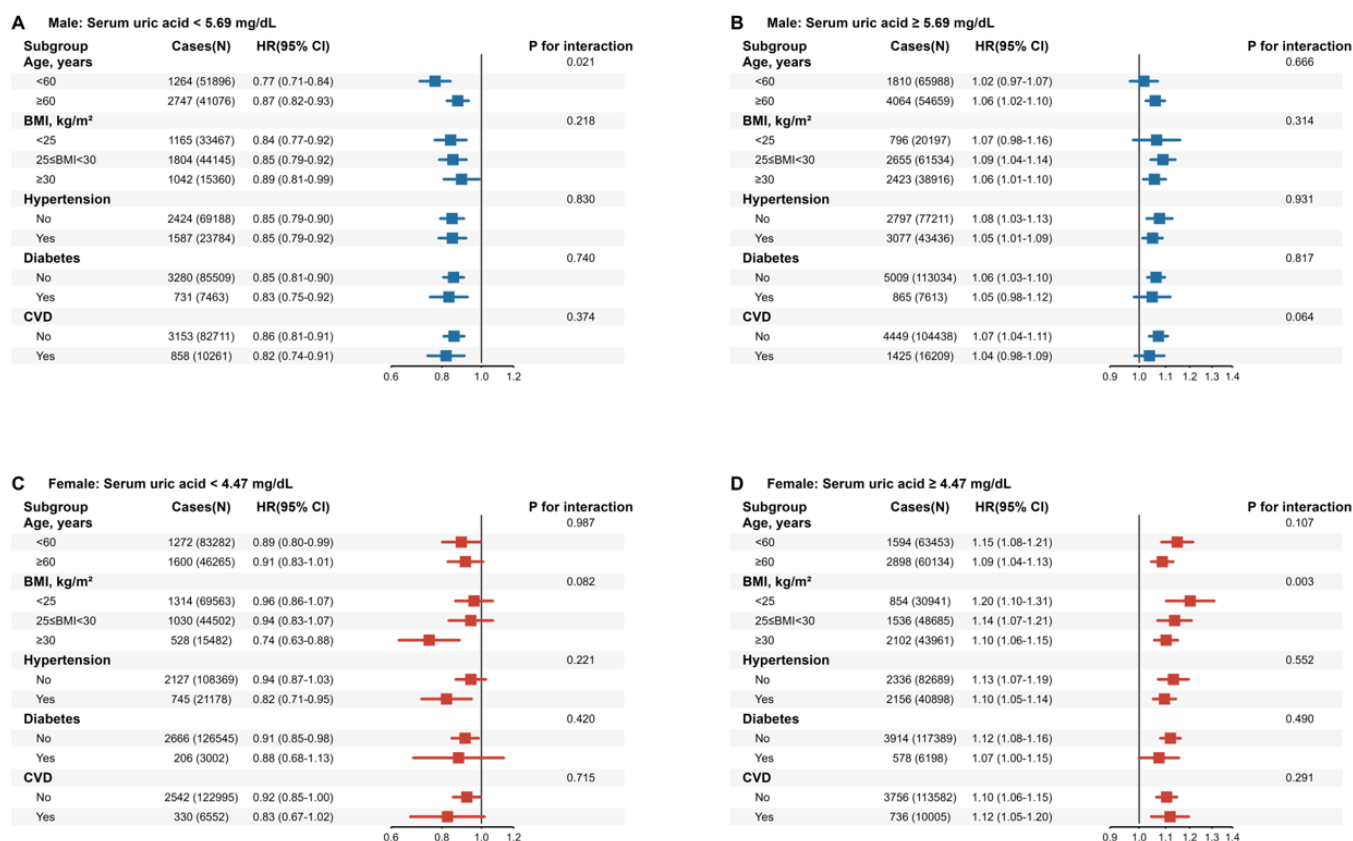


Figure 3

Subgroup analyses of the association between serum uric acid and incident sepsis according to clinical characteristics within sex-specific serum uric acid strata

Forest plots show adjusted HRs and 95% CIs for incident sepsis per 1-mg/dL increase in SUA within sex-specific strata: (A) males with SUA <5.69 mg/dL, (B) males with SUA ≥5.69 mg/dL, (C) females with SUA <4.47 mg/dL, (D) females with SUA ≥4.47 mg/dL. Subgroup variables included age (<60 or ≥60 years), BMI (<25.0, 25.0–29.9, or ≥30.0 kg/m²), hypertension, diabetes, and CVD. Models were adjusted for age, Townsend deprivation index, employment status, educational attainment, ethnicity, smoking status, alcohol consumption status, BMI, diabetes, hypertension, CVD, and eGFR, except for the stratification variable. P values for interaction were calculated.

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

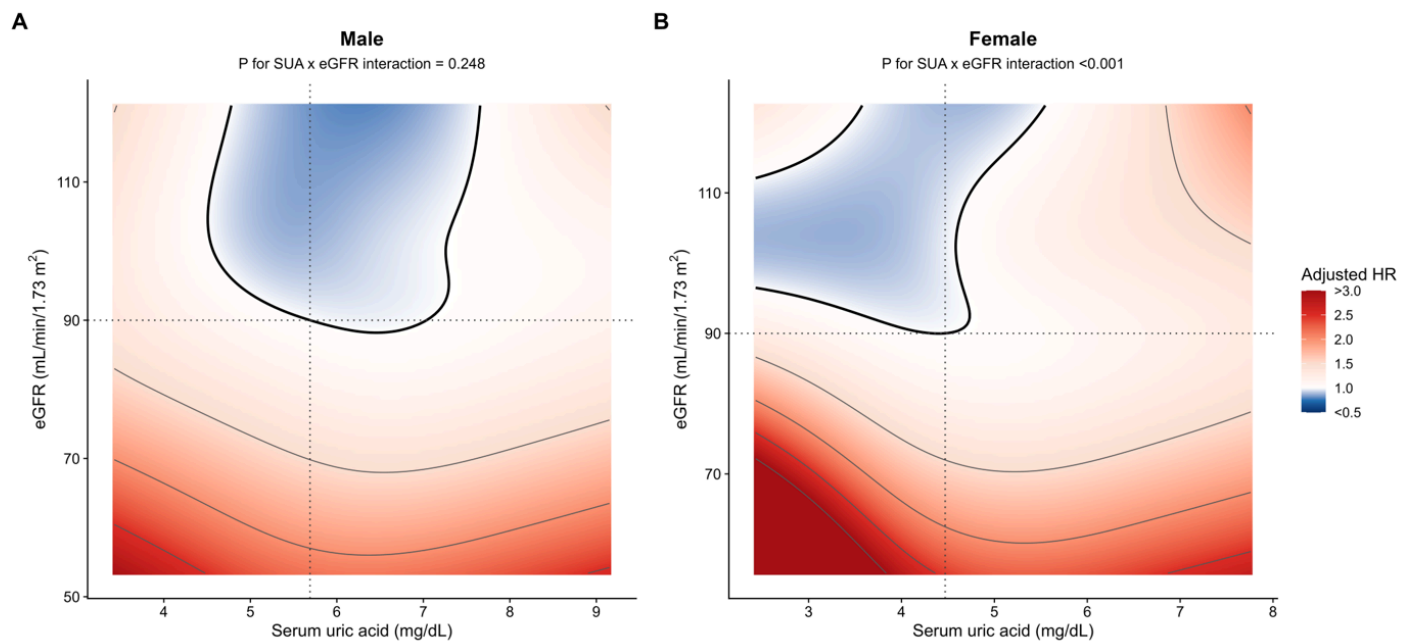


Figure 4

Sex-specific joint associations of serum uric acid and eGFR with incident sepsis.

Predicted HR surfaces from sex-specific Cox models incorporating the SUA–eGFR interaction. Panels A and B show joint associations of SUA and eGFR with incident sepsis in males and females, respectively. HRs were referenced to sex-specific SUA values combined with eGFR = 90 mL/min/1.73 m²: 5.69 mg/dL in males and 4.47 mg/dL in females. Blue indicates HR <1; red indicates HR >1. Contour lines represent adjusted HR levels; the HR = 1 contour is highlighted by a thicker black line. Models were adjusted for age, Townsend deprivation index, employment status, educational attainment, ethnicity, smoking status, alcohol consumption status, BMI, diabetes, hypertension, and CVD. Panel-specific P values refer to the SUA–eGFR interaction.

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; SUA, serum uric acid.

Supplementary Files

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