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Remnant cholesterol inflammatory index and its association with all-cause and cause-specific mortality in middle-aged and elderly populations: evidence from US and Chinese national population surveys

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Abstract

Background The remnant cholesterol inflammatory index (RCII) is a novel metric that combines remnant cholesterol and high-sensitivity C-reactive protein, reflecting the metabolic and inflammatory risk. This study investigates the association between RCII and long-term risks of all-cause and cause-specific mortality in middle-aged and elderly populations in the US and China.

Method We analyzed data from the National Health and Nutrition Examination Survey (NHANES) and the China Health and Retirement Longitudinal Study (CHARLS), including 7,565 and 12,932 participants aged 45 years and older, respectively. The participants were categorized into quartiles based on natural log-transformed RCII (lnRCII) values. Kaplan–Meier survival analysis, Cox proportional hazards models, restricted cubic splines (RCS) and mediation analysis were used to examine the relationship between lnRCII and mortality outcomes, adjusting for potential covariates.

Result The mean age of the participants was 59.90 ± 10.44 years (NHANES) and 58.64 ± 9.78 years (CHARLS), with 53.28% and 52.50% female, respectively. Kaplan–Meier survival analysis showed that higher lnRCII quartiles (≥ 0.79 in NHANES, ≥ -0.13 in CHARLS) were significantly associated with increased all-cause mortality risk ($p < 0.001$). Each standard deviation (SD) increase in lnRCII corresponded to a higher risk of all-cause mortality, and the hazard ratios (HRs) and 95% confidence interval (CI) were 1.29 (95% CI: 1.21–1.36) in NHANES and 1.26 (95% CI: 1.15–1.38) in CHARLS. In NHANES, lnRCII was also associated with elevated risks of cardiovascular mortality (HR = 1.21, 95% CI: 1.08–1.35) and cancer mortality (HR = 1.30, 95% CI: 1.09–1.55). RCS analysis indicated a J-shaped relationship between lnRCII and both all-cause and cardiovascular mortality, and a linear association with cancer mortality. Mediation analysis showed that systolic blood pressure and fasting plasma glucose partially mediated these associations. Subgroup analyses suggested a stronger association between lnRCII and all-cause mortality in middle-aged US participants (p for interaction = 0.010).

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Conclusions Elevated RCII levels are significantly associated with increased all-cause mortality risk middle-aged and elderly populations in both the US and China. In the US population, RCII is also associated with increased risks of cardiovascular and cancer mortality. By integrating metabolic and inflammatory risk factors, RCII may serve as a valuable tool for mortality risk stratification and clinical decision-making.

Keywords Remnant Cholesterol Inflammatory Index, All-Cause Mortality, Cause specific Mortality, Metabolic dysfunction, Inflammation

Introduction

The global rise in aging population presents growing public health challenges, accompanied by an increasing burden of chronic diseases such as cardiovascular disease (CVD) and cancer [1, 2]. CVD remains the leading cause of death worldwide, with ischemic heart disease along responsible for nearly 9 million deaths in 2021 [3]. Key risk factors, including hypertension, dyslipidemia, smoking, and chronic inflammation, contribute to the high incidence and mortality of CVD [4–7]. Cancer is also a major public health concern, with lung cancer along accounting for 2.2 million deaths globally in 2021 [3]. In both CVD and cancer, clinical outcomes are closely influenced by chronic inflammation and metabolic disorders such as obesity and diabetes [8–10]. Early identification and management of these risk factors are essential for reducing the mortality in aging population.

Remnant cholesterol (RC), calculated as the difference between total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), is emerging as a significant marker of cardiovascular risk [11]. RC primarily consists of triglyceride (TG) rich lipoproteins, such as very low-density and intermediate-density lipoproteins [12]. Research indicates that RC contributes to atherosclerosis and cardiovascular events [11, 13, 14], and is also associated with adverse health outcomes such as cancer, stroke, liver disease and depression [15–18]. Its pathogenic effects are thought to be driven by mechanisms including inflammation, lipid accumulation in arterial walls, and oxidative stress [19].

Inflammation is also a critical factor in the progression of both CVD and cancer. C reactive protein (CRP) and high sensitivity CRP (hsCRP) are well-established inflammatory markers associated with increased risks of heart failure, coronary heart disease (CHD), stroke, and various cancers [20–22]. Recent studies suggest that integrating lipid metabolism and inflammation markers could enhance the prediction ability of cardiovascular risk models [23, 24]. Additionally, dysregulated lipid metabolism may affect tumor immunity through mechanisms such as macrophage polarization, thereby impacting cancer prognosis [25, 26].

The remnant cholesterol inflammatory index (RCII) is a novel biomarker that combines RC and hsCRP, reflecting both metabolic and inflammatory risks. While previous research has linked RCII to stroke risk, its association with all-cause and cause-specific mortality remains underexplored [27]. This study aims to evaluate the risk stratification value of RCII for all-cause and cause-specific mortality in middle-aged and elderly populations in the US and China, using data from the National Health and Nutrition Examination Survey (NHANES) and the China Health and Retirement Longitudinal Study (CHARLS).

Method

Study design and population

This study utilized data from two nationally representative cohorts: NHANES (https://www.cdc.gov/nchs/nhanes/index.htm) in the US, and CHRALS (https://charls.pku.edu.cn) in China. Both surveys assess the health, nutritional and socioeconomic status of US or Chinese adults, and adhere to the STROBE guidelines for observational research.

For NHANES, we included data from the 1999–2010 cycles, which provided measurements for TC, HDL-C, LDL-C, and CRP, enabling RCII calculation. The 2011–2014 cycles lacked both CRP and hsCRP data and were therefore excluded. Although the 2015–2018 cycles used hsCRP, the inconsistency in assay type, shorter follow-up (median 36 months), and fewer endpoint events limited their comparability and statistical power. Thus, only the 1999–2010 data were analyzed. Data after 2018 did not include mortality information and were also excluded.

For CHARLS, data from Wave 1 (2011) and Wave 3 (2015) were used, the only waves in which blood samples were collected for laboratory testing, including TC, HDL-C, LDL-C, and hsCRP. Other waves were excluded due to the absence of blood sample collection.

Participants were excluded if they were younger than 45 years or had missing data for TC, HDL-C, LDL-C, CRP/hsCRP, or mortality status (Fig. 1). The final analysis included 7,565 NHANES participants and 12,932 CHARLS participants.

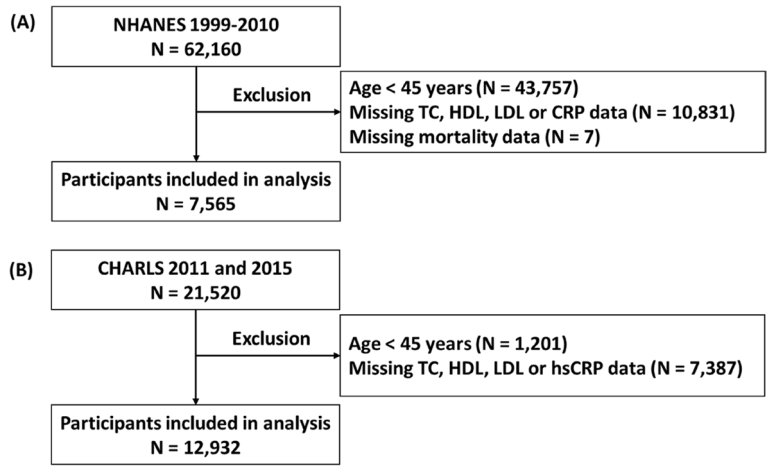

Fig. 1 Flowchart of participants inclusion and exclusion from NHANES (**A**) and CHALRS (**B**)

Calculation of RC and RCII

RC was calculated as: RC (mg/dL) = TC—(HDL-C + LDL-C). As reported by Chen et al., hsCRP (mg/L) was used for the RCII calculation in the CHARLS cohort: RCII = RC * hsCRP (mg/L)/10 [27]. In the NHANES cohort, where CRP (mg/dL) was used, RCII was calculated as: RCII = RC * CRP (mg/dL) for NHANES. Due to the skewed distribution of RCII (Figure S1), values were natural log-transformed (lnRCII) for all statistical analyses.

Clinical outcomes

The primary outcome was all-cause mortality. Secondary outcomes included cardiovascular mortality and cancer mortality. Cause-specific mortality data were available only in NHANES through the National Death Index (NDI), with follow-up through December 31, 2019. CHARLS mortality data were available through Wave 5 (2020).

Covariates

Collected covariates included demographic variables (age, sex, race [NHANES only], educational status, marital status, drinking status, smoking status, body mass index [BMI]) and clinical comorbidities (hypertension, diabetes, dyslipidemia). Comorbidity data were obtained through self-reported questionnaires. For NHANES, smoking status was defined as smoked more than 100 cigarettes in their lifetime [28] and drinking status was classified as consuming as least 12 cups of alcohol in the year prior to the survey[29]. For CHARLS, smoking status was determined by the question "Do you smoke?" and drinking status by the question "Did you drink any alcoholic beverages last year?" [27]. BMI was calculated as weight (kg) divided by height (m) squared. Multicollinearity was assessed using variance inflation factors (VIFs), with all VIFs below 5 (Table S1).

Statistical analysis

NHANES data were analyzed using survey weights to account for its complex sampling design, as recommended by the National Center for Health Statistics (NCHS). CHARLS data were analyzed using conventional unweighted methods.

Continuous variables were reported as means with standard deviation (SD) for normally distributed data, or medians with interquartile ranges (IQR) for skewed data. Categorical variables were presented as frequencies and weighted percentages. Group comparisons were conducted using chi-square tests for categorical variables, one-way ANOVA for normally distributed continuous variables, and Kruskal–Wallis tests for skewed data.

Participants were categorized into quartiles based on lnRCII, RC or CRP/hsCRP levels, with the first quartile serving as the reference. Quartile cutoffs were defined as follows:

NHANES

lnRCII: Q1 (< 0.79), Q2 (0.79–1.75), Q3 (1.75–2.67), Q4 (≥ 2.67).

RC: Q1 (< 18), Q2 (18–25), Q3 (25–35), Q4 (≥ 35).

CRP: Q1 (< 0.1), Q2 (0.1–0.23), Q3 (0.23–0.51), Q4 (≥ 0.51).

CHARLS

lnRCII: Q1 (< − 0.13), Q2 (− 0.13–0.80), Q3 (0.80–1.79), Q4 (≥ 1.79).

RC: Q1 (< 12.37), Q2 (12.37–20.88), Q3 (20.88–32.86), Q4 (≥ 32.86).

hsCRP: Q1 (< 0.57), Q2 (0.57–1.07), Q3 (1.07–2.24), Q4 (≥ 2.24).

Survival outcomes were assessed using Kaplan–Meier curves, with log-rank tests comparing survival differences across quartiles. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality outcomes. Models were adjusted as follows:

Model 1: Unadjusted.
Model 2: Adjusted for age, sex, race (NHANES), education, marital status, drinking, and smoking.
Model 3: Further adjusted for hypertension, diabetes, dyslipidemia, BMI.

Proportional hazards assumption was tested using Schoenfeld residuals, and no significant violations were observed ($p > 0.05$). The adjusted HRs from NHANES and CHALRS were combined using meta-analysis. Restricted cubic spline (RCS) models with 4 knots were performed to explore potential nonlinear associations between lnRCII and mortality outcomes, based on Model 3 covariate adjustments. Mediation analysis, conducted with the "mediation" package in R, examined the mediating role of systolic blood pressure (SBP) and fasting plasma glucose (FPG) in the association between lnRCII and mortality outcomes. Subgroup analyses were performed based on age, sex, BMI, hypertension, diabetes, CHD, and cancer status. Sensitivity analyses were conducted by excluding participants with a history of cancer and CHD, respectively. All analyses were conducted using R software (version 4.4.2) and Review Manager (version 5.3).

Results

Baseline characteristics

The study included 7,565 participants from NHANES and 12,932 participants from CHARLS. The mean age was 59.95 ± 10.44 years in NHANES and 58.64 ± 9.78 years in CHARLS, with 53.28% and 52.50% female participants, respectively (Tables 1, 2). The mean lnRCII values were 1.71 ± 1.74 in NHANES and 0.82 ± 1.56 in CHARLS.

In both cohorts, higher lnRCII levels were associated with older age, higher BMI, elevated SBP, and greater likelihood of smoking (all $p < 0.001$). Participants in higher lnRCII quartiles also had a significantly higher prevalence of hypertension, diabetes, dyslipidemia, and stroke ($p < 0.001$). Notably, CHD was more prevalent in higher lnRCII quartiles in CHARLS ($p < 0.001$), but not in NHANES ($p = 0.346$). Conversely, cancer prevalence increased with lnRCII in NHANES ($p < 0.001$), but not in CHARLS ($p = 0.640$). Higher lnRCII was also associated with elevated TG, white blood cell count, uric acid, HbA1c, and FPG (all $p < 0.001$).

Association between lnRCII and Mortality

During a median follow-up of 167 months in NHANES, 2,698 deaths (30.62%) occurred, including 860 (9.39%) from cardiovascular causes and 613 (7.19%) from cancer (Table 1). Kaplan–Meier analysis showed significantly higher all-cause and cause-specific mortality across increasing lnRCII quartiles (log-rank $p < 0.05$; Fig. 2). In CHARLS, 609 deaths (4.71%) occurred over a median follow-up of 108 months, with higher lnRCII quartiles also associated with increased all-cause mortality (log-rank $p < 0.001$).

Cox regression analysis, using the lowest lnRCII quartile (Q1) as the reference (Fig. 3), demonstrated that in NHANES, HRs for all-cause mortality across lnRCII quartiles were: 1.36 (95% CI: 1.13–1.64) for Q2, 1.61 (95% CI: 1.38–1.88) for Q3, and 1.90 (95% CI: 1.62–2.22) for Q4. In CHARLS, HRs were 1.11 (95% CI: 0.86–1.43) for Q2, 1.55 (95% CI: 1.22–1.97) for Q3, and 1.93 (95% CI: 1.54–2.43) for Q4. In NHANES, the highest lnRCII quartile was also associated with increased cardiovascular mortality (HR = 1.91, 95% CI: 1.51–2.42) and cancer mortality (HR = 1.70, 95% CI: 1.19–2.44).

In unadjusted models, each SD increase in lnRCII was linked to elevated risks of all-cause (HR = 1.30, 95% CI: 1.23–1.37), cardiovascular (HR = 1.29, 95% CI: 1.19–1.40), and cancer mortality (HR = 1.22, 95% CI: 1.07–1.40) in NHANES. And in CHARLS, each SD increase in lnRCII was associated with a 36% higher risk of all-cause mortality (HR = 1.36, 95% CI: 1.25–1.47) (Table 3).

Stratification by RC quartiles in NHANES showed significant associations with all-cause (log rank $p < 0.001$) and cancer mortality (log rank $p = 0.010$), but not with cardiovascular mortality (log rank $p = 0.089$). No significant associations were observed in CHARLS (log rank $p = 0.526$ for all-cause mortality). In contrast, CRP/hsCRP quartiles were significantly associated with all-cause and cause-specific mortality in both cohorts (log-rank $p < 0.05$; Figs. 3, S3).

Multivariable Cox regression analysis confirmed that lnRCII remained independently associated with mortality after adjusting for potential covariates (Models 2 and 3). In NHANES, each SD increase in lnRCII was associated with higher risks of all-cause (HR = 1.29, 95% CI: 1.21–1.36), cardiovascular (HR = 1.21, 95% CI: 1.08–1.35), and cancer mortality (HR = 1.30, 95% CI: 1.09–1.55). In CHARLS, the adjusted HR for all-cause mortality per SD increase in lnRCII was 1.26 (95% CI: 1.15–1.38; Table 3). A meta-analysis combining both cohorts showed a 24% increase in all-cause mortality risk per SD increase in lnRCII (HR = 1.28, 95% CI: 1.22–1.34; Figure S4).

Table 1 Baseline characteristics of clinical information from NHANES

	Total ($n = 7,565$)	Q1 ($n = 1,770$)	Q2 ($n = 1,885$)	Q3 ($n = 1,933$)	Q4 ($n = 1,977$)	*P*
Age, years	59.95 (10.44)	58.04 (8.97)	60.16 (9.84)	60.97 (9.38)	60.63 (10.97)	< 0.001
Female	3848 (53.28)	801 (48.19)	871 (48.36)	993 (52.88)	1183 (63.64)	< 0.001
Race						< 0.001
Mexican American	1347 (4.55)	204 (2.85)	338 (4.61)	383 (5.07)	422 (5.69)	
Other Hispanic	485 (4.16)	111 (3.29)	113 (3.59)	140 (5.26)	121 (4.48)	
Non-Hispanic White	4146 (77.84)	1023 (77.80)	1068 (80.32)	1027 (76.86)	1028 (76.38)	
Non-Hispanic Black	1324 (9.04)	329 (8.68)	308 (8.41)	328 (8.89)	359 (10.17)	
Other Race	263 (4.41)	103 (7.38)	58 (3.07)	55 (3.92)	47 (3.28)	
Education						< 0.001
Less than high school	2548 (21.56)	438 (14.68)	619 (21.36)	725 (22.79)	766 (27.43)	
High school graduate or higher	5000 (78.44)	1331 (85.32)	1264 (78.64)	1203 (77.21)	1202 (72.57)	
Marital status						< 0.001
Not married or living with a partner	2761 (30.61)	574 (25.91)	657 (29.66)	713 (30.84)	817 (36.05)	
Married or living with a partner	4705 (69.39)	1179 (74.09)	1202 (70.34)	1199 (69.16)	1125 (63.95)	
Drinking	4754 (69.74)	1196 (75.02)	1221 (71.38)	1215 (67.79)	1122 (64.76)	< 0.001
Smoking	3956 (53.60)	848 (49.83)	970 (52.35)	1040 (52.44)	1098 (59.77)	< 0.001
Dyslipidemia	6258 (83.28)	1291 (72.81)	1528 (82.72)	1690 (87.57)	1749 (89.96)	< 0.001
Hypertension	4438 (52.12)	860 (39.38)	1095 (51.20)	1180 (55.50)	1303 (62.37)	< 0.001
Chronic Kidney Disease	2028 (20.44)	361 (14.67)	481 (18.33)	551 (21.66)	635 (27.09)	< 0.001
Diabetes mellitus	1886 (18.53)	328 (12.69)	410 (15.63)	520 (20.41)	628 (25.38)	< 0.001
Cancer	1075 (13.91)	242 (12.57)	255 (12.92)	261 (13.66)	317 (16.48)	0.013
Coronary Heart Disease	528 (6.10)	105 (4.93)	135 (6.53)	148 (6.57)	140 (6.36)	0.346
Stroke	445 (4.32)	82 (2.85)	97 (3.58)	112 (4.56)	154 (6.28)	< 0.001
SBP, mmHg	128.00 (116.00, 142.00)	122.00 (112.00, 136.00)	126.00 (116.00, 140.00)	130.00 (118.00, 144.00)	132.00 (118.00, 144.00)	< 0.001
BMI, kg/m^2	27.65 (24.27, 31.70)	24.70 (22.15, 27.67)	27.19 (24.40, 30.49)	28.78 (25.52, 32.57)	30.82 (26.70, 36.21)	< 0.001
TC, mg/dL	204.00 (180.00, 231.00)	200.00 (177.00, 224.00)	203.00 (178.00, 230.00)	206.00 (183.00, 234.00)	208.00 (184.00, 237.00)	< 0.001
HDL-C, mg/dL	52.00 (43.00, 64.00)	59.00 (49.00, 71.00)	52.00 (44.00, 65.00)	49.00 (42.00, 60.00)	47.00 (40.00, 58.00)	< 0.001
LDL-C, mg/dL	122.00 (100.00, 146.00)	118.00 (98.00, 141.00)	123.00 (99.00, 145.00)	123.00 (103.00, 151.00)	124.00 (100.00, 148.00)	< 0.001
TG, mg/dL	123.00 (89.00, 174.00)	88.00 (67.00, 113.00)	115.00 (86.00, 159.00)	140.00 (106.00, 187.00)	164.00 (125.00, 227.00)	< 0.001
WBC, 10^3/μL	6.71 (2.32)	5.97 (1.40)	6.45 (2.03)	6.79 (1.76)	7.63 (2.37)	< 0.001
Platelets, 10^3/μL	258.57 (82.34)	242.68 (61.99)	249.60 (58.47)	261.87 (51.59)	280.02 (96.63)	< 0.001
eGFR, mL/min/1.73 m^2	92.42 (76.55, 104.90)	94.21 (80.65, 105.76)	92.16 (77.22, 106.68)	92.35 (75.75, 104.46)	90.50 (73.14, 104.64)	< 0.001
Uric acid, mg/dL	5.50 (4.60, 6.50)	5.00 (4.20, 5.90)	5.50 (4.50, 6.40)	5.70 (4.70, 6.60)	5.80 (4.90, 6.80)	< 0.001
HbA1c, %	5.50 (5.30, 5.80)	5.40 (5.20, 5.70)	5.50 (5.20, 5.70)	5.50 (5.30, 5.90)	5.60 (5.30, 6.00)	< 0.001
FPG, mg/dL	100.50 (93.50, 110.90)	97.20 (92.00, 105.10)	100.00 (93.90, 109.60)	101.10 (94.40, 111.60)	103.80 (95.40, 115.90)	< 0.001
CRP, mg/dL	0.23 (0.10, 0.51)	0.06 (0.04, 0.09)	0.16 (0.12, 0.22)	0.32 (0.24, 0.44)	0.86 (0.58, 1.37)	< 0.001
RC, mg/dL	25.00 (18.00, 35.00)	18.00 (13.00, 23.00)	23.00 (17.00, 32.00)	28.00 (21.00, 38.00)	33.00 (25.00, 45.00)	< 0.001
RCII	5.76 (2.21, 14.49)	1.08 (0.65, 1.65)	3.64 (2.88, 4.60)	8.99 (7.14, 11.31)	27.14 (19.00, 41.60)	< 0.001
lnRCII	1.71 (1.74)	− 0.08 (0.56)	1.29 (0.29)	2.19 (0.29)	3.42 (0.59)	< 0.001
All-cause deaths	2698 (30.62)	502 (21.21)	641 (28.44)	722 (34.12)	833 (38.67)	< 0.001
CVD deaths	860 (9.39)	165 (6.26)	219 (9.45)	216 (10.30)	260 (11.54)	< 0.001
Cancer deaths	613 (7.19)	108 (5.38)	150 (6.96)	166 (7.61)	189 (8.80)	0.017

Abbreviations: BMI body mass index, *CRP* C-reactive protein, *CVD* cardiovascular disease, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin A1c, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *RC* remnant cholesterol, *RCII* remnant cholesterol inflammatory index, *SBP* systolic blood pressure, *TC* total cholesterol, *TG* triglyceride, *WBC* white blood cell

Values are presented as mean (SD) or median (IQR) for continuous variables and as frequency (weighted percentage) for categorical variables

Participants were grouped by lnRCII quartiles: Q1: lnRCII < 0.79, Q2: 0.79 ≤ lnRCII < 1.75; Q3: 1.75 ≤ lnRCII < 2.67, Q4: lnRCII ≥ 2.67

Table 2 Baseline characteristics of clinical information from CHARLS

	Total (n = 12,932)	Q1 (n = 3,.233)	Q2 (n = 3,233)	Q3 (n = 3,233)	Q4 (n = 3,233)	*P*
Age, years	58.64 (9.78)	58.04 (9.65)	58.44 (9.61)	58.67 (9.79)	59.43 (10.03)	< 0.001
Female	6789 (52.50)	1756 (54.31)	1675 (51.81)	1677 (51.87)	1681 (52.00)	0.125
Education						< 0.001
Less than high school	10,611 (82.18)	2761 (85.61)	2657 (82.26)	2601 (80.50)	2592 (80.35)	
High school graduate or higher	2301 (17.82)	464 (14.39)	573 (17.74)	630 (19.50)	634 (19.65)	
Marital status						0.028
Not married or living with a partner	1540 (11.92)	349 (10.81)	380 (11.76)	384 (11.88)	427 (13.22)	
Married or living with a partner	11,384 (88.08)	2880 (89.19)	2852 (88.24)	2849 (88.12)	2803 (86.78)	
Smoking	5042 (39.18)	1171 (36.38)	1249 (38.75)	1303 (40.48)	1319 (41.12)	< 0.001
Drinking	3311 (25.70)	824 (25.61)	867 (26.88)	798 (24.76)	822 (25.57)	0.276
Hypertension	3050 (24.43)	537 (16.95)	661 (21.12)	830 (26.72)	1022 (33.19)	< 0.001
Dyslipidemia	1164 (9.40)	193 (6.18)	238 (7.68)	308 (9.96)	425 (13.87)	< 0.001
Chronic Kidney Disease	790 (6.28)	208 (6.56)	195 (6.21)	187 (5.95)	200 (6.39)	0.778
Diabetes mellitus	706 (5.63)	124 (3.92)	123 (3.93)	194 (6.20)	265 (8.53)	< 0.001
Coronary Heart Disease	1458 (11.60)	324 (10.21)	327 (10.42)	374 (11.91)	433 (13.89)	< 0.001
Stroke	283 (2.24)	47 (1.48)	53 (1.68)	75 (2.38)	108 (3.44)	< 0.001
Cancer	127 (1.01)	27 (0.85)	31 (0.98)	37 (1.17)	32 (1.02)	0.640
SBP, mmHg	130.00 (116.00, 145.00)	125.00 (113.00,140.00)	128.00 (115.00,143.00)	132.00 (118.00,148.00)	133.00 (119.00,148.00)	< 0.001
BMI, kg/m^2	23.28 (20.97, 25.96)	21.88 (20.04,24.01)	22.97 (20.79,25.39)	23.94 (21.60,26.49)	24.77 (22.11,27.63)	< 0.001
TC, mg/dL	188.66 (165.46, 214.18)	181.70 (159.67,205.67)	186.87 (164.69,210.31)	190.98 (167.78,216.50)	195.62 (170.10,224.23)	< 0.001
HDL-C, mg/dL	49.10 (40.54, 59.15)	57.60 (49.10,67.65)	51.03 (43.30,59.92)	46.78 (39.43,54.90)	40.98 (34.41,50.26)	< 0.001
LDL-C, mg/dL	112.11 (91.24, 134.92)	112.11 (92.28,133.38)	113.27 (92.40,135.31)	114.05 (93.94,137.24)	109.02 (85.44,134.15)	< 0.001
TG, mg/dL	107.08 (76.11, 158.41)	74.34 (58.41,93.81)	101.78 (77.88,133.63)	125.67 (92.93,170.80)	170.80 (112.39,258.42)	< 0.001
WBC, 10^3/μL	6.23 (2.08)	5.64 (1.61)	5.97 (1.69)	6.35 (1.82)	6.94 (2.76)	< 0.001
Platelets, 10^3/μL	211.27 (74.05)	205.49 (70.51)	209.27 (72.93)	212.84 (78.17)	217.50 (73.86)	< 0.001
eGFR, mL/min/1.73 m^2	92.40 (87.84, 98.08)	93.36 (88.65,98.96)	92.48 (87.88,98.54)	92.12 (87.62,97.70)	91.92 (87.25,97.05)	< 0.001
Uric acid, mg/dL	4.37 (3.62, 5.26)	3.99 (3.34,4.76)	4.25 (3.55,5.10)	4.54 (3.78,5.44)	4.77 (3.94,5.72)	< 0.001
HbA1c, %	5.20 (4.90, 5.50)	5.10 (4.80,5.40)	5.20 (4.90,5.50)	5.20 (4.90,5.60)	5.30 (5.00,5.70)	< 0.001
FPG, mg/dL	101.70 (93.60, 113.04)	98.82 (91.89,106.87)	100.62 (92.34,109.91)	102.06 (93.78,113.94)	107.10 (97.02,124.37)	< 0.001
hsCRP, mg/L	1.07 (0.57, 2.24)	0.45 (0.31,0.65)	0.74 (0.54,1.09)	1.39 (0.99,2.04)	3.74 (2.19,7.07)	< 0.001
RC, mg/dL	20.88 (12.37, 32.86)	9.66 (5.03,14.69)	18.94 (13.51,26.29)	25.52 (18.17,35.14)	36.68 (23.97,56.44)	< 0.001
RCII	2.23 (0.88, 6.01)	0.45 (0.25,0.66)	1.43 (1.13,1.81)	3.51 (2.82,4.54)	12.69 (8.38,23.94)	< 0.001
lnRCII	0.82 (1.56)	− 1.10 (1.00)	0.35 (0.26)	1.27 (0.28)	2.76 (0.82)	< 0.001
All-cause deaths	609 (4.71)	115 (3.56)	123 (3.80)	166 (5.13)	205 (6.34)	< 0.001

Abbreviations: BMI body mass index, *CRP* C-reactive protein, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin A1c, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *RC* remnant cholesterol, *RCII* remnant cholesterol inflammatory index, *SBP* systolic blood pressure, *TC* total cholesterol, *TG* triglyceride, *WBC* white blood cell

Values are presented as mean (SD) or median (IQR) for continuous variables and as frequency (weighted percentage) for categorical variables

Participants were grouped by lnRCII quartiles: Q1: lnRCII < − 0.13, Q2: − 0.13 ≤ lnRCII < 0.80; Q3: 0.80 ≤ lnRCII < 1.79, Q4: lnRCII ≥ 1.79

In comparison, multivariable Cox models showed that RC was no longer significantly associated with all-cause or cardiovascular mortality. An association with cancer mortality remained only in the highest RC quartile (HR = 1.63, 95% CI: 1.17–2.27, Table S2). CRP, on the other hand, remained independently associated with both

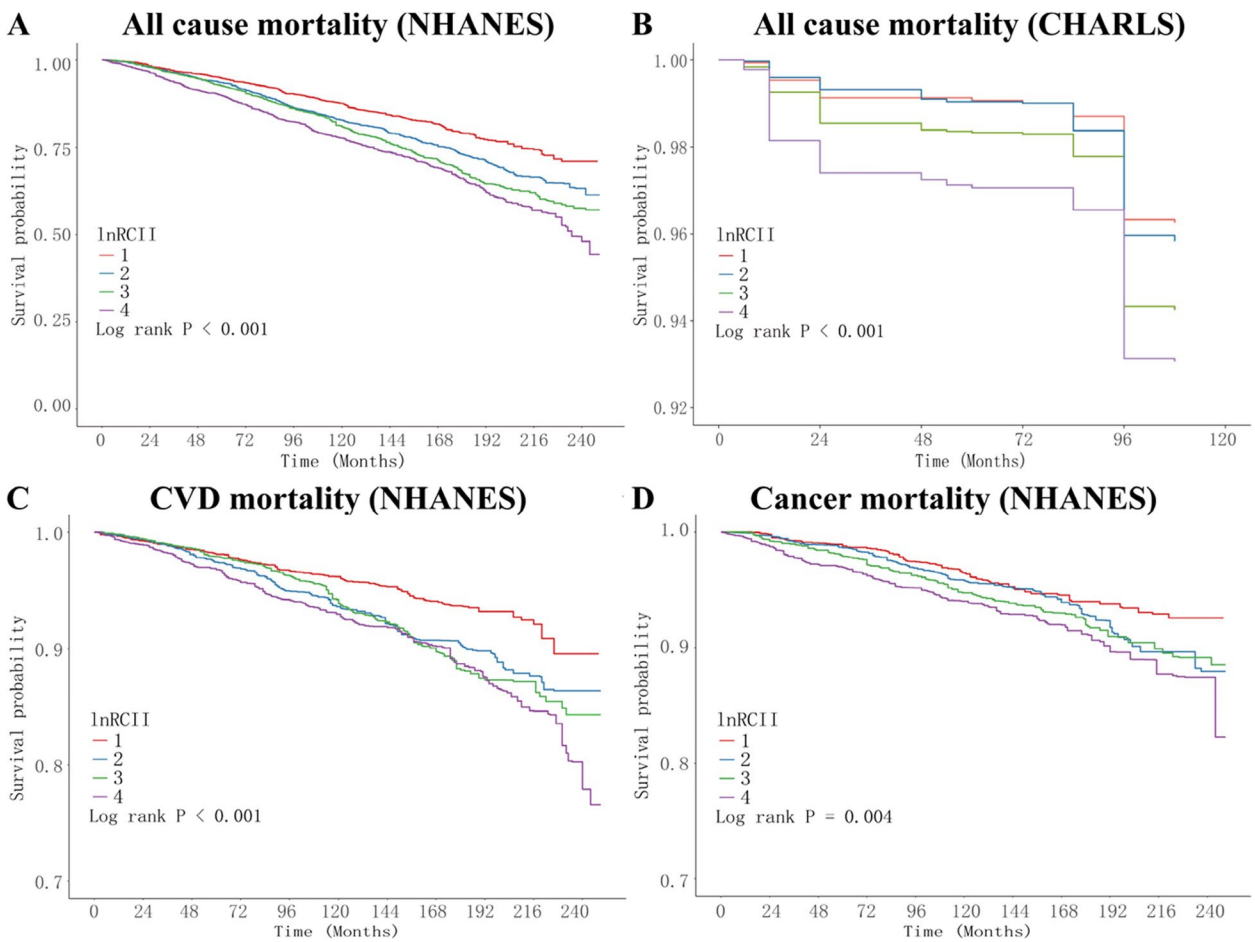

Fig. 2 Kaplan–Meier survival curves by lnRCII quartiles for mortality outcomes. Kaplan–Meier survival curves depict the association of lnRCII quartiles (1–4) with mortality outcomes for participants from NHANES and CHARLS cohorts. Analyses include all-cause mortality for NHANES (**A**) and CHARLS (**B**) cohort, and cardiovascular mortality (**C**) and cancer mortality (**D**) for NHANES cohort. Log-rank tests were used to evaluate differences in survival probabilities among quartile groups

all-cause and cardiovascular mortality, but showed no significant association with cancer mortality (Table S3).

RC, CRP/hsCRP, and lnRCII demonstrated incremental predictive value when added to the basic model for mortality risk (Table S4). Specifically, the C-statistics for the model with lnRCII for all-cause mortality were 0.7943 (95% CI: 0.7851—0.8035) in NHANES and 0.7859 (95% CI: 0.7668—0.8049) in CHARLS. Compared to the model with RC + CRP, the model with lnRCII showed a slightly lower C-statistic for cardiovascular mortality (0.8259 [95% CI: 0.8114—0.8404] vs 0.8264 [95% CI: 0.8118—0.8410]) but a higher C-statistic for cancer mortality (0.7593 [95% CI: 0.7386—0.7801] vs 0.7582 [95% CI: 0.7375—0.7788]) Table 4.

Non-linear relationship between lnRCII and mortality

RCS models, adjusted for full covariates (Model 3), revealed a J-shaped relationship between lnRCII and all-cause mortality and cardiovascular mortality (p for nonlinearity < 0.05), while a linear association was observed with cancer mortality (p for nonlinearity = 0.059, Fig. 4). When analyzing RCII directly (non-log-transformed), inverted L-shaped associations were observed with mortality outcomes (p for nonlinearity < 0.05; Figure S5).

For comparison, RC exhibited a U-shaped association with cardiovascular mortality in NHANES (p for nonlinearity = 0.016), but a linear association with all-cause and cancer mortality (p for nonlinearity > 0.05; Figure S6). In the case of CRP/hsCRP, an inverted L-shaped association was observed between CRP/hsCRP and different mortality outcomes (p for nonlinearity < 0.05; Figure S7).

Mediation analysis

Mediation analysis (Fig. 5) revealed that SBP and FPG partially mediated the relationship between lnRCII

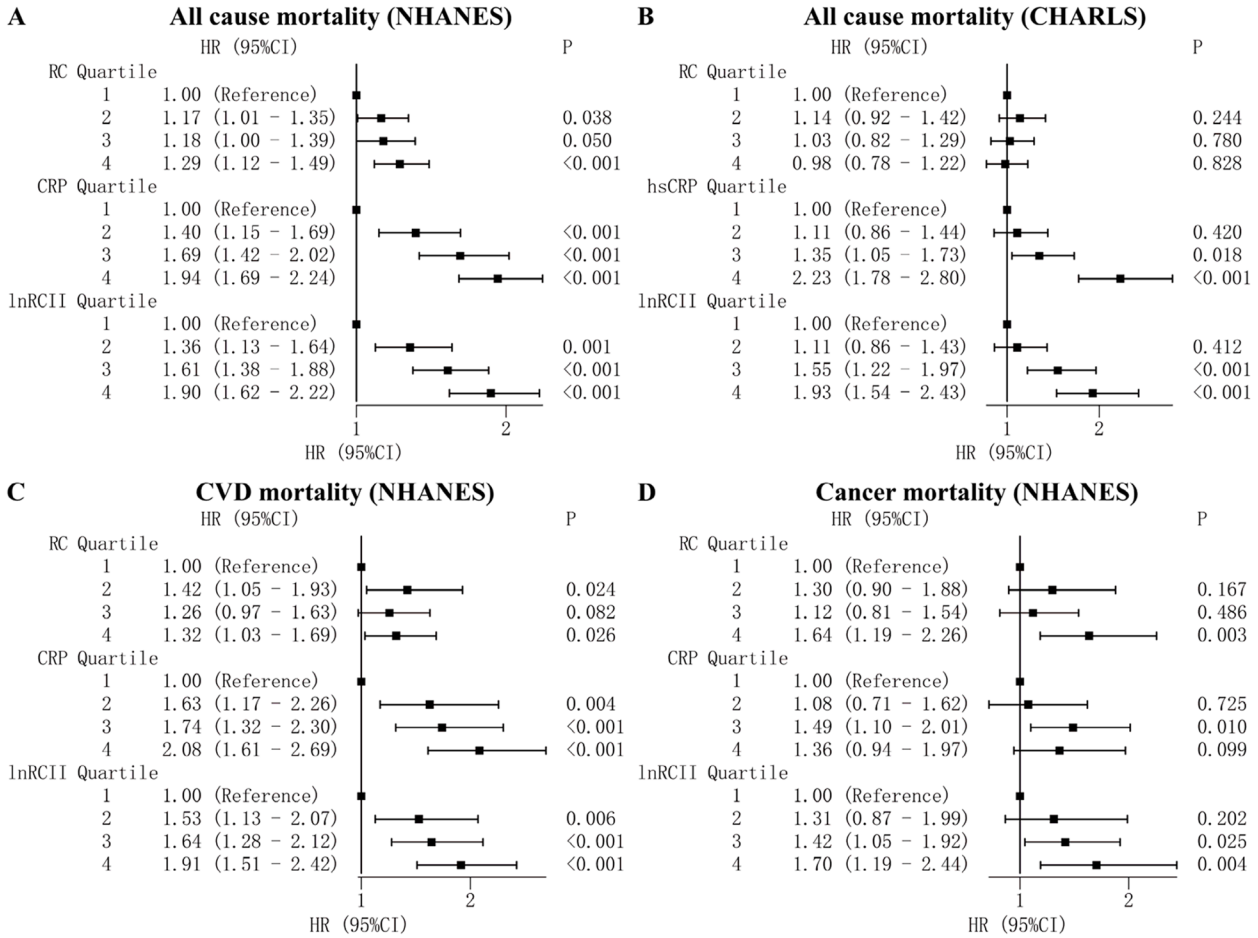

Fig. 3 Mortality risk across lnRCII, RC and CRP/hsCRP quartiles. Participants were categorized into quartiles (1–4) based on lnRCII, RC, or CRP/hsCRP levels, with the first quartile serving as the reference group. Analyses include all-cause mortality for NHANES (**A**) and CHARLS (**B**) cohort, and cardiovascular mortality (**C**) and cancer mortality (**D**) for NHANES cohort, with p-values indicating the significance of the associations

and mortality outcomes. In NHANES, SBP and FPG accounted for 4.77% and 1.60% of the association with all-cause mortality, respectively. In CHARLS, SBP mediated 1.41% and FPG mediated 12.6% of the effect. For cardiovascular mortality, SBP and FPG mediated 7.61% and 4.06% of the effect, respectively. Neither variable mediated the association between lnRCII and cancer mortality.

Subgroup and sensitivity analysis

Subgroup analyses examined potential effect modification by demographic factors (age, sex, BMI) and comorbidities (hypertension, diabetes, CHD, cancer). In NHANES, the association between lnRCII and all-cause mortality was stronger among middle-aged participants (p for interaction = 0.010), a pattern not observed in CHARLS (p for interaction = 0.599). In CHARLS, participants with cancer showed a stronger association between lnRCII and all-cause mortality (p for interaction = 0.032). Further analyses (Table S5) showed that the associations between lnRCII and cardiovascular and cancer mortality in NHANES were generally consistent across subgroups (p for interaction > 0.05), except for cancer mortality, where a stronger association was observed among participants without hypertension (p for interaction = 0.027). After excluding cancer patients, lnRCII remained significantly associated with all-cause mortality in both the NHANES and CHARLS cohorts, as well as with cause-specific mortality in the NHANES cohort. Similarly, excluding individuals with CHD did not affect the significant associations between lnRCII and mortality outcomes in either cohort.

Discussion

This study evaluated the association between the RCII and all-cause and cause-specific mortality using data from two nationally representative cohorts, NHANES and CHARLS. lnRCII was independently and positively

Table 3 Cox regression models for the association between lnRCII and mortality outcomes

lnRCII	Person-years	No. of deaths	Model 1		Model 2		Model 3	
			HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
All-cause mortality (NHANES)								
Q1	27,345	502	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	28,154	641	1.36 (1.13—1.64)	0.001	1.09 (0.91—1.31)	0.355	1.13 (0.94—1.35)	0.186
Q3	29,571	722	1.61 (1.38—1.88)	< 0.001	1.22 (1.05—1.43)	0.011	1.28 (1.08—1.51)	0.004
Q4	28,271	833	1.90 (1.62—2.22)	< 0.001	1.67 (1.44—1.94)	< 0.001	1.76 (1.50—2.08)	< 0.001
P for trend				< 0.001		< 0.001		< 0.001
Per SD increase			1.30 (1.23—1.37)	< 0.001	1.26 (1.19—1.33)	< 0.001	1.29 (1.21—1.36)	< 0.001
All-cause mortality (CHARLS)								
Q1	27,965	115	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	27,318	123	1.11 (0.86—1.43)	0.412	1.06 (0.82—1.37)	0.637	1.03 (0.77—1.36)	0.852
Q3	26,672	166	1.55 (1.22—1.97)	< 0.001	1.46 (1.15—1.86)	0.002	1.36 (1.05—1.77)	0.022
Q4	26,413	205	1.93 (1.54—2.43)	< 0.001	1.68 (1.34—2.12)	< 0.001	1.58 (1.22—2.04)	< 0.001
P for trend				< 0.001		< 0.001		< 0.001
Per SD increase			1.36 (1.25—1.47)	< 0.001	1.28 (1.18—1.38)	< 0.001	1.26 (1.15—1.38)	< 0.001
CVD mortality (NHANES)								
Q1	27,345	165	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	28,154	219	1.53 (1.13—2.07)	0.006	1.18 (0.87—1.60)	0.278	1.13 (0.82—1.55)	0.455
Q3	29,571	216	1.64 (1.28—2.12)	< 0.001	1.20 (0.94—1.54)	0.135	1.09 (0.84—1.41)	0.52
Q4	28,271	260	1.91 (1.51—2.42)	< 0.001	1.67 (1.32—2.11)	< 0.001	1.45 (1.11—1.89)	0.007
P for trend				< 0.001		< 0.001		0.015
Per SD increase			1.29 (1.19—1.40)	< 0.001	1.27 (1.15—1.41)	< 0.001	1.21 (1.08—1.35)	< 0.001
Cancer mortality (NHANES)								
Q1	27,345	108	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	28,154	150	1.31 (0.87—1.99)	0.202	1.18 (0.76—1.84)	0.453	1.20 (0.75—1.90)	0.448
Q3	29,571	166	1.42 (1.05—1.92)	0.025	1.17 (0.81—1.68)	0.397	1.28 (0.87—1.88)	0.213
Q4	28,271	189	1.70 (1.19—2.44)	0.004	1.70 (1.10—2.64)	0.017	1.98 (1.28—3.08)	0.002
P for trend				0.005		0.034		0.005
Per SD increase			1.22 (1.07—1.40)	0.003	1.22 (1.02—1.46)	0.029	1.30 (1.09—1.55)	0.003

HRs with 95% CIs were calculated to evaluate the association between lnRCII and mortality or cause-specific mortality in the NHANES and CHALRS cohorts. The analysis was conducted using both quartile-based categorization and per SD increase models, where participants were grouped into lnRCII quartiles with the first quartile serving as the reference, and HRs were also calculated for each SD increase in lnRCII to evaluate continuous risk associations

Model 1: Unadjusted

Model 2: Adjusted for age, sex, race (NHANES), education level, marital status, drinking, smoking

Model 3: Adjusted for age, sex, race (NHANES), education level, marital status, drinking, smoking, hypertension, diabetes, dyslipidemia, BMI,

associated with all-cause mortality in both US and Chinese middle-aged and elderly population. In the US population, lnRCII was also linked to higher risks of cardiovascular and cancer mortality. RCS analysis showed a J-shaped association between lnRCII and both all-cause and cardiovascular mortality, and a linear relationship with cancer mortality. Mediation analysis indicated that systolic blood pressure and fasting plasma glucose partially explained the observed associations. Subgroup analysis suggested a stronger relationship between lnRCII and all-cause mortality among middle-aged US participants.

Metabolic risk factors are well-established contributors to both CVD and cancer [5, 30, 31], highlighting the need for effective risk control strategies. Within lipid metabolism, LDL-C plays a central role in atherosclerosis through mechanisms such as lipid accumulation and endothelial dysfunction [32, 33]. Statin therapy has significantly reduced global CVD burden by lowering LDL-C levels [34]. Beyond CVD, LDL-C has also been linked to cancer progression, such as the proliferation and migration of cancer cells [35]. And statin therapy may enhance the efficacy of immune checkpoint blockade therapy in different cancer models [36]. However,

Table 4 Subgroup analysis of the association between lnRCII and all-cause mortality

	All-cause mortality (NHANES)			All-cause mortality (CHARLS)		
	HR (95%CI)	*P*	*P* for interaction	HR (95%CI)	*P*	*P* for interaction
All patients	1.29 (1.21 - 1.36)	< 0.001		1.26 (1.15 - 1.38)	< 0.001	
Age			0.010			0.599
45≤Age< 60	1.49 (1.25 - 1.77)	< 0.001		1.19 (0.97 - 1.47)	0.101	
≥ 60	1.24 (1.17 - 1.31)	< 0.001		1.28 (1.15 - 1.41)	< 0.001	
Sex			0.124			0.683
Male	1.34 (1.23 - 1.46)	< 0.001		1.25 (1.11 - 1.40)	< 0.001	
Female	1.24 (1.12 - 1.36)	< 0.001		1.28 (1.11 - 1.48)	< 0.001	
BMI, kg/m^2			0.403			0.160
5	1.25 (1.14 - 1.38)	< 0.001		1.29 (1.17 - 1.43)	< 0.001	
25≤BMI< 30	1.30 (1.16 - 1.46)	< 0.001		1.44 (1.14 - 1.81)	0.002	
≥ 30	1.38 (1.17 - 1.63)	< 0.001		0.85 (0.50 - 1.44)	0.544	
Hypertension			0.296			0.817
No	1.35 (1.18 - 1.53)	< 0.001		1.25 (1.12 - 1.39)	< 0.001	
Yes	1.26 (1.18 - 1.35)	< 0.001		1.27 (1.08 - 1.49)	0.003	
Diabetes			0.826			0.535
No	1.30 (1.21 - 1.40)	< 0.001		1.25 (1.13 - 1.37)	< 0.001	
Yes	1.25 (1.13 - 1.38)	< 0.001		1.42 (1.08 - 1.88)	0.013	
Cancer			0.506			0.032
No	1.27 (1.18 - 1.36)	< 0.001		1.24 (1.13 - 1.35)	< 0.001	
Yes	1.37 (1.17 - 1.61)	< 0.001		2.20 (1.16 - 4.18)	0.015	
CHD			0.837			0.843
No	1.29 (1.21 - 1.37)	< 0.001		1.26 (1.14 - 1.39)	< 0.001	
Yes	1.27 (1.03 - 1.56)	0.023		1.27 (1.02 - 1.58)	0.031	

HRs were calculated to evaluate the association between each SD increase in lnRCII and all-cause mortality in the NHANES and CHARLS cohorts, with adjustments for covariates included in Model 3. Subgroup analyses were stratified by age, sex, BMI, hypertension status, diabetes status, cancer status, and coronary heart disease (CHD) status

residual cardiovascular risk persists despite LDL-C lowering, suggesting that additional pathways may contribute to adverse outcomes [37].

RC, a marker often underused in clinical practice, has been linked to inflammation and increased risk of CVD [38]. However, its prognostic value remains inconsistent across studies. Large-scale cohorts such as the Copenhagen General Population Study (13-year follow-up of 87,192 individuals) [13] and the ChinaHEART study (8-year follow-up of 3,403,414 individuals) [18], reported strong associations between elevated RC and increased cardiovascular mortality, yet weaker or inconsistent links to all-cause mortality. The Copenhagen study found no association between RC and cancer mortality, while the ChinaHEART study observed lower cancer mortality with higher RC levels [13, 18]. Other findings suggest a potential protective effect of RC in certain populations. For example, in patients with heart failure, higher RC levels were associated with lower all-cause mortality [39]. In diabetic populations, RC exhibited a U-shaped relationship with all-cause mortality, with intermediate levels correlating with the lowest mortality risk [40]. An analysis of NHANES data from 2003–2015 also found RC significantly associated with cancer mortality but not cardiovascular mortality [39]. Consistent with this, our results showed a strong association between RC and cancer mortality, but not cardiovascular mortality, in NHANES.

The variability in RC-related outcomes may be explained by its dual biological effects. While elevated RC contributes to atherosclerosis, ischemic heart disease, stroke and cancer through lipid deposition and inflammatory pathways [15, 36, 41, 42], it may also enhance myocardial energy metabolism and enhance immune responses, such as natural killer cell activity, which could be protective in certain contexts [39, 43, 44]. Furthermore, low HDL-C level, often observed in individuals with high RC, have been independently linked to increased cancer mortality [45]. These complex interactions suggest that the prognostic value of RC may be context-specific and influenced by underlying metabolic and inflammatory states.

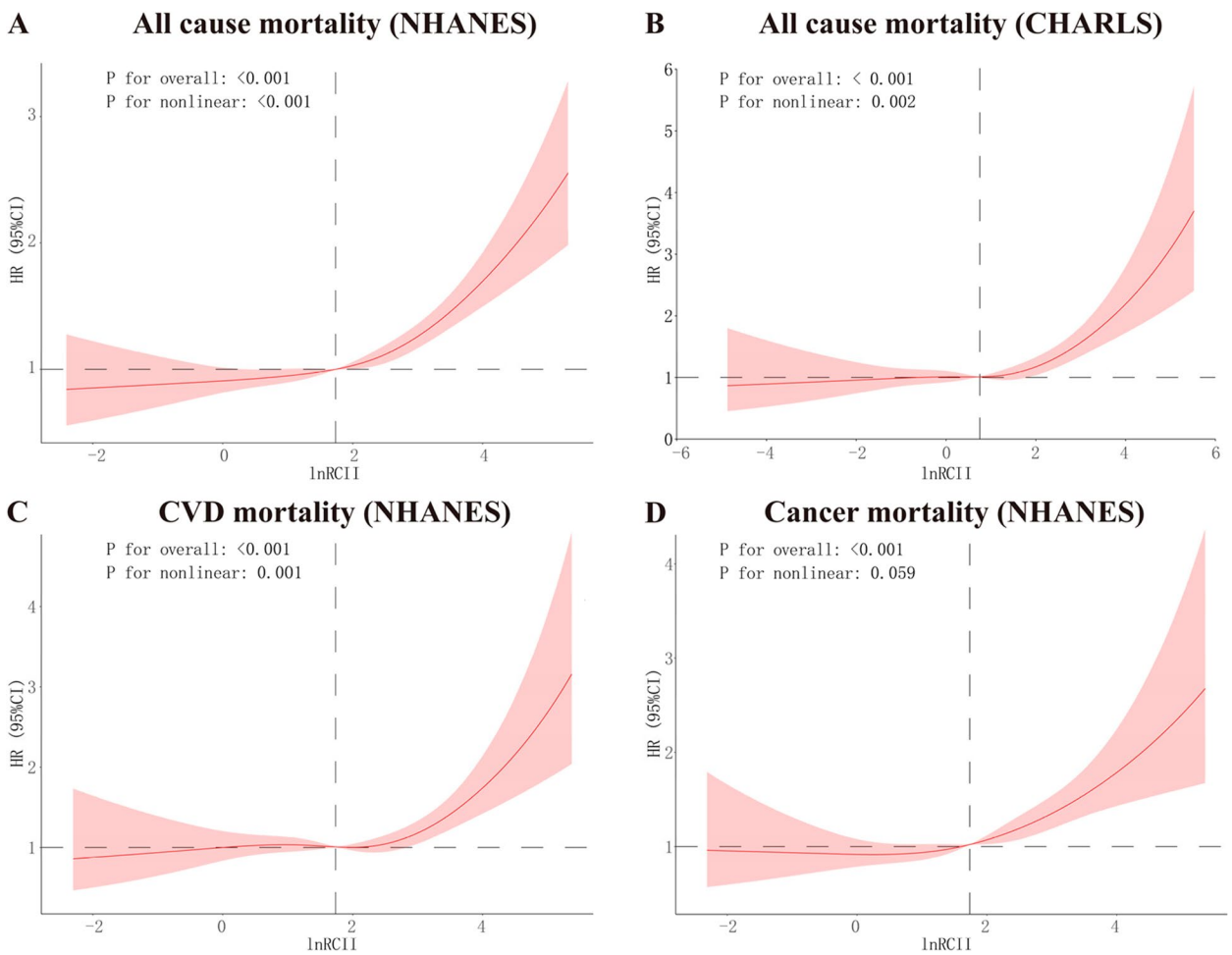

Fig. 4 Association between lnRCII and mortality outcomes. RCS plots illustrating the association between lnRCII and mortality outcomes in the NHANES and CHARLS cohorts. Analyses include all-cause mortality for NHANES (**A**) and CHARLS (**B**) cohort, and cardiovascular mortality (**C**) and cancer mortality (**D**) for NHANES cohort. Adjusted for covariates in model 3. The figure displays the adjusted HR (solid lines) with 95% CI (shaded areas)

Both CRP and hsCRP are widely used markers of systemic inflammation, though they differ in sensitivity, with hsCRP offering greater sensitivity for detecting low levels of inflammation compared to CRP [46]. As such, CRP and hsCRP are not directly interchangeable due to differences in their detection limits and clinical implications. However, recent studies have shown that, despite slight differences in their measurements, CRP and hsCRP often provide similar information for cardiovascular risk stratification. For example, in a study by Han et al., 91.4% agreement was observed between CRP and hsCRP in cardiovascular risk prediction, with only 8.6% reclassification in the risk groups, and both biomarkers shared the same threshold for high cardiovascular risk (> 3 mg/L) [47]. Meanwhile, both CRP [48, 49] and hsCRP [50, 51] have been shown to enhance risk assessment when combined with RC. In our study, we used CRP in the NHANES cohort and hsCRP in the CHARLS cohort due to differences in the available biomarkers across datasets. Despite using different biomarkers in the two cohorts, our findings consistently showed that the RCII values derived from both CRP (NHANES) and hsCRP (CHARLS) had similar predictive abilities for mortality risk. This supports the idea that, while CRP and hsCRP are not directly interchangeable, they provide comparable value in risk stratification when combined with RC.

Previous studies have shown that the risk stratification value of RC was enhanced when combined with CRP or hsCRP [48, 49, 52]. This concept led to the development of the RCII, which integrates both metabolic and inflammatory risk markers to improve risk stratification ability [27]. Prior research on RCII has focused solely on stroke risk [27], and our study further extends expands its application to all-cause and cause-specific mortality.

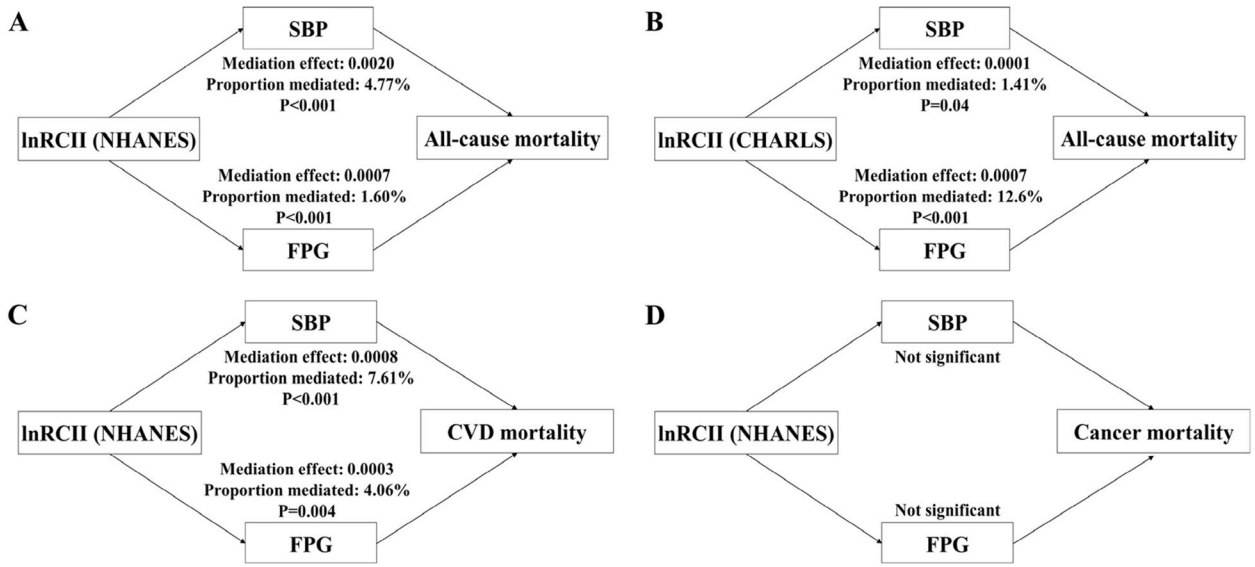

Fig. 5 Mediation analysis of mortality risk factors. The mediation effects of systolic blood pressure (SBP) and fasting plasma glucose (FPG) on the relationship between lnRCII and all-cause mortality (**A** for NHANES, **B** for CHARLS), cardiovascular (CVD) mortality (**C**), and cancer mortality (**D**) were shown. Adjusted for age, sex, race (NHANES), education level, marital status, drinking, smoking, hypertension (with the exception of the SBP model), diabetes (with the exception of the FPG model), dyslipidemia, BMI

In both cohorts, RCII, calculated using either CRP or hsCRP, showed consistent inverted L-shaped association with all-cause mortality, which transformed into a J-shaped relationship after natural log transformation. Each SD increase in lnRCII was associated with a 23% and 26% higher risk of all-cause mortality in NHANES and CHARLS, respectively, supporting RCII's reliability as a mortality risk marker across populations. For cause-specific outcomes, RCII strengthened the associations between RC and both cardiovascular and cancer mortality. Notably, it also addressed the limited association between CRP and cancer-related mortality, highlighting the benefit of combining metabolic and inflammatory markers for more comprehensive risk stratification.

Lipid metabolism dysfunction and inflammation are interrelated mechanisms underlying chronic disease pathogenesis. RCII captures both aspects, enhancing its risk stratification scope. RC contributes to atherosclerosis by facilitating lipid accumulation, triggering oxidative stress and endothelial dysfunction [15, 36, 41, 42]. It may also influence cancer progression through HDL-related mechanisms and tumor immunity modulation [35, 45]. CRP/hsCRP, on the other hand, amplifies these effects by contributing to vascular injury, monocyte recruitment, and inflammation-driven angiogenesis, all of which are relevant in both atherosclerosis and cancer biology [53, 54]. The RCII, which integrates both lipid-driven and inflammation-driven risk pathways, likely amplifies these synergistic effects, contributing to vascular damage, metabolic dysregulation, and impaired immune surveillance, thereby increasing susceptibility to both cardiovascular and cancer-related mortality.

The mediation analysis further revealed that SBP and FPG partially mediated the association between lnRCII and mortality, particularly for cardiovascular outcomes. These findings underscore the interconnected nature of dyslipidemia, hypertension, and diabetes as manifestations of underlying metabolic dysfunction. These disorders are often linked to insulin resistance [55], contributing to endothelial injury, vascular remodeling, and progression of cardiovascular disease [56, 57]. This highlights the importance of comprehensive metabolic risk control in clinical practice.

Interestingly, FPG played a greater mediating role in CHARLS than NHANES, accounting for 12.6% vs. 1.45% of the association between lnRCII and all-cause mortality, respectively. This discrepancy may reflect population-level metabolic differences. Previous studies suggest that Asian populations are more prone to glucose metabolism dysregulation at lower BMI levels and with mild lipid metabolism abnormalities, and may experience more severe complications from diabetes [58]. Global burden of disease data also indicate that elevated FPG contributes more significantly to ischemic heart disease mortality in resource-limited regions, including East Asia [30].

Subgroup analysis in NHANES indicated a stronger association between lnRCII and all-cause mortality in middle-aged individuals (aged 45–60 years). This

aligns with previous findings, such as those from the UK Biobank, showing stronger effects of metabolic and genetic risk factors on mortality in individuals under 65 years [59]. A meta-analysis also reported that earlier onset of diabetes is associated with higher mortality, with each one-year decrease in age of diagnosis linked to a 4% increase in risk [60]. These results suggest that middle-aged individuals may be more vulnerable to the adverse effects of metabolic stress and chronic inflammation, whereas in older adults, competing risks and survival bias may attenuate these associations. In contrast, no age-related interaction was observed in CHARLS, possibly due to differences in baseline metabolic status, healthcare access, or lifestyle patterns, which requires further investigation. Additionally, a potential modifying effect of cancer diagnosis was observed in CHARLS, where individuals with cancer showed a stronger association between lnRCII and all-cause mortality. However, given the limited number of cancer cases and reliance on self-reported diagnoses, this finding should be interpreted with caution and warrants validation in future studies.

Overall, this study highlights the complex interplay between metabolic dysfunction, inflammation, and mortality. RCII, by integrating RC and CRP/hsCRP, provides a more comprehensive measure of risk and demonstrates consistent associations with all-cause, cardiovascular, and cancer mortality. These associations are partly mediated by other metabolic factors such as blood pressure and glucose, and may vary across age groups and populations. RCII may serve as a practical and informative tool for mortality risk stratification and early intervention in clinical practice.

Limitations

This study has several limitations. First, while RC reflects a cumulative risk model, the available data did not allow us to calculate cumulative RC or RCII, limiting our ability to fully verify this model. Second, cause-specific mortality data were not available for the Chinese cohort, which may restrict comparability across populations and limit generalizability to other ethnic or geographic groups. Third, the reasons behind the differing performance of RCII across age groups and populations remain underexplored, and further research in diverse populations are needed to assess the external validity of RCII in different contexts. Finally, due to differences between the two cohorts, CRP and hsCRP were used separately, and future research comparing these biomarkers within the same cohort would provide more meaningful insights into their comparative ability to assess risk when calculating RCII.

Conclusion

RCII shows significant association with all-cause, cardiovascular, and cancer mortality. By combining metabolic and inflammatory markers, it provides a more comprehensive assessment of mortality risk in middle-aged and elderly populations in both the US and China. Given its simplicity and strong predictive ability, RCII could serve as a valuable tool for clinical risk stratification, particularly for identifying high-risk individuals. However, further validation in larger, multi-ethnic cohorts and long-term prospective studies is needed to confirm its utility and establish its role in clinical practice.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-025-02580-z.

Supplementary Material 1.

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Authors' contributions
Y. W. and L. B. completed manuscript drafting, data analysis, interpretation and visualization. Y. W., Q. L. and Q. W. completed data collection. T. L. and P. Z. contributed to the approval of the final version, and agree to be accountable for the accuracy. All authors have read and approved the manuscript.

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Data availability
The data supporting the findings of this study are publicly available in the NHANES database (https://www.cdc.gov/nchs/nhanes/index.htm) and CHARLS database (https://charls.pku.edu.cn). Data analyzed during the study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The National Center for Health Statistics and Ethics Review Board approved the protocol for NHANES. And the Institutional Review Board of Peking University approved the protocol for CHARLS. All participants provided written informed consent.

Competing interest
The authors declare no competing interests.

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