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Joint association of the inflammatory marker and cardiovascular-kidney-metabolic syndrome stages with all-cause and cardiovascular disease mortality: a national prospective study

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Abstract

Background Cardiovascular-kidney-metabolic (CKM) syndrome and systemic inflammation significantly contribute to mortality. However, the joint associations of CKM stages and systemic inflammation with all-cause and cardiovascular disease (CVD) mortality remain unclear. This study aimed to evaluate the independent and joint associations of CKM stages and systemic inflammation with all-cause and CVD mortality in a representative cohort of United States adults.

Methods We analyzed data from 29,459 adults aged ≥ 20 years from the National Health and Nutrition Examination Survey (1999–2018). CKM stages were classified based on metabolic risk factors, CVD, and chronic kidney disease. Systemic inflammation was assessed using multiple indicators, and time-dependent ROC analysis identified the systemic inflammatory response index (SIRI) as the most effective inflammatory marker. The associations of CKM stages and SIRI with mortality were evaluated.

Results Over a median follow-up of 109 months, 5,583 all-cause deaths and 1,843 CVD-specific deaths occurred. Both advanced CKM stages and elevated SIRI were associated with higher risks of all-cause and CVD mortality. Individuals with advanced CKM stages (Stages 3–4) and elevated SIRI (> 0.81) had the highest risks of all-cause (HR: 1.84, 95% CI: 1.65–2.05) and CVD mortality (HR: 2.50, 95% CI: 2.00–3.12). These associations were particularly pronounced in adults aged < 60 years (*P* for interaction < 0.001).

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Conclusions Advanced CKM stages and elevated SIRI are associated with increased risks of all-cause and CVD mortality, particularly in younger adults. These findings highlight the significance of targeted interventions to address systemic inflammation and CKM progression, potentially improving long-term outcomes in high-risk populations.

Keywords Cardiovascular-kidney-metabolic syndrome, Systemic inflammatory response index, Cardiovascular disease, Obesity, Chronic kidney disease

Introduction

Cardiovascular disease (CVD), chronic kidney disease (CKD), and metabolic disorders, such as diabetes, have emerged as a cluster of chronic conditions that impose a substantial burden on healthcare systems worldwide [1–4]. These diseases have overlapping risk factors, including hypertension, obesity, and dyslipidemia. Additionally, they have interrelated pathophysiological mechanisms that exacerbate their adverse health outcomes [5]. Recently, the concept of cardiovascular-kidney-metabolic (CKM) syndrome was introduced by the American Heart Association (AHA) as a comprehensive framework for understanding, preventing, and managing these interconnected conditions [6]. CKM syndrome has profound implications for patient prognosis, leading to poorer clinical outcomes and higher mortality rates that exceed the combined risks of each condition individually [5, 7]. Studies have demonstrated that higher stages of CKM syndrome have been linked to a significant increase in all-cause mortality [7]. This interconnected syndrome poses a major challenge for health systems because of its impact on long-term survival and quality of life.

Systemic inflammation has been widely acknowledged as a critical factor in the development and progression of chronic diseases, including CVD, CKD, and diabetes. Various inflammatory markers have been established to assess the presence and severity of systemic inflammation, which plays a pivotal role in these conditions. For instance, the systemic immune-inflammation index (SII) has emerged as a novel indicator of inflammation and has shown strong prognostic value in predicting outcomes across various diseases [8]. In addition to SII, other indices such as the systemic inflammation response index (SIRI) have also shown strong predictive power. SIRI has been shown to outperform SII in predicting all-cause and CVD mortality in obese populations [9]. Furthermore, elevated SIRI is closely associated with increased mortality risk in patients with CKD, particularly in the early stages [10]. Collectively, these findings highlight the potential role of systemic inflammation in shaping the prognosis of individuals with CKM syndrome, suggesting that inflammatory markers may provide valuable insights for clinical decision-making.

This study aims to address this gap by evaluating the independent and joint effects of CKM stages and inflammatory status with all-cause and CVD mortality based on data from the National Health and Nutrition Examination Survey (NHANES) spanning 1999 to 2018. Subgroup analyses will also be performed to assess where factors such as age and sex modify these associations. By focusing on the relationship between CKM stages and inflammatory status, this research aims to uncover key risk patterns and provide a more comprehensive understanding of mortality predictors across the general adult population. This approach offers valuable insights into how systemic inflammation and CKM progression together influence mortality risk, ultimately contributing to improved risk stratification and public health strategies.

Methods

This prospective cohort study used a nationally representative sample from the NHANES, conducted biennially since 1999 in the United States. The study protocol was approved by the National Center for Health Statistics Ethics Review Board, and signed informed consent was obtained.

Study population

A total of 40,764 adults aged 20 years or older, with sufficient data to determine CKM stages, were recruited from ten consecutive NHANES cycles (1999–2018). Among them, 709 participants were excluded for being currently pregnant, 75 were excluded due to unknown survival data, and 1,100 were excluded for missing 2-year/4-year Mobile Examination Center (MEC) exam weights. Additionally, 1,963 participants were excluded because of incomplete inflammatory index data. Further exclusions were made for missing data on key covariates, including marital status (n=327), poverty-income ratio (PIR, n=3,185), education (n=31), smoking (n=22), drinking (n=3,067), Healthy Eating Index-2015 (HEI-2015, n=822), and physical activity (n=4). Ultimately, 29,459 participants with sufficient information were included (Fig. 1).

Assessments of CKM syndrome

CKM syndrome is characterized as the coexistence of subclinical or clinical CVD, CKD, and metabolic disorders. It is categorized into five stages based on a presidential advisory from the AHA (Table S1) [6]. Specifically, Stage 0 indicates all normal conditions; Stage 1 includes only obesity or prediabetes; Stage 2 involves other metabolic disorders or CKD; Stage 3 includes subclinical CVD

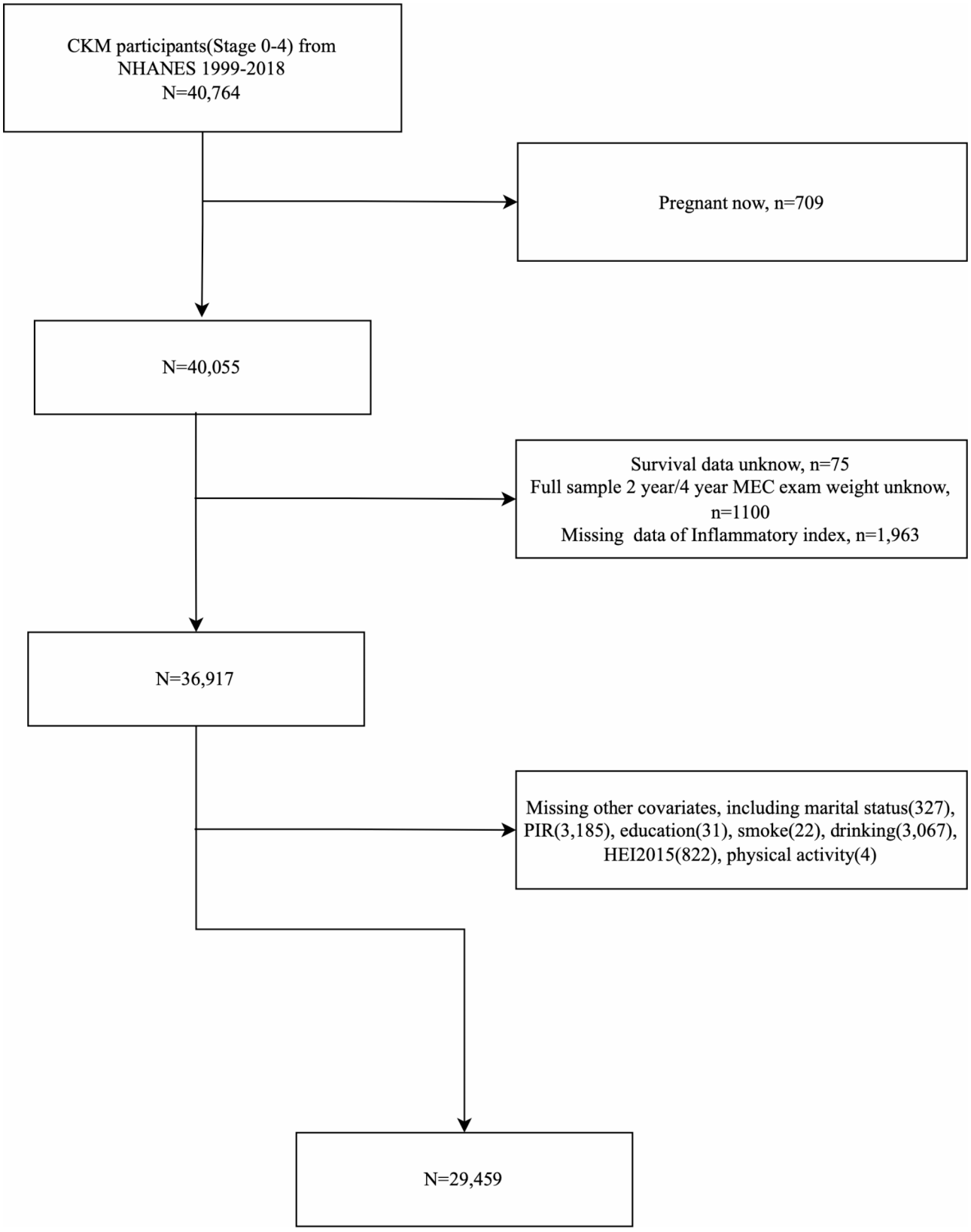

Fig. 1 Flowchart detailing the selection process for eligible participants. CKM, cardiovascular-kidney-metabolic syndrome, MEC, Mobile Examination Center, PIR, family income-to-poverty ratio, HEI2015, Healthy eating index-2015

equivalents, as assessed by the AHA's PREVENT equations [11]; and Stage 4 is marked by clinical manifestations of CVD.

Calculation of inflammatory markers

Morning venous blood samples were drawn at the NHANES MEC after an overnight fast, following NHANES quality assurance and quality control protocols. The inflammatory markers SII, pan-immune-inflammation value (PIV), SIRI, neutrophil-percentage-to-albumin ratio (NPAR), platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and albumin-to-globulin ratio (AGR) were calculated (Supplemental Table S2).

Assessment of covariates

Covariates were chosen based on established knowledge of the impact of lifestyle factors on health outcomes. In this study, specific covariates were included for both descriptive and inferential analyses. (1) Self-reported sociodemographic characteristics included age, sex, race/ethnicity, marital status, educational level, PIR, defined as the ratio of self-reported family income to the poverty threshold, and HEI-2015, calculated from a 24-hour dietary recall; (2) Personal behavioral variables included smoking status, drinking habits, and physical activity levels (PA) were detailed in Supplemental Table S3.

Ascertainment of mortality

Mortality data, updated through December 31, 2019, were obtained from the National Death Index, based on death certificate records from the National Center for Health Statistics. The primary outcome and the secondary outcome were all-cause mortality and CVD mortality. CVD mortality was defined as death due to heart disease or cerebrovascular disease (ICD-10 codes I00–I09, I11, I13, I20–I51, or I60–I69). Follow-up time spanned from the date of interview to either December 31, 2019, or the date of death, whichever came first.

Statistical analysis

In accordance with NHANES guidelines, the analyses applied sample weights, clustering, and stratification to ensure national representation. New weights were calculated due to the combination of 10 cycles in this study. Baseline characteristics were described across the five CKM stages, with continuous and categorical variables presented as mean ± standard error (SE) and frequency (weighted percentages), respectively. Kaplan-Meier (KM) curves displayed survival probabilities across CKM stages, while time-dependent ROC (timeROC) identified the most effective inflammatory marker. Cox proportional hazards regression models, incorporating restricted cubic splines (RCS) with four knots, were used to evaluate the connection between inflammatory markers and mortality, with the optimal cut-off identified by the inflection point with the highest likelihood for nonlinear relationships. To estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between CKM stage, SIRI, and mortality, we employed weighted multivariable Cox proportional hazards regression models. To explore the joint associations, individuals were grouped by CKM stage and inflammatory marker, and weighted multivariable sensitivity analyses and subgroup analyses were performed.

Statistical analyses were performed using R software version 4.3.1, with two-sided tests applied. A P-value < 0.05 was considered indicative of statistical significance.

Results

Baseline characteristics

The baseline characteristics of the study population, categorized by CKM stages, are presented in Table 1. Among the 29,459 participants (weighted population: 124,806,273; weighted mean [SE] age: 49.83 ± 0.21 years; 49.47% male), significant differences were observed across the five CKM stages, including age, sex, education level, marital status, smoking and drinking status, physical activity, PIR, albumin, and systemic inflammatory markers such as SIRI (all $P < 0.0001$, Table 1 and Supplemental Table S4). Generally, participants in the more advanced stages of CKM syndrome were more likely to be older, male, with lower PIR, higher SIRI, and were more likely to be physically inactive and current smokers. Mortality rates also increased with CKM stage progression. All-cause mortality occurred in 13.78% of participants, and CVD mortality in 4.33%. Both mortality rates increased progressively from Stage 0 to Stage 4. Specifically, all-cause mortality was lowest in Stage 0 at 2.80% and highest in Stage 4 at 41.14%, and CVD was lowest in Stage 0 at 0.41% and highest in Stage 4 at 16.64% (both $P < 0.0001$).

Association between CKM stage or SIRI with all-cause and CVD mortality

Over a mean follow-up period of 109 months (interquartile range: 61–162 months), 5,583 deaths occurred. As shown in Fig. 2A and B, the KM survival curves demostrate significant differences in all-cause and CVD mortality across the five CKM stages (both $P < 0.0001$). All-cause and CVD mortality was similarly elevated in the advanced stages (Stages 3 and 4). Notably, the mortality rates in CKM Stages 3 and 4 were comparable. KM survival curves for early (stages 0–2) and advanced (stages 3–4) CKM groups showed significant differences in all-cause and CVD mortality (Fig. S1, both $P < 0.0001$).

The AUC of SIRI was superior to that of other inflammatory markers in predicting both overall and

Table 1 Baseline characteristics of the study population according to different stages of CKM syndrome

Characteristics	CKM syndrome stages						*P*
	Total	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	
Unweighted number	29,459	1,897	3,980	17,309	2,857	3,416	
Weighted number	124,806,273	10,470,275	19,262,442	75,167,736	8,307,830	11,597,990	
Age, year	49.83 ± 0.21	35.91 ± 0.37	40.63 ± 0.36	49.46 ± 0.19	70.70 ± 0.22	65.19 ± 0.33	< 0.0001
PIR	3.01 ± 0.03	3.19 ± 0.06	3.14 ± 0.04	3.05 ± 0.03	2.71 ± 0.04	2.63 ± 0.05	< 0.0001
HEI2015	50.36 ± 0.18	51.22 ± 0.54	49.76 ± 0.29	50.00 ± 0.19	52.32 ± 0.37	51.47 ± 0.33	< 0.0001
Albumin, g/dL	4.26 ± 0.00	4.39 ± 0.01	4.27 ± 0.01	4.26 ± 0.01	4.17 ± 0.01	4.15 ± 0.01	< 0.0001
SIRI	1.27 ± 0.01	1.04 ± 0.02	1.09 ± 0.02	1.27 ± 0.01	1.57 ± 0.03	1.62 ± 0.03	< 0.0001
Sex, *n* (weighted %)							< 0.0001
Male	14,849(49.47)	785(38.44)	1,978(50.56)	8,361(49.22)	1,725(55.97)	2,000(54.57)	
female	14,610(50.53)	1,112(61.56)	2,002(49.44)	8,948(50.78)	1,132(44.03)	1,416(45.43)	
Race, *n* (weighted %)							< 0.0001
Mexican American	4,963 (7.39)	222(5.16)	755(9.57)	3,165(8.00)	465(4.93)	356(3.63)	
Non-Hispanic Black	5,859(10.04)	297 (7.82)	861(11.53)	3,401(9.87)	629(11.06)	671(9.97)	
Non-Hispanic White	14,180(71.90)	1,013(75.27)	1,689(67.59)	7,996(71.03)	1,443(76.28)	2,039(78.52)	
Other Hispanic	2,243(4.90)	116(4.38)	363(6.20)	1,394(5.11)	186(3.55)	184(2.79)	
Other Race	2,214(5.77)	249(7.38)	312(5.11)	1,353(6.00)	134(4.18)	166(5.08)	
Marital Status, *n* (weighted %)							< 0.0001
non-single	17,894(64.86)	1,043(59.42)	2,449(65.44)	10,734(66.18)	1,720(62.85)	1,948(61.73)	
single	11,565(35.14)	854(40.58)	1,531(34.57)	6,575(33.83)	1,137(37.15)	1,468(38.27)	
Education, *n* (weighted %)							< 0.0001
< high school	3,533(5.76)	85(2.62)	289(3.83)	2,007(5.40)	599(11.68)	553(9.86)	
high school	11,338(36.12)	577(27.38)	1,389(31.39)	6,747(36.83)	1,164(42.26)	1,461(42.92)	
> high school	14,588(58.12)	1,235(70.00)	2,302(64.78)	8,555(57.77)	1,094(46.07)	1,402(47.23)	
Smoke, *n* (weighted %)							< 0.0001
never	15,221(51.71)	1,177(60.48)	2,368(58.19)	9,482(53.37)	884(29.66)	1,310(38.07)	
former	8,177(27.42)	274(15.87)	798(22.56)	4,121(24.92)	1,521(55.61)	1,463(41.85)	
now	6,061(20.87)	446(23.65)	814(19.25)	3,706(21.70)	452(14.73)	643(20.08)	
Drinking, *n* (weighted %)							< 0.0001
never	4,164(11.23)	248(10.74)	453(9.47)	2,542(11.21)	418(13.71)	503(13.07)	
former	5,815(16.31)	146(6.75)	480(10.80)	3,114(15.32)	915(28.89)	1,160(31.46)	
mild	9,934(36.58)	684(37.19)	1,387(36.59)	5,644(35.91)	1051(41.83)	1,168(36.61)	
moderate	4,150(16.31)	381(21.63)	710(19.44)	2,547(16.80)	245(8.76)	267(8.51)	
heavy	5,396(19.58)	438(23.69)	950(23.71)	3,462(20.77)	228(6.80)	318(10.42)	
Physical activity, *n* (weighted %)							< 0.0001
no	15,656(47.44)	855(41.30)	1,879(43.46)	9,061(46.73)	1,751(56.80)	2,110(57.43)	
moderate	7,302(27.13)	454(25.27)	946(24.97)	4,306(27.71)	743(29.54)	853(26.86)	
vigorous	6,501(25.44)	588(33.43)	1,155(31.57)	3,942(25.56)	363(13.66)	453(15.71)	
All-caused death, *n* (weighted %)							< 0.0001
no	23,876(86.22)	1,831(97.20)	3,798(96.93)	14,804(89.19)	1,630(58.86)	1,813(58.86)	
yes	5,583(13.78)	66(2.80)	182(3.07)	2,505(10.81)	1,227(41.14)	1,603(41.14)	
CVD-caused death, *n* (weighted %)							< 0.0001
no	27,616(95.67)	1,886(99.60)	3,938(99.21)	16,575(97.12)	2,461(86.57)	2,756(83.36)	
yes	1,843(4.33)	11(0.41)	42(0.79)	734(2.88)	396(13.43)	660(16.64)	

PIR, poverty-income ratio; HEI2015, Healthy Eating Index-2015; SIRI, systemic inflammation response index; CVD, cardiovascular disease

CVD-specific survival, as shown in Fig. 3A and B. RCS curves were employed to assess the non-linear relationship between SIRI and both all-cause and cardiovascular mortality, adjusting for confounding factors such as age, race, gender, marital status, PIR, smoking, drinking, education, physical activity, and HEI-2015 (Fig. 3C and D). The analysis revealed a U-shaped risk trajectory (all *P*-values for nonlinearity < 0.0001). The full adjusted RCS curves indicated that a SIRI value of 0.81 corresponded to the lowest risk of all-cause mortality and was thus selected as the cut-off point. Using the piecewise regression models, the inflection point for all-cause and CVD mortality was confirmed to be 0.81 (Table 2). The risk of all-cause mortality was inversely linked with

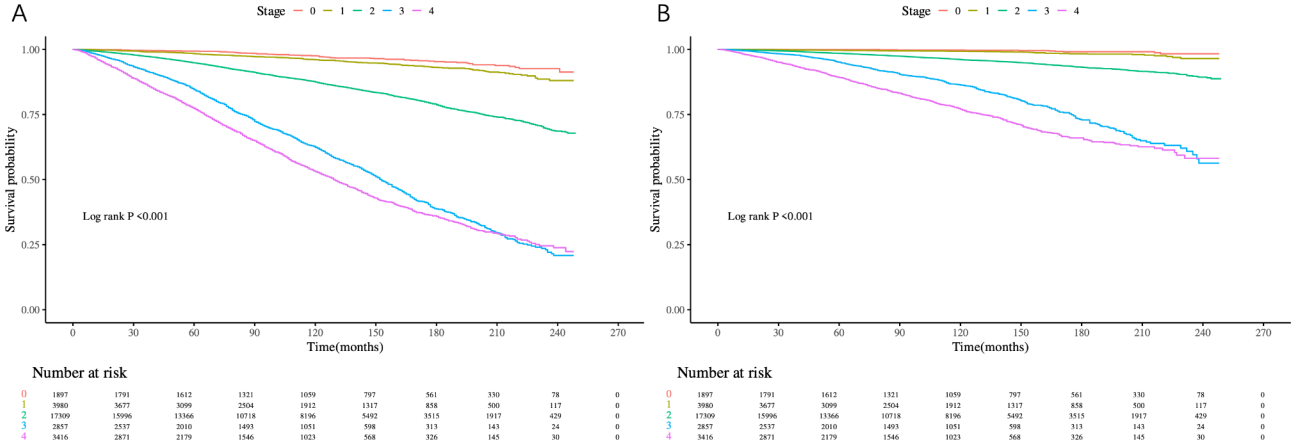

Fig. 2 Kaplan-Meier curves displayed for all-cause mortality (**A**) and CVD mortality (**B**) across five CKM stages

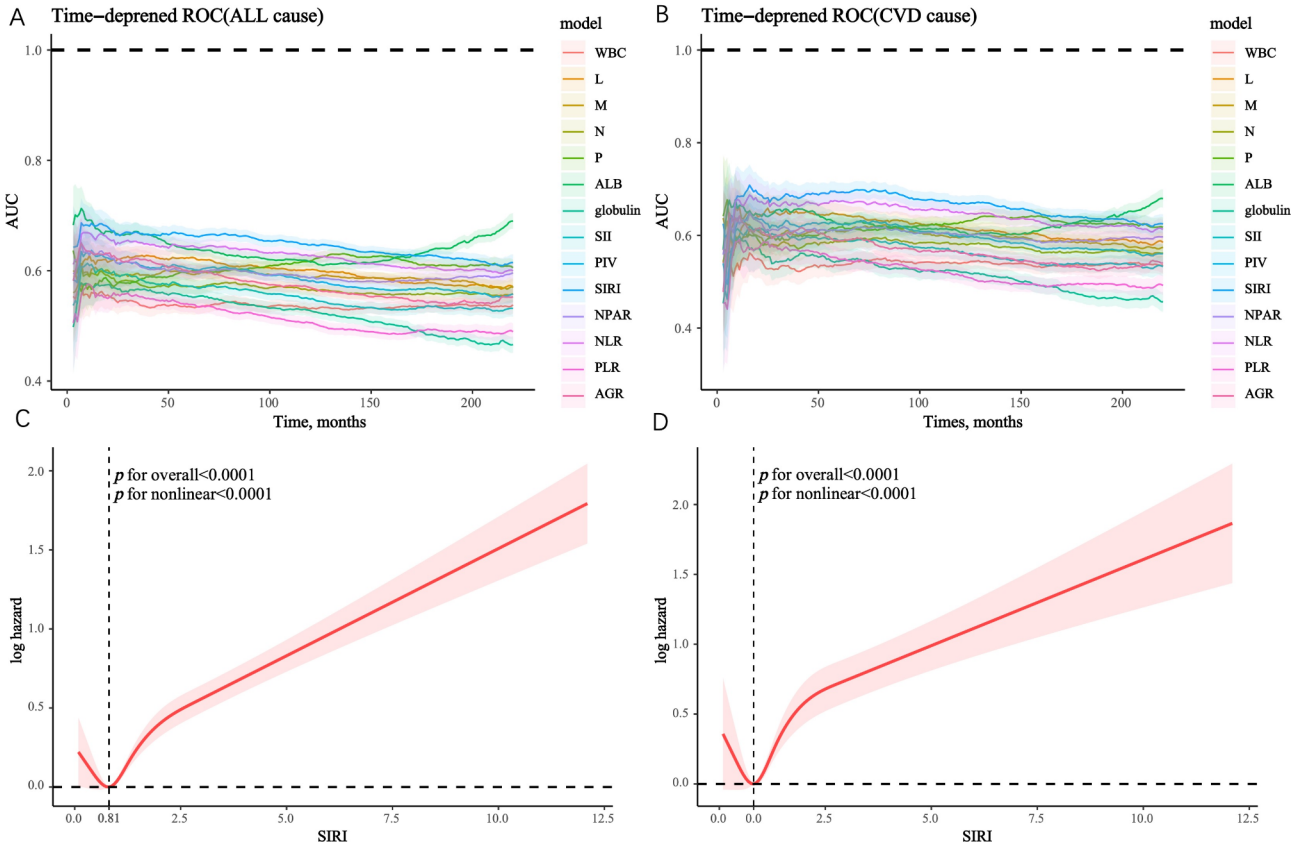

Fig. 3 The time-dependent ROC of inflammation markers for diagnosing all-cause mortality (**A**) and CVD mortality (**B**). Association between SIRI and all-cause (**C**) and CVD mortality (**D**). Adjusted for age, sex, race, marital, family income-to-poverty ratio, education, physical activity, smoke, drinking, and Healthy eating index-2015. SII, systemic immune-inflammation index; PIV, pan-immune-inflammation value; SIRI, systemic inflammatory response index; NPAR, neutrophil-percentage-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; AGR, albumin-to-globulin ratio

SIRI up to an inflection point of 0.81 (HR 0.578, 95% CI: 0.360–0.927, $P=0.023$). Beyond 0.81, SIRI showed a positive association with both all-cause (HR 1.179, 95% CI: 1.139–1.220, $P<0.0001$) and CVD mortality (HR 1.181, 95% CI: 1.127–1.238, $P<0.0001$).

Three Cox regression models were used to evaluate the correlation between CKM stage or SIRI with all-cause and CVD mortality. Participants in CKM Stage 4 or with SIRI > 0.81 have higher risk of all-cause and CVD mortality (Table 3). After adjustment, individuals with CKM Stage 4 had significantly increased risks of all-cause and

Table 2 Threshold effect analysis of the SIRI on all-cause and CVD mortality

	Adjusted HR (95% CI)	*P*
All-cause mortality		
SIRI		
<=0.81	0.578(0.360,0.927)	0.023
> 0.81	1.179(1.139,1.220)	< 0.0001
CVD mortality		
SIRI		
<=0.81	0.590(0.259,1.343)	0.208
> 0.81	1.181(1.127,1.238)	< 0.0001

Adjusted for age, sex, race, marital status, PIR, education, physical activity, smoking, drinking, and HEI-2015

CVD mortality compared to those with CKM Stage 0, with HRs of 2.548 (95% CI: 1.877–3.457) and 5.670 (95% CI: 2.978–10.794), respectively. Additionally, the HRs for all-cause and CVD mortality significantly increased as CKM stage advanced (*P* for trend < 0.001). In addition, compared with individuals with SIRI ≤ 0.81, those with SIRI > 0.81 had significantly higher risks of all-cause and CVD mortality, with HRs of 1.243 (95% CI, 1.141–1.353) and 1.326 (95% CI, 1.124–1.563), respectively.

Joint association of CKM stage and SIRI with all-cause and CVD mortality

In the joint analyses, participant with both CKM Stage 3 or 4 and SIRI > 0.81 had the highest risk of all-cause and CVD-specific mortality (Table 4; Fig. 4). Specifically, individuals in CKM Stage 3 or 4 with SIRI > 0.81 had a 1.840-fold increased risk of all-cause mortality (95% CI, 1.653–2.049) and a 2.499-fold increased risk of CVD-related mortality (95% CI, 2.002–3.119) compared to those in CKM Stage 0–2 with SIRI ≤ 0.81. Moreover, individuals with CKM Stage 3–4 and SIRI ≤ 0.81 had a HR of 1.526 (95% CI, 1.312–1.775) for all-cause mortality and 1.919 (95% CI, 1.482–2.486) for CVD mortality. These findings highlight the compounded risk in advanced CKM stages with elevated SIRI. The results remained consistent in sensitivity analyses, including when CKM was divided into 3 groups, or when excluding participants who died within the first 24 months (Supplemental Table S5 and Supplemental Table S6).

Subgroup analysis

Subgroup analyses were conducted to assess whether the joint effect of CKM stage and SIRI on all-cause and CVD mortality was influenced by baseline or demographic factors, including sex, age (<60 and ≥60 years),

Table 3 Association of CKM stage or SIRI with all-cause and CVD-specific mortality

Mortality outcome	Death/No.	Weighted death (%)	Hazard ratio (95% CI)		
			Model 1	Model 2	Model 3
All causes					
CKM stage					
CKM Stage 0	66/1897	293,069(2.80)	1 [reference]	1 [reference]	1 [reference]
CKM Stage 1	182/3980	591,710(3.07)	1.326(0.935, 1.881)	0.885(0.623,1.256)	0.848(0.598,1.203)
CKM Stage 2	2505/17,309	8,127,337(10.81)	4.621(3.467, 6.159)	1.540(1.147,2.067)	1.447(1.092,1.918)
CKM Stage 3	1227/2857	3,417,821(41.14)	23.390(17.268,31.682)	1.895(1.394,2.576)	1.616(1.197,2.183)
CKM Stage 4	1603/3416	4,770,984(41.14)	24.104(17.577,33.054)	2.967(2.172,4.053)	2.548(1.877,3.457)
P for trend			< 0.0001	< 0.0001	< 0.0001
SIRI					
≤ 0.81	1181/9834	3,422,842(8.87)	1 [reference]	1 [reference]	1 [reference]
> 0.81	4402/19,625	13,778,080(15.98)	1.881(1.725,2.052)	1.293(1.194,1.401)	1.243(1.141,1.353)
CVD					
CKM stage					
CKM Stage 0	11/1897	42,400(0.40)	1 [reference]	1 [reference]	1 [reference]
CKM Stage 1	42/3980	152,093(0.79)	2.365(0.940, 5.949)	1.478(0.668, 3.270)	1.392(0.610, 3.179)
CKM Stage 2	734/17,309	2,167,421(2.88)	8.555(4.087, 17.906)	2.442(1.294, 4.605)	2.275(1.176, 4.400)
CKM Stage 3	396/2857	1,115,730(13.43)	53.158(24.124,117.135)	3.218(1.606, 6.451)	2.842(1.385, 5.831)
CKM Stage 4	660/3416	1,929,776(16.64)	67.926(33.126,139.287)	6.451(3.441,12.096)	5.670(2.978,10.794)
P for trend			< 0.0001	< 0.0001	< 0.0001
SIRI					
≤ 0.81	352/9834	978,534(2.53)	1 [reference]	1 [reference]	1 [reference]
> 0.81	1491/19,625	4,428,886(5.14)	2.113(1.804,2.475)	1.358(1.153,1.600)	1.326(1.124,1.563)

Model 1: No adjustments

Model 2: Adjusted for age, sex, race, marital, PIR, and education

Model 3: Adjusted for age, sex, race, marital, PIR, education, physical activity, smoke, drinking, and HEI-2015

Table 4 Joint association between CKM stage or SIRI with all-cause and CVD-specific mortality

Mortality outcome	SIRI	Death/No.	Weighted death (%)	Hazard ratio (95% CI)		
				Model 1	Model 2	Model 3
All causes						
CKM stage 0–2	≤ 0.81	680/8436	2,067,449(5.95)	1 [reference]	1 [reference]	1 [reference]
	> 0.81	2073/14,750	6,944,667 (9.90)	1.673(1.510, 1.854)	1.321(1.194,1.462)	1.248(1.124,1.387)
CKM stage 3–4	≤ 0.81	501/1398	1,355,393(35.08)	7.256(6.236, 8.443)	1.767(1.531,2.039)	1.526(1.312,1.775)
	> 0.81	2329/4875	6,833,413(42.60)	10.183(9.077,11.424)	2.104(1.900,2.331)	1.840(1.653,2.049)
***P*for trend**				< 0.0001	< 0.0001	< 0.0001
CVD			517,011(1.49)			
CKM stage 0–2	≤ 0.81	180/8436	1,844,902(2.63)	1 [reference]	1 [reference]	1 [reference]
	> 0.81	607/14,750	461,522(11.94)	1.775(1.447, 2.177)	1.341(1.088,1.651)	1.302(1.054,1.608)
CKM stage 3–4	≤ 0.81	172/1398	2,583,984(16.11)	9.912(7.759,12.662)	2.076(1.602,2.691)	1.919(1.482,2.486)
	> 0.81	884/4875	517,011(1.49)	15.449(12.677,18.827)	2.695(2.166,3.354)	2.499(2.002,3.119)
***P*for trend**				< 0.0001	< 0.0001	< 0.0001

Model 1: No adjustments

Model 2: Adjusted for age, sex, race, marital, PIR, and education

Model 3: Adjusted for age, sex, race, marital, PIR, education, physical activity, smoke, drinking, and HEI-2015

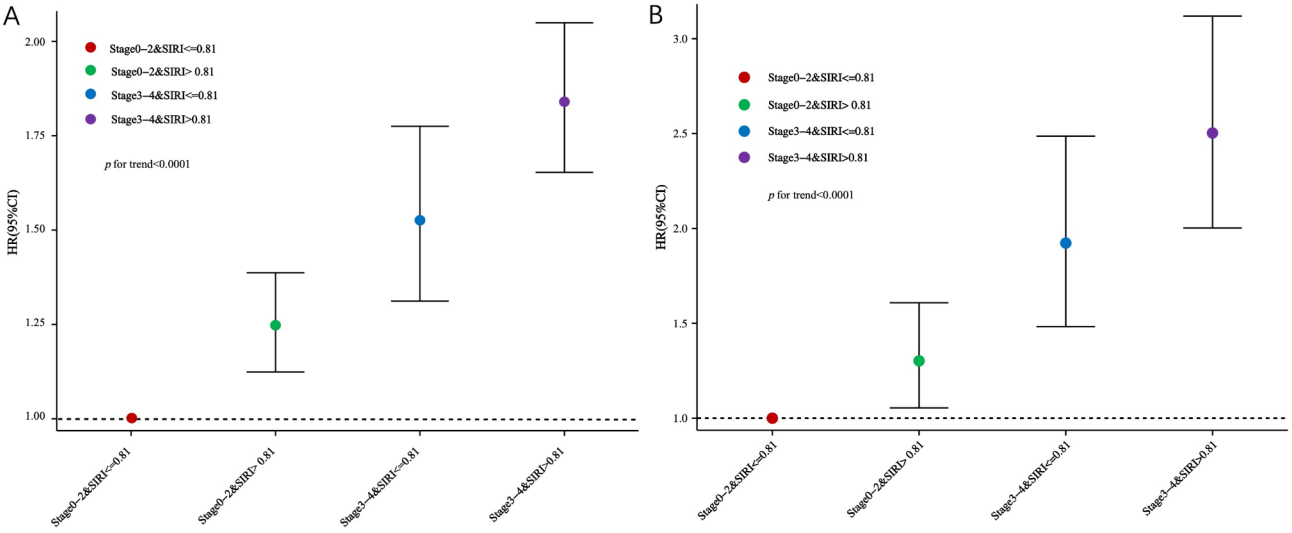

Fig. 4 Joint association of CKM stages and SIRI value with all-cause mortality and CVD mortality

smoking, drinking, and physical activity (Supplemental Tables S7 and S8). Age and smoking significantly modified this association (*P* for interaction < 0.05), while consistent results were observed across the other subgroups. Notably, the impact of CKM stage and SIRI on both all-cause and CVD mortality was stronger in adults under 60 compared to those aged 60 and older (*P* for interaction < 0.0001). In adults aged 60 and older, those with CKM Stage 3 or 4 and SIRI > 0.81 had higher risks of all-cause and CVD mortality than those with CKM Stage 0, 1, or 2 and SIRI ≤ 0.81, with HRs of 1.617 (95% CI: 1.442–1.814) and 2.083 (95% CI: 1.649–2.630), respectively. Moreover, in adults under 60, individuals with CKM Stage 3 or 4 and SIRI > 0.81 also exhibited significantly higher risks of all-cause and CVD mortality compared to those with CKM Stage 0, 1, or 2 and SIRI ≤ 0.81, with HRs of 3.289 (95% CI: 2.577–4.197) and 6.123 (95% CI: 3.942–9.510), respectively.

Discussion

In this extensive cohort analysis, drawing on NHANES data from 1999 to 2018, we examined both the independent and combined associations between CKM syndrome stages and systemic inflammation, as measured by the SIRI, with all-cause and CVD mortality. Our findings demonstrate that advanced CKM stages and elevated SIRI are each independently associated with increased risks of all-cause and CVD mortality. Notably, individuals with both advanced CKM stages (Stages 3 or 4) and high SIRI (> 0.81) exhibited the highest mortality risks. This effect was particularly pronounced in adults under 60 years of age. These results highlight the potential value of

integrating inflammatory markers such as SIRI into CKM syndrome risk stratification models, offering clinicians more precise tools for identifying high-risk individuals and optimizing interventions.

Previous studies have emphasized the individual and collective impact of CVD, diabetes, obesity, and CKD on mortality rates in the general population [3, 12–14]. As key components of CKM syndrome, these conditions not only independently increase mortality risk but also exert a compounded burden when they coexist. For instance, the coexistence of diabetes and CKD significantly increases mortality risk compared to either condition alone. A study using NHANES data reported that individuals with both type 2 diabetes and CKD had a 10-year cumulative all-cause mortality rate of 31.1%, over four times higher than the 7.7% observed in those without either condition. In contrast, individuals with diabetes but no CKD had a mortality rate of 11.5%, highlighting the critical role of CKD in amplifying mortality risk among people with diabetes [15]. Similarly, diabetes has a well-established adverse impact on long-term mortality, and this effect is further heightened when combined with CVD and CKD. A large cohort study involving type 2 diabetes patients found that those with coexisting CKD and CVD had nearly five times the risk of all-cause mortality compared to those without complications [16]. These findings highlight the synergistic effects inherent in CKM syndrome, where the interplay of metabolic, cardiovascular, and renal dysfunction accelerates mortality risk. Our study contributes to this body of evidence by specifically quantifying the mortality risk across CKM stages in a nationally representative United States population. In our study, we observed a stepwise increase in mortality risk with advancing CKM stages, underscoring the predictive value of CKM syndrome staging for early identification of high-risk individuals. This aligns with previous research indicating that CKM staging is a useful tool for risk stratification and early intervention [7]. The higher mortality observed in individuals at advanced CKM stages highlights the urgent need for early interventions aimed at halting disease progression, offering opportunities to reduce overall mortality and improve long-term patient outcomes.

Systemic inflammation has been consistently linked to poor survival outcomes across various studies, including our own. It is increasingly recognized as a key driver of cardiovascular and all-cause mortality, particularly among individuals with metabolic disorders and renal dysfunctions [17]. For instance, a large population-based study found that elevated low-grade inflammation was linked to a 1.44 times higher risk of overall mortality (95% CI: 1.17–1.77), particularly among individuals with cardiovascular disease and type 2 diabetes [18]. Among the various inflammatory markers, SIRI has gained attention as a comprehensive indicator of chronic inflammation, linked to multiple conditions such as metabolic disorders, cancer, and stroke [19–21]. Notably, a meta-analysis of 14 cohort studies indicated that in patients with acute ischemic stroke, elevated SIRI was associated with a 1.57-fold increase in the likelihood of poorer short-term functional outcomes, highlighting its prognostic value [22]. Similar associations have been observed in patients with diabetes, CKD, and heart failure, reinforcing the potential role of SIRI as a robust predictor of all-cause and cardiovascular mortality [10, 23, 24]. Our findings are consistent with these studies, further supporting the significance of systemic inflammation, as measured by SIRI, in predicting mortality among individuals with CKM syndrome. Recognizing the prognostic value of SIRI may aid clinicians in identifying high-risk patients and implementing targeted interventions to mitigate inflammation and reduce mortality risk.

The observed joint effect of SIRI and CKM stages on mortality risk may be explained by the interconnected mechanisms of systemic inflammation and oxidative stress, which are central to the pathophysiology of cardiovascular, kidney, and metabolic diseases, the key components of CKM syndrome [5, 17]. Dysfunctional visceral adipose tissue secretes proinflammatory cytokines, contributing to insulin resistance, endothelial dysfunction, and a pro-atherogenic state, thereby perpetuating a vicious cycle that accelerates CKM progression [25–27]. Elevated SIRI is indicative of heightened systemic inflammation, characterized by elevated neutrophils and monocytes alongside decreased lymphocytes, which points to immune dysregulation. This inflammatory milieu promotes atherosclerosis, renal fibrosis, and metabolic instability, further advancing CKM stages [5]. Additionally, oxidative stress amplifies vascular and renal damage through reactive oxygen species (ROS), which further contributes to CKM progression [28]. In patients with advanced CKM stages, significant metabolic derangements, vascular injury, or renal impairment are already present. The coexistence of elevated systemic inflammation may synergistically amplify these pathogenic processes, increasing mortality risk. Moreover, elevated SIRI in the context of advanced CKM syndrome may also reflect more extensive systemic damage, including fibrosis and impaired cellular repair mechanisms. Our findings suggest that individuals with both advanced CKM stages and elevated SIRI are subject to compounded mortality risks potentially through shared mechanisms of chronic inflammation, endothelial dysfunction, and metabolic dysregulation. Understanding this combined inflammatory-metabolic pathway is vital for developing targeted interventions to mitigate the mortality risks.

Interestingly, subgroup analysis revealed a stronger joint effect of CKM stages and SIRI on mortality risk in individuals younger than 60 years. Several factors may explain this finding. First, younger individuals with advanced CKM

syndrome may present with more aggressive disease phenotypes or genetic predispositions, leading to earlier onset and rapid progression of metabolic, cardiovascular, and renal dysfunction [29]. Second, early-onset conditions such as diabetes and hypertension are associated with an increased risk of adverse outcomes [30, 31]. Additionally, lifestyle factors common among younger adults, such as sedentary behavior, unhealthy diets, obesity, smoking, and alcohol consumption, may further exacerbate mortality risk [32]. Furthermore, younger patients are more likely to overlook symptoms in the early stages of the disease and fail to receive adequate intervention, despite these stages being critical periods for the accumulation of inflammatory and metabolic abnormalities. Recognizing and addressing these risk factors in younger adults is essential to effectively reducing long-term health risks.

This study has several limitations that should be acknowledged. First, as an observational study using NHANES data, the findings are correlational, and causal inferences cannot be established between CKM stages, SIRI, and mortality. Second, some variables such as physical activity, smoking, and dietary habits are based on self-reported data, which introduces the risk of recall bias and inaccuracies. Third, due to the unavailability of CRP data in certain years of the study period, we were unable to include CRP as an inflammatory marker in the analysis. Instead, we relied on SIRI, which was derived from routine blood tests available throughout the study period. Additionally, neutrophil counts, a component of SIRI, may be influenced by medications such as steroids. However, as our study included the general population and the number of individuals on such medications was relatively small, we did not include medication use as a confounding factor. The cross-sectional nature of NHANES data further limits the ability to assess changes in CKM stages, inflammation levels, or health behaviors over time, making it difficult to capture disease progression. Despite adjustments for multiple covariates, residual confounding from unaccounted factors, such as genetic predispositions, medication use, or socioeconomic status, may still persist. Moreover, although NHANES provides a representative sample of the U.S. population, the generalizability of the findings to other populations may be limited. Lastly, while SIRI serves as a valuable marker of inflammation, it may not fully capture the complexity of systemic inflammation, and additional biomarkers could provide a more comprehensive understanding.

Conclusions

In conclusion, this large, nationally representative study of the adult population in the United States found that the combination of advanced CKM stages and elevated SIRI was associated with increased all-cause and cardiovascular mortality, with a particularly pronounced effect in younger adults under 60 years of age. These findings have important public health implications, particularly for the management of inflammation and CKM progression in high-risk individuals. By further exploring these relationships, healthcare providers and researchers may devise targeted interventions and approaches to enhance long-term outcomes for CKM syndrome patients.

Abbreviations

CKM	Cardiovascular-kidney-metabolic syndrome
AHA	American Heart Association
CVD	Cardiovascular disease
NHANES	National Health and Nutrition Examination Survey
SIRI	Systemic inflammatory response index
CKD	Chronic kidney disease
MEC	Mobile examination center
HEI-2015	Healthy Eating Index-2015
SII	Systemic immune-inflammation index
PIV	Pan-immune-inflammation value
NPAR	Neutrophil-percentage-to-albumin ratio
PLR	Platelet-to-lymphocyte ratio
NLR	Neutrophil-to-lymphocyte ratio
AGR	Albumin-to-globulin ratio
RCS	Restricted cubic splines

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions

Yifei Cao conceptualized the study, performed the formal analysis, conducted the primary data analysis, interpreted the results, and drafted the original manuscript. Wenfeng Wang curated the data, contributed to the interpretation of results, and drafted the original manuscript. Shidong Xie contributed to the interpretation of results, assisted in data analysis, and drafted the original manuscript. Yanfang Xu conceptualized the study, supervised the analysis, critically reviewed and revised the manuscript, and acquired funding for the study. Zishan Lin conceptualized the study, supervised the research process, critically reviewed and revised the manuscript, and acquired funding for the study. All authors have read and approved the final manuscript.

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Data availability

The data in the current study can be found on the website https://www.cdc.gov/nchs/nhanes/.

Declarations

Ethics approval and consent to participate

Ethics approval and consent to participate The National Center for Health Statistics and Ethics Review Board approved the protocol for NHANES, and all participants provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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