Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Combined Association of Serum Uric Acid and High-Sensitivity C-Reactive Protein with Chronic Kidney Disease: A Nationwide Cross-sectional Population-based Study

Sang-Suk Choi
St. Vincent's Hospital, The Catholic University of Korea
Seung-Hyun Ko
St. Vincent's Hospital, The Catholic University of Korea
Kyu-Na Lee
Soongsil University
Kyung Do Han
Soongsil University
Hyung Wook Kim
St. Vincent's Hospital, The Catholic University of Korea
Jaeyun Lee
St. Vincent's Hospital, The Catholic University of Korea
Hyeran Park
St. Vincent's Hospital, The Catholic University of Korea
Hyunglae Kim
hlkim0526@catholic.ac.kr

St. Vincent's Hospital, The Catholic University of Korea

Research Article

Keywords: Chronic kidney disease, Uric acid, High-sensitivity C-reactive protein, Inflammation, KNHANES, Cross-sectional study, Population-based study

Posted Date: June 9th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9658917/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Chronic kidney disease (CKD) is a major public health concern. While serum uric acid (UA) and high-sensitivity C-reactive protein (hsCRP) are established individual predictors of renal impairment, their combined effect on CKD remains underexplored.

Methods

We analyzed data from 9,116 adults (aged ≥ 19 years) using the Korea National Health and Nutrition Examination Survey 2022–2023. Participants were categorized into four groups based on the highest quartile cutoffs for UA (≥ 5.9 mg/dL) and hsCRP (≥ 1.1 mg/L): Low-Low, Low-High, High-Low, and High-High. CKD was defined as an estimated glomerular filtration rate < 60 mL/min/1.73 m² or a urine albumin-to-creatinine ratio ≥ 30 mg/g. Adjusted odds ratios (aORs) were calculated using multivariable logistic regression.

Results

Elevated UA and hsCRP were independently associated with CKD. When considered jointly, the odds of CKD were higher in the Low-High and High-Low groups and highest in the High-High group (aOR, 2.60; 95% confidence interval, 1.87–3.61) compared with the Low-Low reference group. In subgroup analyses, this combined association was significantly more pronounced in older adults (≥ 65 years), women, and individuals with pre-existing hypertension or hypercholesterolemia (all p for interaction < 0.05).

Conclusions

Concomitant elevation of serum UA and hsCRP is associated with a higher prevalence of CKD, reflecting significant interplay between metabolic and inflammatory pathways. Integrative monitoring of both biomarkers may facilitate early identification of individuals with increased likelihood of CKD and support targeted preventive strategies.

Introduction

Chronic kidney disease (CKD) is a global public health concern that affects approximately 10% of adults worldwide and substantially increases the risk of cardiovascular disease, end-stage kidney disease (ESKD), and premature mortality[1–5]. Early identification of modifiable risk factors is essential, particularly in the general population where subclinical renal dysfunction often remains unrecognized. Although hypertension, diabetes, and obesity are established determinants of CKD, accumulating

evidence suggests that other metabolic and inflammatory pathways also contribute to renal injury and its progression[6, 7].

Serum uric acid (UA), a byproduct of purine metabolism, has been implicated as a potential mediator of kidney injury[8]. Hyperuricemia is associated with incident CKD, accelerated eGFR decline, and albuminuria[9–11], and experimental data have suggested that UA promotes endothelial dysfunction, oxidative stress, and activation of the intra-renal renin–angiotensin–aldosterone system[12, 13]. However, whether UA is a causal factor or merely a marker of metabolic dysfunction remains unclear, as randomized trials and meta-analyses have yielded inconsistent results[14–16].

High-sensitivity C-reactive protein (hsCRP), an acute-phase reactant synthesized in response to pro-inflammatory cytokines, reflects systemic low-grade inflammation and has been associated with albuminuria and CKD progression[17–19]. However, inflammatory pathways in CKD are complex, and hsCRP alone may not fully capture inflammatory risk[20].

Because metabolic stress and systemic inflammation frequently coexist in individuals with cardiometabolic risk factors, their combined effects may better reflect renal vulnerability than either pathway alone[21]. However, the joint association of UA and hsCRP with CKD in the general population has not been sufficiently investigated. Therefore, using data from the Korea National Health and Nutrition Examination Survey (KNHANES), we examined the independent and combined associations of serum UA and hsCRP with CKD prevalence. We hypothesized that concomitant elevation of UA and hsCRP would be associated with a higher prevalence of CKD, reflecting a metabolic–inflammatory interaction in renal pathology.

Methods

Data Source and Study Population

The data for this study were obtained from KNHANES 2022–2023, a nationwide, cross-sectional survey conducted by the Korea Disease Control and Prevention Agency. This survey employs a stratified multistage probability sampling design to ensure a representative sample of the non-institutionalized Korean population. The survey consisted of three main components: a health interview, a medical examination, and a nutrition survey.

As shown in the participant flowchart (Fig. 1), we initially identified 13,194 individuals from the 2022–2023 KNHANES. We excluded participants aged under 19 years (n = 1,965), those missing essential data for serum UA, hsCRP, or serum creatinine (n = 583), and those with missing covariates (n = 1,530). The final analysis included 9,116 participants. This study was approved by the Institutional Review Board of The Catholic University of Korea, St. Vincent's Hospital (VC25ZISI0233, approved on October 22, 2025), and the requirement for informed consent was waived due to the use of anonymized public data.

Definition of Outcomes and Covariates

The primary outcome was the prevalence of CKD, which was defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m², calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, or a urine albumin-to-creatinine ratio of 30 mg/g or higher. Because KNHANES collects single-visit measurements, persistence of kidney abnormality for ≥ 3 months as required by the KDIGO clinical definition of CKD could not be ascertained.

The main exposure variables were serum UA and hsCRP. Both markers were divided into quartiles based on their distribution in the study population. "High" levels were defined as the highest quartile (Q4), while the lower three quartiles (Q1–Q3) served as the reference group. Specifically, the cutoff values for high UA and high hsCRP were ≥ 5.9 mg/dL (Q1–Q3: 0.5–5.8 mg/dL; Q4: 5.9–11.9 mg/dL) and ≥ 1.1 mg/L (Q1–Q3: 0.2–1.0 mg/L; Q4: 1.1–85.7 mg/L), respectively. Based on these cutoffs, participants were categorized into four groups: Low-Low (UA < 5.9 mg/dL and hsCRP < 1.1 mg/L), Low UA/High hsCRP, High UA/Low hsCRP, and High-High (UA ≥ 5.9 mg/dL and hsCRP ≥ 1.1 mg/L).

Alcohol consumption was quantified based on the average daily amount of pure alcohol intake and participants were categorized as non-drinkers (0 g/day), mild drinkers (0–29 g/day), or heavy drinkers (≥ 30 g/day). Smoking status was classified into never, former, and current smokers. Aerobic physical activity was defined as "yes" if participants met the Global Physical Activity Questionnaire criteria for moderate-to-vigorous physical activity.

Comorbidities were defined through a combination of health interview responses, physical examinations, and laboratory findings. Hypertension was defined as a systolic blood pressure (SBP) ≥ 140 mmHg, a diastolic blood pressure (DBP) ≥ 90 mmHg, or the current use of antihypertensive medication. Diabetes mellitus was identified by a fasting plasma glucose level ≥ 126 mg/dL, a glycated hemoglobin (HbA1c) level ≥ 6.5%, a previous physician's diagnosis, or the use of insulin or oral hypoglycemic agents. Hypercholesterolemia was defined as a total cholesterol level ≥ 240 mg/dL or the current use of lipid-lowering agents. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m²), and abdominal obesity was defined as a waist circumference ≥ 90 cm for men and ≥ 85 cm for women.

Statistical Analysis

Baseline characteristics of the study population were presented as weighted mean ± standard error (SE) for continuous variables and as weighted percentage with SE for categorical variables. To compare differences among the four groups categorized by combinations of serum UA and hsCRP levels, analysis of variance was used for continuous variables, and the chi-square test was employed for categorical variables. Multivariable logistic regression analysis was performed to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for the prevalence of CKD. We constructed three models to control for potential confounders: Model 1 was unadjusted; Model 2 was adjusted for age and sex; and Model 3 was fully adjusted for age, sex, household income, BMI, smoking status, alcohol consumption, physical

activity, diabetes mellitus, hypertension, and hypercholesterolemia. Additionally, subgroup analyses were conducted to evaluate the consistency of associations across strata of clinical characteristics, and interaction terms were tested to assess whether the relationship between the combined biomarkers and CKD varied by these subgroups. All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline Characteristics of the Study Population

The baseline characteristics of the 9,116 study participants, categorized by the combination of serum UA and hsCRP levels, are presented in Table 1. Demographic characteristics differed significantly across the groups ($p < 0.001$). The High-High group (elevated UA and hsCRP) was predominantly male (79.6%) and comprised a larger proportion of younger adults aged 20–39 years (42.0%) compared to the Low-Low group (27.3%) ($p < 0.001$).

Table 1
Baseline characteristics according to uric acid and hsCRP groups

Characteristics	Total (n = 9,116)	Low–Low (n = 5,452)	Low–High (n = 1,444)	High–Low (n = 1,475)	High–High (n = 745)	p-value
Demographic characteristics						
Age group (%)						< 0.001
20–39 years	31.13 (0.85)	27.26 (0.88)	25.56 (1.65)	41.69 (1.69)	41.97 (2.07)	
40–64 years	48.28 (0.69)	51.12 (0.84)	48.83 (1.64)	43.28 (1.48)	40.15 (1.99)	
≥ 65 years	20.59 (0.64)	21.62 (0.74)	25.61 (1.21)	15.04 (1.01)	17.88 (1.40)	
Male (%)	50.31 (0.52)	35.27 (0.76)	40.66 (1.59)	88.31 (0.80)	79.63 (1.51)	< 0.001
Education ≥ college (%)	46.37 (0.97)	45.78 (1.10)	39.13 (1.70)	52.57 (1.65)	48.57 (2.21)	< 0.001
Low household income (%)	14.67 (0.56)	14.73 (0.63)	19.47 (1.24)	10.43 (0.88)	15.66 (1.49)	< 0.001
Anthropometric measures						
BMI (kg/m²)	24.22 ± 0.05	23.06 ± 0.06	25.44 ± 0.14	25.14 ± 0.10	27.58 ± 0.18	< 0.001
Waist circumference (cm)	83.99 ± 0.15	80.33 ± 0.18	87.08 ± 0.35	87.78 ± 0.27	94.01 ± 0.44	< 0.001
Abdominal obesity (%)	35.37 (0.64)	25.14 (0.71)	48.42 (1.49)	41.23 (1.46)	66.42 (1.91)	< 0.001
Lifestyle factors						
Smoking status (%)						< 0.001
Never	60.22 (0.64)	69.01 (0.80)	63.58 (1.47)	39.56 (1.45)	43.38 (2.14)	

Values are presented as mean ± standard error or percentage (standard error) unless otherwise indicated. Triglyceride levels are presented as median (interquartile range).

hsCRP, High-sensitivity C-reactive protein; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Characteristics	Total (n = 9,116)	Low–Low (n = 5,452)	Low–High (n = 1,444)	High–Low (n = 1,475)	High–High (n = 745)	p-value
Demographic characteristics						
Former	22.47 (0.49)	18.07 (0.64)	19.68 (1.29)	33.61 (1.30)	30.92 (1.98)	
Current	17.32 (0.56)	12.92 (0.61)	16.75 (1.18)	26.83 (1.36)	25.69 (1.87)	
Alcohol consumption (%)						< 0.001
None	24.77 (0.62)	27.48 (0.78)	30.90 (1.42)	14.37 (0.92)	19.96 (1.79)	
Mild	66.60 (0.69)	66.58 (0.81)	61.89 (1.54)	70.05 (1.35)	66.91 (2.10)	
Heavy	8.64 (0.40)	5.94 (0.40)	7.21 (0.86)	15.58 (1.12)	13.13 (1.56)	
Aerobic physical activity (%)	49.81 (0.72)	48.80 (0.91)	43.49 (1.64)	57.70 (1.44)	49.57 (2.18)	< 0.001
Comorbidities						
Diabetes mellitus (%)	12.31 (0.39)	11.71 (0.49)	18.07 (1.12)	10.24 (0.83)	11.19 (1.29)	< 0.001
Hypertension (%)	27.73 (0.71)	25.98 (0.87)	31.50 (1.44)	26.89 (1.32)	34.48 (1.88)	< 0.001
Hypercholesterolemia (%)	27.08 (0.59)	28.15 (0.75)	28.88 (1.34)	23.85 (1.31)	24.29 (1.73)	0.004
Blood pressure						
SBP (mmHg)	118.23 ± 0.26	116.23 ± 0.31	120.05 ± 0.51	120.44 ± 0.40	123.13 ± 0.57	< 0.001
DBP (mmHg)	74.03 ± 0.16	72.84 ± 0.19	74.38 ± 0.32	75.74 ± 0.30	77.39 ± 0.42	< 0.001
Metabolic parameters						
Fasting glucose (mg/dL)	99.52 ± 0.28	98.05 ± 0.30	104.73 ± 0.96	99.25 ± 0.46	100.99 ± 0.76	< 0.001

Values are presented as mean ± standard error or percentage (standard error) unless otherwise indicated. Triglyceride levels are presented as median (interquartile range).

hsCRP, High-sensitivity C-reactive protein; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Characteristics	Total (n = 9,116)	Low–Low (n = 5,452)	Low–High (n = 1,444)	High–Low (n = 1,475)	High–High (n = 745)	p-value
Demographic characteristics						
HbA1c (%)	5.55 ± 0.01	5.52 ± 0.01	5.76 ± 0.03	5.47 ± 0.02	5.59 ± 0.02	< 0.001
Lipid profile						
Total cholesterol (mg/dL)	188.73 ± 0.57	185.96 ± 0.66	189.46 ± 1.31	193.03 ± 1.21	195.84 ± 1.63	< 0.001
HDL-C (mg/dL)	56.98 ± 0.21	60.95 ± 0.24	53.62 ± 0.42	52.62 ± 0.41	46.62 ± 0.50	< 0.001
LDL-C (mg/dL)	115.63 ± 0.51	112.02 ± 0.59	117.29 ± 1.17	120.74 ± 1.11	124.87 ± 1.53	< 0.001
Triglyceride (mg/dL)	108.32 (106.72–109.95)	94.74 (93.16–96.34)	117.79 (114.06–121.64)	128.84 (124.74–133.07)	152.28 (145.62–159.24)	< 0.001

Values are presented as mean ± standard error or percentage (standard error) unless otherwise indicated. Triglyceride levels are presented as median (interquartile range).

hsCRP, High-sensitivity C-reactive protein; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Despite being relatively younger, the High-High group exhibited more pronounced metabolic risk factors and chronic conditions. Compared to the reference group, individuals in the High-High group had significantly poorer anthropometric and metabolic parameters, including the highest BMI, waist circumference, SBP, and fasting glucose levels (all $p < 0.001$). Dyslipidemia was also prominent, characterized by elevated triglycerides and LDL cholesterol with reduced HDL cholesterol ($p < 0.001$). Unhealthy lifestyle behaviors were more prevalent in this group, with the highest rates of current smoking (25.7%) and heavy alcohol consumption (13.1%) ($p < 0.001$).

Independent and Combined Associations with CKD

Table 2 shows the independent and combined associations of serum UA and hsCRP levels with the prevalence of CKD. In the independent analysis, the highest quartile of UA was significantly associated with CKD (adjusted odds ratio [aOR], 1.86; 95% CI, 1.49–2.33) compared to the lowest quartiles (Q1–Q3) after adjusting for potential confounders including age, sex, BMI, and comorbidities (Model 3). Similarly, elevated hsCRP (Q4) was independently associated with increased odds of CKD (aOR, 1.44; 95% CI, 1.17–1.78).

Table 2
Associations of uric acid and hsCRP with chronic kidney disease

Variables	Unweighted Total no.	Unweighted Event no.	Weighted % (SE)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Serum uric acid						
Low (Q1–Q3)	6,896	464	5.9 (0.4)	1 (Reference)	1 (Reference)	1 (Reference)
High (Q4)	2,220	269	8.6 (0.6)	1.52 (1.27–1.82)	1.96 (1.57–2.44)	1.86 (1.49–2.33)
hsCRP						
Low (Q1–Q3)	6,927	476	5.8 (0.4)	1 (Reference)	1 (Reference)	1 (Reference)
High (Q4)	2,189	257	9.5 (0.7)	1.72 (1.41–2.08)	1.62 (1.32–1.98)	1.44 (1.17–1.78)
Combined status						
Low-Low	5,452	326	5.2 (0.4)	1 (Reference)	1 (Reference)	1 (Reference)
Low UA/High hsCRP	1,444	138	8.3 (0.8)	1.63 (1.28–2.07)	1.48 (1.15–1.89)	1.32 (1.02–1.70)
High UA/Low hsCRP	1,475	150	7.3 (0.8)	1.42 (1.12–1.81)	1.82 (1.38–2.39)	1.73 (1.31–2.29)
High-High	745	119	11.5 (1.2)	2.35 (1.79–3.08)	2.88 (2.09–3.97)	2.60 (1.87–3.61)
p value				< 0.0001	< 0.0001	< 0.0001

Values are presented as odds ratios (ORs) with 95% confidence intervals (CIs).

Outcome: CKD (eGFR < 60mL/min/1.73 m^2 or UACR ≥ 30mg/g)

Uric acid cutoff value: Q1-Q3 (0.5–5.8 mg/dL), Q4 (5.9–11.9 mg/dL)

hsCRP cutoff value: Q1-Q3 (0.2-1.0 mg/L), Q4 (1.1–85.7 mg/L)

Model 1: Unadjusted

Model 2: Adjusted for age and sex

Model 3: Adjusted for age, sex, household income, BMI, smoking status, alcohol consumption, physical activity, diabetes mellitus, hypertension, and hypercholesterolemia

In the combined analysis, the odds of CKD were higher in the Low-High and High-Low groups and highest in the High-High group (Fig. 2). Compared to the reference group (Low-Low), the odds of having CKD were significantly higher in the High-Low group (elevated UA only: aOR, 1.73; 95% CI, 1.31–2.29) and the Low-High group (elevated hsCRP only: aOR, 1.32; 95% CI, 1.02–1.70). Notably, the High-High group exhibited the highest odds of CKD, with an aOR of 2.60 (95% CI, 1.87–3.61). The combined status of UA and hsCRP was significantly associated with CKD prevalence ($p < 0.001$).

Subgroup Analyses

Figure 3 and Table 3 present the results of subgroup analyses stratified by clinical characteristics. The combined association of elevated UA and hsCRP with CKD prevalence was directionally consistent across all examined strata; however, the magnitude of association was significantly modified by age, sex, hypertension, and hypercholesterolemia (all p for interaction < 0.05).

Table 3
Subgroup analyses of uric acid–hsCRP groups and chronic kidney disease

Subgroup	UA–hsCRP status	Unweighted total (n)	Event (n)	Weighted % (SE)	aOR (95% CI)	p for interaction
Age < 65 years	Low-Low	3847	141	3.5 (0.3)	1 (Reference)	**0.029**
	Low-High	908	50	5.1 (0.8)	1.205 (0.816–1.781)	
	High-Low	1138	56	4.0 (0.7)	1.247 (0.836–1.860)	
	High-High	531	46	7.8 (1.2)	2.241 (1.449–3.466)	
Age ≥ 65 years	Low-Low	1605	185	11.9 (1.0)	1 (Reference)	
	Low-High	536	88	17.6 (1.9)	1.526 (1.084–2.149)	
	High-Low	337	94	27.8 (2.7)	2.683 (1.900–3.788)	
	High-High	214	73	30.4 (3.6)	3.256 (2.189–4.843)	
Male	Low-Low	1677	135	6.5 (0.6)	1 (Reference)	**0.003**
	Low-High	526	66	10.4 (1.5)	1.563 (1.066–2.292)	
	High-Low	1232	97	5.7 (0.7)	1.374 (0.983–1.922)	
	High-High	565	89	10.7 (1.3)	2.405 (1.664–3.476)	
Female	Low-Low	3775	191	4.6 (0.4)	1 (Reference)	
	Low-High	918	72	6.8 (0.9)	1.174 (0.809–1.704)	

Subgroup	UA–hsCRP status	Unweighted total (n)	Event (n)	Weighted % (SE)	aOR (95% CI)	p for interaction
	High-Low	243	53	19.1 (2.8)	3.446 (2.217–5.357)	
	High-High	180	30	14.5 (2.9)	3.133 (1.786–5.498)	
Obesity No	Low-Low	4038	198	4.4 (0.4)	1 (Reference)	0.577
	Low-High	750	72	7.4 (1.0)	1.310 (0.929–1.848)	
	High-Low	778	80	7.2 (1.0)	1.833 (1.274–2.637)	
	High-High	270	58	16.2 (2.4)	3.319 (2.092–5.264)	
Obesity Yes	Low-Low	1414	128	7.6 (0.8)	1 (Reference)	
	Low-High	694	66	9.1 (1.3)	1.362 (0.909–2.042)	
	High-Low	697	70	7.4 (1.0)	1.648 (1.161–2.339)	
	High-High	475	61	9.4 (1.3)	2.269 (1.485–3.468)	
Never/Former	Low-Low	4849	286	5.1 (0.4)	1 (Reference)	0.226
	Low-High	1231	118	8.0 (0.8)	1.340 (1.015–1.769)	
	High-Low	1102	127	8.4 (0.9)	2.037 (1.516–2.736)	
	High-High	559	91	11.5 (1.4)	2.741 (1.891–3.973)	

Subgroup	UA–hsCRP status	Unweighted total (n)	Event (n)	Weighted % (SE)	aOR (95% CI)	p for interaction
Current smoking	Low-Low	603	40	5.9 (1.0)	1 (Reference)	
	Low-High	213	20	9.3 (2.4)	1.360 (0.653–2.833)	
	High-Low	373	23	4.2 (1.2)	0.974 (0.488–1.947)	
	High-High	186	28	11.4 (2.2)	2.449 (1.376–4.357)	
Non/Mild drinking	Low-Low	5173	305	5.2 (0.4)	1 (Reference)	0.257
	Low-High	1351	129	8.1 (0.8)	1.344 (1.032–1.750)	
	High-Low	1257	140	7.7 (0.9)	1.868 (1.395–2.502)	
	High-High	656	111	12.1 (1.3)	2.942 (2.084–4.155)	
Heavy drinking	Low-Low	279	21	6.7 (1.6)	1 (Reference)	
	Low-High	93	9	10.4 (3.8)	1.322 (0.486–3.599)	
	High-Low	218	10	5.0 (1.7)	1.025 (0.423–2.487)	
	High-High	89	8	7.3 (2.7)	1.194 (0.449–3.180)	
Physical activity No	Low-Low	2956	213	6.3 (0.5)	1 (Reference)	0.132
	Low-High	871	96	9.5 (1.1)	1.340 (0.968–1.855)	

Subgroup	UA–hsCRP status	Unweighted total (n)	Event (n)	Weighted % (SE)	aOR (95% CI)	p for interaction
	High-Low	686	104	11.6 (1.4)	2.319 (1.654–3.250)	
	High-High	400	74	14.0 (1.8)	2.690 (1.822–3.973)	
Physical activity Yes	Low-Low	2496	113	4.1 (0.5)	1 (Reference)	
	Low-High	573	42	6.6 (1.2)	1.384 (0.873–2.194)	
	High-Low	789	46	4.1 (0.8)	1.158 (0.703–1.908)	
	High-High	345	45	9.0 (1.6)	2.634 (1.604–4.324)	
Normoglycemia	Low-Low	3129	92	2.7 (0.3)	1 (Reference)	0.539
	Low-High	658	30	3.6 (0.7)	1.169 (0.722–1.892)	
	High-Low	749	34	3.1 (0.6)	1.429 (0.893–2.287)	
	High-High	331	38	8.1 (1.6)	3.274 (1.922–5.575)	
Pre-diabetes	Low-Low	1577	95	5.4 (0.6)	1 (Reference)	
	Low-High	507	50	8.3 (1.2)	1.542 (1.036–2.295)	
	High-Low	519	53	8.4 (1.4)	2.243 (1.491–3.374)	
	High-High	313	42	10.4 (1.7)	2.525 (1.602–3.979)	

Subgroup	UA–hsCRP status	Unweighted total (n)	Event (n)	Weighted % (SE)	aOR (95% CI)	p for interaction
Diabetes mellitus	Low-Low	746	139	18.7 (1.7)	1 (Reference)	
	Low-High	279	58	21.1 (3.0)	1.334 (0.865–2.059)	
	High-Low	207	63	26.5 (3.3)	1.621 (1.034–2.542)	
	High-High	101	39	30.0 (5.2)	2.341 (1.295–4.229)	
Hypertension No	Low-Low	3781	112	2.8 (0.4)	1 (Reference)	**0.001**
	Low-High	914	51	5.2 (0.9)	1.635 (1.060–2.521)	
	High-Low	968	34	2.3 (0.4)	1.009 (0.658–1.547)	
	High-High	442	33	5.3 (1.1)	2.288 (1.351–3.874)	
Hypertension Yes	Low-Low	1671	214	12.2 (0.9)	1 (Reference)	
	Low-High	530	87	14.9 (1.6)	1.164 (0.837–1.620)	
	High-Low	507	116	20.7 (2.1)	2.378 (1.695–3.336)	
	High-High	303	86	23.3 (2.8)	2.932 (1.990–4.319)	
Hypercholesterolemia No	Low-Low	3690	178	4.1 (0.3)	1 (Reference)	**0.002**
	Low-High	982	86	7.7 (1.0)	1.443 (1.047–1.989)	

Subgroup	UA–hsCRP status	Unweighted total (n)	Event (n)	Weighted % (SE)	aOR (95% CI)	p for interaction
	High-Low	1075	77	4.6 (0.7)	1.206 (0.849–1.713)	
	High-High	538	72	9.8 (1.3)	2.378 (1.633–3.465)	
Hypercholesterolemia Yes	Low-Low	1762	148	8.2 (0.8)	1 (Reference)	
	Low-High	462	52	9.6 (1.5)	1.157 (0.752–1.780)	
	High-Low	400	73	15.8 (2.2)	2.950 (1.952–4.458)	
	High-High	207	47	16.6 (2.5)	3.218 (1.987–5.210)	

For age, the association was significantly stronger in older adults (≥ 65 years) with an aOR of 3.26 (95% CI, 2.19–4.84) compared with younger adults (< 65 years; aOR, 2.24; 95% CI, 1.45–3.47) (p for interaction = 0.029). Female sex showed a stronger association with CKD (aOR, 3.13; 95% CI, 1.79–5.50) than male sex (aOR, 2.41; 95% CI, 1.66–3.48) (p for interaction = 0.003).

The combined effect of elevated UA and hsCRP on CKD was more pronounced in patients with pre-existing comorbidities. Participants with hypertension had significantly higher odds of CKD (aOR, 2.93; 95% CI, 1.99–4.32) compared with normotensive individuals (aOR, 2.29; 95% CI, 1.35–3.87) (p for interaction = 0.001). Similarly, participants with hypercholesterolemia showed higher odds of CKD (aOR, 3.22; 95% CI, 1.99–5.21) than those without (aOR, 2.38; 95% CI, 1.63–3.47) (p for interaction = 0.002). In contrast, although the odds of CKD were elevated in both obese and non-obese individuals compared with the Low-Low reference group, the interaction was not statistically significant (p for interaction = 0.577). Diabetes status did not significantly modify the association either (p for interaction = 0.539), with a consistently elevated odds of CKD compared with the Low-Low reference group regardless of glycemic status.

Discussion

In this large-scale, nationwide population-based study, we demonstrated that elevated serum UA and hsCRP were independently associated with CKD, and their concomitant elevation was associated with the highest odds of CKD. Individuals in the High–High group had 2.6-fold higher odds of CKD compared with those in the Low-Low group. Notably, this combined association was particularly pronounced in

specific clinical subgroups including older adults, women, and those with pre-existing hypertension or hypercholesterolemia.

While previous research firmly established hyperuricemia[22–24] and systemic inflammation[25, 26] as individual predictors of renal function impairment, our study fills a critical gap by shifting the focus from single-marker analysis to a detailed combination profile. Recent prospective studies have begun to highlight the joint adverse effects of concomitant high UA and CRP on cardiovascular disease[27] and cardiac conduction block[28], as well as metabolic syndrome components[29]. However, few studies have specifically quantified their combined association with CKD prevalence in a general population. Most prior renal studies treated UA and hsCRP as independent confounders rather than interacting biological factors. By integrating these markers, we provide a more comprehensive view of the metabolic-inflammatory interaction in renal pathology. Our findings suggest that the coexistence of metabolic stress (represented by UA) and systemic low-grade inflammation (represented by hsCRP) creates a cumulative burden that exceeds the impact of each factor in isolation.

The cumulative association observed in this cross-sectional analysis may be biologically conceptualized as a 'double-hit' framework of renal injury, although our design cannot establish such causality. UA acts as a primary metabolic insult, inducing endothelial dysfunction via oxidative stress and activating the intra-renal renin–angiotensin–aldosterone system, which leads to glomerular hypertension[30–32]. Simultaneously, elevated hsCRP signifies a state of chronic low-grade inflammation that promotes mesangial expansion and tubulointerstitial fibrosis[33, 34]. Beyond independent action, UA can directly upregulate CRP expression in human vascular smooth muscle and endothelial cells through MAPK and NF-κB pathways[35].

Notably, the magnitude of this association was significantly modified by the presence of hypertension and hypercholesterolemia. Pre-existing vascular vulnerabilities in these patients may predispose the renal microvasculature to a combination of metabolic and inflammatory burdens[36]. Furthermore, the more pronounced association observed in women supports the hypothesis that the loss of estrogen’s uricosuric and anti-inflammatory effects after menopause makes the renal system particularly sensitive[37]. These findings suggest that serum UA and hsCRP may serve as markers of renal vulnerability, helping to identify individuals who may benefit from more intensive renal protective strategies.

Despite our robust findings, several limitations should be acknowledged. First, the cross-sectional design precludes causal inference and determination of temporal sequence; in particular, reverse causation cannot be excluded, as reduced kidney function itself can elevate serum UA through impaired excretion and elevate hsCRP through uremia-related low-grade inflammation, leaving the directionality of the observed associations uncertain. Second, the outcome was operationalized using single-visit measurements of eGFR and urine albumin-to-creatinine ratio (uACR) and therefore does not satisfy the KDIGO clinical definition of CKD, which requires persistence of kidney abnormality for ≥ 3 months. Because uACR can be transiently elevated during acute inflammatory or infectious states, and because

hsCRP itself reflects systemic inflammation, single-visit ascertainment may have introduced outcome misclassification that could partly amplify the observed hsCRP–CKD association; the findings should therefore be interpreted as describing single-visit CKD prevalence rather than confirmed clinical CKD. Third, serum UA and hsCRP were measured at a single time point, which cannot capture long-term cumulative exposure to chronic low-grade inflammation or metabolic stress. Fourth, the highest hsCRP quartile extended to 85.7 mg/L; values exceeding 10 mg/L typically reflect acute-phase responses rather than chronic low-grade inflammation per AHA/CDC guidance. Sensitivity analyses excluding such participants would have strengthened interpretation but were beyond the scope of the present analysis. Fifth, a unified UA cutoff was applied across sexes, which contributed to the observed male predominance (≈ 80%) in the High-High group. Sex-specific UA cutoffs may yield different group distributions and merit confirmation in future analyses, although they would also generate smaller subgroups within the joint UA–hsCRP categorization. Sixth, the four-category approach in this study demonstrates a joint association rather than a formally tested statistical interaction between UA and hsCRP; we did not include a multiplicative UA × hsCRP product term, so the additional joint contribution beyond the independent effects of each marker cannot be quantitatively expressed in the present analysis. Seventh, we did not separately adjust for urate-lowering agents (e.g., allopurinol, febuxostat) because medication-level data on these specific agents were not available in the public KNHANES variables used; residual confounding from such treatments cannot be excluded. Eighth, although we adjusted for major sociodemographic, lifestyle, and clinical confounders, residual confounding from unmeasured factors—such as specific dietary purine and salt intake, hydration status, or medication adherence—cannot be entirely excluded. Finally, the study population was exclusively Korean adults, and the findings may not be generalizable to populations with different genetic, dietary, or environmental backgrounds without external validation.

A key strength of this study is the use of a large, nationally representative dataset, which enhances statistical power and supports the generalizability of our findings. Our results suggest that a multi-targeted approach addressing both metabolic and inflammatory pathways may warrant consideration in the context of CKD prevention. For example, therapeutic strategies focusing solely on lowering serum UA (e.g., xanthine oxidase inhibitors) may have limited impacts if concomitant systemic inflammation remains unaddressed[38, 39]. Our cross-sectional findings should not be interpreted as evidence in favor of pharmacologic UA reduction. Rather, they identify a clinically definable subgroup—individuals with combined metabolic–inflammatory burden—who may warrant closer renal monitoring and intensified management of established cardiometabolic risk factors. Future prospective longitudinal studies are needed to clarify temporal directionality and to test whether combined biomarker-guided strategies improve renal outcomes compared with conventional risk-factor management.

Conclusions

In this nationwide cross-sectional analysis of Korean adults, the combination of high serum UA and hsCRP was a useful biomarker to identify individuals with the highest odds of CKD. This cumulative association was particularly pronounced in patients with underlying hypertension or

hypercholesterolemia, suggesting significant interplay between metabolic and inflammatory pathways in renal damage. Clinicians should consider integrative monitoring of both biomarkers to facilitate early identification of individuals with increased likelihood of CKD and to support multifaceted preventive strategies.

Abbreviations

CKD
chronic kidney disease
UA
uric acid
hsCRP
high-sensitivity C-reactive protein
eGFR
estimated glomerular filtration rate
uACR
urine albumin-to-creatinine ratio
CKD-EPI
Chronic Kidney Disease Epidemiology Collaboration
KNHANES
Korea National Health and Nutrition Examination Survey
aOR
adjusted odds ratio
CI
confidence interval
SBP
systolic blood pressure
DBP
diastolic blood pressure
BMI
body mass index
HDL-C
high-density lipoprotein cholesterol
LDL-C
low-density lipoprotein cholesterol
ESKD
end-stage kidney disease
KDIGO
Kidney Disease Improving Global Outcomes.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of The Catholic University of Korea, St. Vincent's Hospital (approval number VC25ZISI0233; approved on October 22, 2025). The requirement for individual informed consent was waived by the IRB owing to the retrospective use of anonymized public-use data from the Korea National Health and Nutrition Examination Survey. All methods were performed in accordance with the principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed in the current study are publicly available from the Korea National Health and Nutrition Examination Survey (KNHANES) of the Korea Disease Control and Prevention Agency at https://knhanes.kdca.go.kr/knhanes/eng/index.do. Analytic code is available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

None of the authors received any funding for this study.

Authors' contributions

SSC and HK conceived and designed the study. KNL and KDH performed the statistical analysis. SSC drafted the initial manuscript. SHK, HWK, YKK, JL, and HP contributed to data interpretation and critically revised the manuscript for important intellectual content. HK supervised the project as the corresponding author. All authors read and approved the final manuscript.

Acknowledgements

The authors thank the Korea Disease Control and Prevention Agency for making the KNHANES dataset publicly available.

References

1. Francis A, Harhay MN, Ong ACM, Tummalapalli SL, Ortiz A, Fogo AB, Fliser D, Roy-Chaudhury P, Fontana M, Nangaku M, et al. Chronic kidney disease and the global public health agenda: an

international consensus. Nat Rev Nephrol. 2024;20(7):473–85.
2. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296–305.
3. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, Hobbs FD. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. PLoS ONE. 2016;11(7):e0158765.
4. Marx-Schütt K, Cherney DZI, Jankowski J, Matsushita K, Nardone M, Marx N. Cardiovascular disease in chronic kidney disease. Eur Heart J. 2025;46(23):2148–60.
5. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375(9731):2073–81.
6. Lin L, Tan W, Pan X, Tian E, Wu Z, Yang J. Metabolic Syndrome-Related Kidney Injury: A Review and Update. Front Endocrinol 2022, Volume 13–2022.
7. Wang S, Zeng J, Chen Y, Sun F, Ma H, Zhang L, Lin Z, Wang C, Wang Y, Yang Q, et al. Association between Systemic Inflammation and Worsening Renal Function in Cardiovascular-Kidney-Metabolic Syndrome. Am J Nephrol. 2025;56(6):751–61.
8. Giordano C, Karasik O, King-Morris K, Asmar A. Uric Acid as a Marker of Kidney Disease: Review of the Current Literature. Dis Markers. 2015;2015(1):382918.
9. Kritmetapak K, Charoensri S, Thaopanya R, Pongchaiyakul C. Elevated Serum Uric Acid is Associated with Rapid Decline in Kidney Function: A 10-Year Follow-Up Study. Int J Gen Med. 2020;13:945–53.
10. Takata T, Mae Y, Hoi S, Iyama T, Isomoto H. Hyperuricemia in Chronic Kidney Disease: Emerging Pathophysiology and a Novel Therapeutic Strategy. Int J Mol Sci 2025, 26(18).
11. Wu N, Xia J, Chen S, Yu C, Xu Y, Xu C, Yan T, Li N, Liu Y, Pan X-F. Serum uric acid and risk of incident chronic kidney disease: a national cohort study and updated meta-analysis. Nutr Metabolism. 2021;18(1):94.
12. Zhang Y, He F, Yu X, Li T, Zhou L, Shen B. Hyperuricemia-induced kidney injury: a narrative review of mechanisms and therapeutic advances. BMC Nephrol. 2025;26(1):629.
13. Gherghina ME, Peride I, Tiglis M, Neagu TP, Niculae A, Checherita IA. Uric Acid and Oxidative Stress-Relationship with Cardiovascular, Metabolic, and Renal Impairment. Int J Mol Sci 2022, 23(6).
14. Luo Q, Cai Y, Zhao Q, Tian L, Liu Y, Liu W. Effects of allopurinol on renal function in patients with diabetes: a systematic review and meta-analysis. Ren Fail. 2022;44(1):806–14.
15. Chen Q, Wang Z, Zhou J, Chen Z, Li Y, Li S, Zhao H, Badve SV, Lv J. Effect of Urate-Lowering Therapy on Cardiovascular and Kidney Outcomes: A Systematic Review and Meta-Analysis. Clin J Am Soc Nephrol. 2020;15(11):1576–86.
16. Mackenzie IS, Hawkey CJ, Ford I, Greenlaw N, Pigazzani F, Rogers A, Struthers AD, Begg AG, Wei L, Avery AJ, et al. Allopurinol versus usual care in UK patients with ischaemic heart disease (ALL-

HEART): a multicentre, prospective, randomised, open-label, blinded-endpoint trial. Lancet. 2022;400(10359):1195–205.

17. Veulchamy S, Matheou A, Zavlis O, White S, McDonnell T, Habte-Asres H, Lay A, Shalamanova L, Whyte MB, Gibson M, et al. High sensitivity C-reactive protein subsequent rise in urine albumin/creatinine ratio/fall in estimated glomerular filtration rate over 24 years in people with type 2 diabetes. Cardiovasc Endocrinol Metab. 2025;14(4):e00248.
18. Sabanayagam C, Lee J, Shankar A, Lim SC, Wong TY, Tai ES. C-reactive protein and microalbuminuria in a multi-ethnic Asian population. Nephrol Dialysis Transplantation. 2009;25(4):1167–72.
19. Kubo S, Kitamura A, Imano H, Cui R, Yamagishi K, Umesawa M, Muraki I, Kiyama M, Okada T, Iso H. Serum Albumin and High-Sensitivity C-reactive Protein are Independent Risk Factors of Chronic Kidney Disease in Middle-Aged Japanese Individuals: the Circulatory Risk in Communities Study. J Atheroscler Thromb. 2016;23(9):1089–98.
20. Amdur RL, Feldman HI, Gupta J, Yang W, Kanetsky P, Shlipak M, Rahman M, Lash JP, Townsend RR, Ojo A, et al. Inflammation and Progression of CKD: The CRIC Study. Clin J Am Soc Nephrol. 2016;11(9):1546–56.
21. Cirillo P, Sautin YY, Kanellis J, Kang DH, Gesualdo L, Nakagawa T, Johnson RJ. Systemic inflammation, metabolic syndrome and progressive renal disease. Nephrol Dial Transpl. 2009;24(5):1384–7.
22. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, Tuttle KR, Rodriguez-Iturbe B, Herrera-Acosta J, Mazzali M. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension* 2003, 41(6):1183–90.
23. Obermayr RP, Temml C, Gutjahr G, Knechtelsdorfer M, Oberbauer R, Klauser-Braun R. Elevated uric acid increases the risk for kidney disease. J Am Soc Nephrol. 2008;19(12):2407–13.
24. Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M, Truong L, Harris R, Johnson RJ. A role for uric acid in the progression of renal disease. J Am Soc Nephrol. 2002;13(12):2888–97.
25. Ridker PM. A Test in Context: High-Sensitivity C-Reactive Protein. J Am Coll Cardiol. 2016;67(6):712–23.
26. Gupta J, Mitra N, Kanetsky PA, Devaney J, Wing MR, Reilly M, Shah VO, Balakrishnan VS, Guzman NJ, Girndt M, et al. Association between albuminuria, kidney function, and inflammatory biomarker profile in CKD in CRIC. Clin J Am Soc Nephrol. 2012;7(12):1938–46.
27. Li N, Wu S, Shu R, Song H, Wang J, Chen S, Yang W, Wang G, Yang J, Yang X, et al. The combination of high uric acid and high C-reactive protein increased the risk of cardiovascular disease: A 15-year prospective cohort study. Nutr Metab Cardiovasc Dis. 2024;34(6):1508–17.
28. Li N, Cui L, Tse G, Korantzopoulos P, Letsas KP, Bazoukis G, Chen S, Zhang N, Yang X, Liu P, et al. The Combination of Hyperuricemia and Elevated High-Sensitivity C-Reactive Protein Increased the Risk of Cardiac Conduction Block. J Inflamm Res. 2024;17:3725–36.

29. Kim YK, Yang YM. An analysis of the associations of high-sensitivity C-reactive protein and uric acid with metabolic syndrome components in Korean adults by sex: a cross-sectional study using the Korea national health and nutrition examination survey 2016–2018. BMC Endocr Disord. 2023;23(1):163.
30. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med. 2008;359(17):1811–21.
31. Sanchez-Lozada LG, Lanaspa MA, Cristobal-Garcia M, Garcia-Arroyo F, Soto V, Cruz-Robles D, Nakagawa T, Yu MA, Kang DH, Johnson RJ. Uric acid-induced endothelial dysfunction is associated with mitochondrial alterations and decreased intracellular ATP concentrations. Nephron Exp Nephrol. 2012;121(3–4):e71–78.
32. Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL, Lan HY, Kivlighn S, Johnson RJ. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension. 2001;38(5):1101–6.
33. Fried L, Solomon C, Shlipak M, Seliger S, Stehman-Breen C, Bleyer AJ, Chaves P, Furberg C, Kuller L, Newman A. Inflammatory and prothrombotic markers and the progression of renal disease in elderly individuals. J Am Soc Nephrol. 2004;15(12):3184–91.
34. Han M, Zhou J, Wan Z, Chen M, Yan M, Feng W, Wang G, Zhang J, Zhang L, Yan L, et al. Remnant cholesterol, high-sensitivity C-reactive protein, and risk of incident coronary heart disease among patients with chronic kidney disease based on UK biobank. Nutr Metab (Lond). 2025;22(1):83.
35. Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. J Am Soc Nephrol. 2005;16(12):3553–62.
36. Chen XY, Lu F, Zhang J, Xu CX, Du XF, Liang MB, Chen LJ, Zhong JM. The effect of hyperuricemia and its interaction with hypertension towards chronic kidney disease in patients with type 2 diabetes: evidence from a cross- sectional study in Eastern China. Front Endocrinol (Lausanne). 2024;15:1415459.
37. Hak AE, Choi HK. Menopause, postmenopausal hormone use and serum uric acid levels in US women–the Third National Health and Nutrition Examination Survey. Arthritis Res Ther. 2008;10(5):R116.
38. Goicoechea M, de Vinuesa SG, Verdalles U, Ruiz-Caro C, Ampuero J, Rincon A, Arroyo D, Luno J. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol. 2010;5(8):1388–93.
39. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017;377(12):1119–31.

Figures

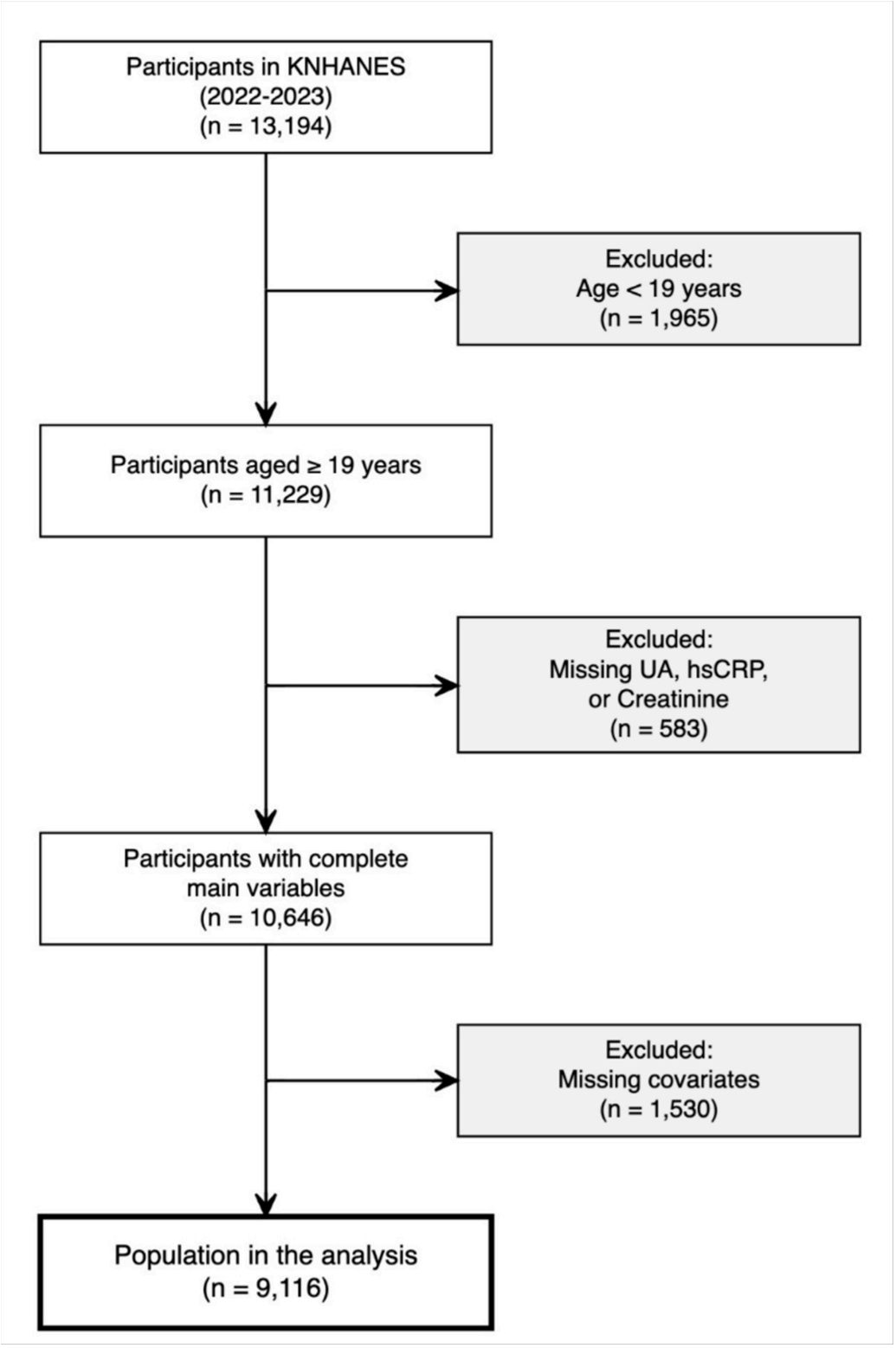


Figure 1

Flowchart of study participant selection from the Korea National Health and Nutrition Examination Survey (KNHANES) 2022-2023

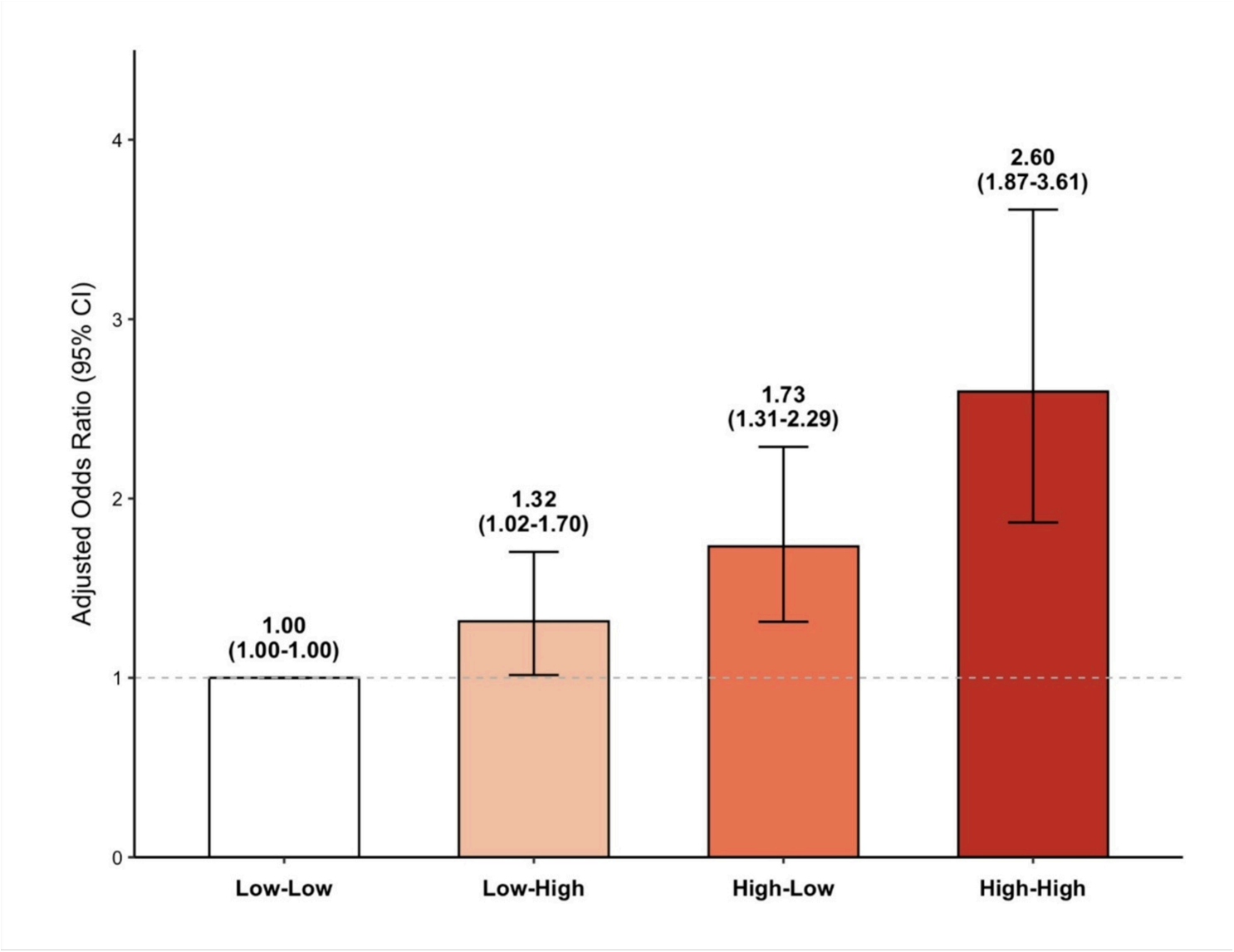


Figure 2

Multivariable-adjusted odds ratios for chronic kidney disease according to combined uric acid and hsCRP categories.

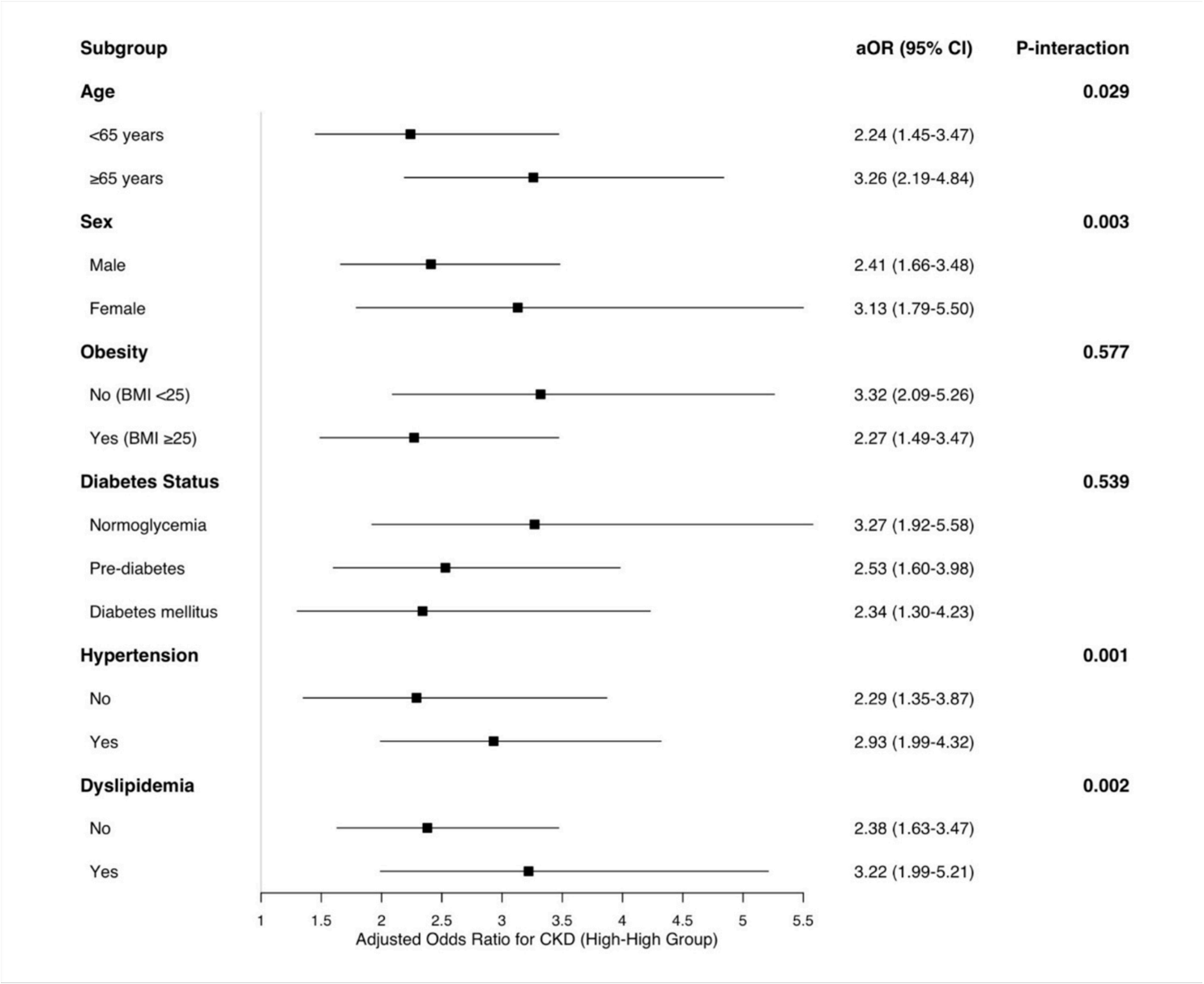


Figure 3

Forest plot of adjusted odds ratios for chronic kidney disease according to uric acid–hsCRP groups across clinical subgroups.