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Residual Cholesterol Inflammatory Index: A Predictor of Cardiovascular–Kidney–Metabolic Syndrome; Insights from NHANES and CHARLS Cohorts

ABSTRACT

Background: Cardiovascular–kidney–metabolic syndrome (CKM) is a multi-organ metabolic disorder with an increased risk of morbidity and mortality among populations worldwide. Identifying effective biomarkers for early risk assessment is important. The residual cholesterol (RC) inflammatory index (RCII), which is derived from the combination of RC and C-reactive protein (CRP), represents a novel biomarker that captures the interplay between dyslipidemia and systemic inflammation.

The interaction between RCII and CKM risk in the general populations of the US and China and evaluated its dose-response pattern, nonlinear relationship, and subgroup variations were evaluated.

Methods: Data were retrieved by accessing 2 nationally representative cohorts: the US National Health and Nutrition Examination Survey (NHANES, n = 10,669) and the China Health and Retirement Longitudinal Study (CHARLS, n = 9,496). Multivariate logistic regression models (Model 1-3) were constructed to determine the relationship between RCII (as a continuous and quartile-categorized variable) and CKM. Progressive adjustments were made for demographic, socioeconomic, lifestyle, and anthropometric factors. In addition, a restricted cubic spline (RCS) analysis was conducted to examine nonlinearity and stratified analyses to assess effect modification across subgroups.

Results: Increased RCII was significantly linked with increased CKM risk in both models. In fully adjusted models, each 1-unit increment in RCII was associated with a 4% increase in CKM risk in NHANES (odds ratio (OR) = 1.04, 95% CI: 1.03-1.06, $P < .001$) and a 3% increase in CHARLS (OR = 1.03, 95% CI: 1.02-1.05, $P < .001$). Quartile analysis revealed a strong dose-response pattern. In CHARLS, individuals in the highest quartile (Q4) exhibited a 9.60-fold higher CKM risk compared with that in Q1 (95% CI: 7.83-11.80). RCS models confirmed a nonlinear, upward-sloping relationship between RCII and CKM risk in both datasets. Subgroup analysis revealed robust associations across most strata, with a significant interaction by race in NHANES and by hypertension, diabetes, stroke, and smoking status in CHARLS.

Conclusion: RCII exhibited an independent and positive association with CKM risk in the US and Chinese populations, with consistent dose-response and nonlinear trends. This index may be a practical and integrative biomarker for identifying individuals with an increased CKM risk, particularly during the early stages of metabolic dysregulation. Prospective studies are warranted to validate their predictive performance and establish clinically relevant thresholds for risk stratification.

Keywords: CHARLS, CKM, inflammation index, inflammation interaction, lipid, NHANES, residual cholesterol, restricted cubic spline

INTRODUCTION

Cardiovascular–kidney–metabolic syndrome (CKM) caused several physiological actions including adiposity, type 2 diabetes mellitus, cardiovascular impairment, and chronic kidney complications.[1,2] These pathophysiological changes are interconnected through metabolic abnormalities that trigger the cascade of dyslipidemia and inflammatory responses for individuals by damaging the endothelial cells, which ultimately cause the blockage that induces atherosclerosis, plaque

ORIGINAL INVESTIGATION

Mengchen Zhang[1]
Linlin Huang[1]
Tian Zhang[1]
Guobin Song[1]
Xiaobin Ren[1]
Lijuan Zhang[1]
Aiyun Han[2,3]

[1]*Department of General Medicine, Shijiazhuang People's Hospital, Shijiazhuang, Hebei, China*
[2]*Department of Urology, Shijiazhuang People's Hospital, Shijiazhuang, Hebei, China*
[3]*Shijiazhuang Key Laboratory of Oncology and Geriatric Diseases, Hebei, China*

Corresponding author:
Aiyun Han
✉ hanaiyun0802@sina.com

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formation, and cardiovascular dysfunctions. The inflammatory response-related 2 biomarkers have been reported in the literature for the evaluation of CKM: one works on the basis of Systemic Inflammation Response Index (SIRI)[3] and the second works by recording chronic low-grade inflammation, particularly effective for patients suffering from T2DM and CKM.[4]

Residual cholesterol (RC) is basically the cholesterol ester in the form of triglycerides which, upon lipolysis, is converted to low-density lipoproteins and glycerin derivatives.

Residual cholesterol due to its triglyceride content has dominant arterial wall accumulation efficacy, which triggers cardiovascular risk, plaque development, and atherosclerosis related complications.[5,6] During the progression of atherosclerosis, the role of RC is pronounced. It penetrates the arterial intima and binds to the extracellular matrix to promote smooth muscle cell proliferation and macrophage activation, which accelerates atherogenesis.[7] Once infiltrated into the arterial wall, RC accumulates within the intima, inducing endothelial dysfunction, vascular inflammation, and cholesterol deposition.

Systemic inflammation is a key mechanism underlying multiple chronic disorders that affect the cardiovascular, renal, and metabolic systems. This process is important in atherosclerosis initiation and progression, which is a chronic, progressive vascular inflammatory condition defined by lipid deposition, plaque formation, endothelial dysfunction, and aberrant immune activation.[8] Endothelial inflammatory responses are particularly important to this process and are typified by increased levels of C-reactive protein (CRP), a pro-inflammatory cytokine.[9] These mediators exacerbate endothelial malfunction, atherosclerosis, and vascular stiffness, which promote the progression of hypertension (HTN), chronic kidney disease (CKD), insulin resistance, and heart failure. As an acute-phase reactant, CRP is a marker of inflammation and an independent cardiovascular disease (CVD) risk factor. C-reactive protein is involved in multiple stages of atherogenesis, from leukocyte recruitment to the rupture of unstable plaques.[10] CKD patients frequently exhibit systemic and vascular inflammation, which is closely associated with increased levels of CRP and other inflammatory cytokines.

The conventional methods for the lipid profile assessment primarily focused on low-density lipoprotein. This approach may overlook the residual risk factors from the RC level, which can implement considerable cardiovascular and renal risk.[11]

The RC-Inflammation Index (RCII), which is derived from RC and CRP levels, has not been extensively examined relative to CKM. Data from the US National Health and Nutrition Examination Survey (NHANES, 1999-2010) and the China Health and Retirement Longitudinal Study (CHARLS, 2011-2012) were used to determine the interaction between RCII and CKM. The results highlight the effect of RC and inflammation on CKM development and support the potential RCII value as a novel indicator for CKM risk assessment.

HIGHLIGHTS

- Early and precise detection of cardiovascular–kidney–metabolic syndrome (CKM) is highly desirable.
- Small molecule–based biomarkers help in the early diagnosis and reduce the mortality risk.
- The present study focused on scrutinizing the utility of the residual cholesterol inflammatory index (RCII) as a potential biomarker for cardiorenal-metabolic risk determination.
- The relationship between RCII and CKM risk was determined through multivariate logistic regression models, with RCII analyzed as a continuous variable and across quartile categories.
- The results illustrated the consistent alignment between higher RCII levels and enhanced risk of CKM in both cohorts.

METHODS

Study Design

This study used data from 2 nationally representative datasets: the China CHARLS and the US NHANES. Baseline data were obtained from the 2011-2012 cycle of CHARLS, a longitudinal survey of middle-aged and older adults in China.[12] NHANES data were pooled across 10 cycles (1999-2010), which consisted of biennial cross-sectional surveys of the noninstitutionalized civilian population in the US, conducted using a stratified multistage probability sampling design.

Both surveys collected comprehensive observations on the population characteristics, physiological conditions, medication use, and laboratory test results. National Health and Nutrition Examination Survey and CHARLS received ethical approval from their respective review boards, with NHANES authorized by the National Center for Health Statistics (NCHS) Ethics Review Board. Appropriate sampling weights were applied to ensure that the estimates could be generalized to the national populations of each country. The study was conducted in accordance with the Declaration of Helsinki.

Flowcharts for participant selection are presented in Figures 1 and 2.

CKM Definition

A universally accepted CKM diagnostic criterion has not been established. In the present study, CKM represented the coexistence of cardiometabolic syndrome (CMS) and CKD.[13,14] The CMS diagnostic criteria relied upon the NCEP-ATP III guidelines.[15] A CMS diagnosis was established when 3 or more of the following criteria were met:

1. Central obesity: Waist circumference (WC) of at least 102 cm for men and 88 cm for women
2. Hypertriglyceridemia: Serum triglycerides (TG) $\geq$ 150 mg/dL
3. Low high-density lipoprotein (HDL): HDL $<$ 40 mg/dL in men or $<$ 50 mg/dL in women

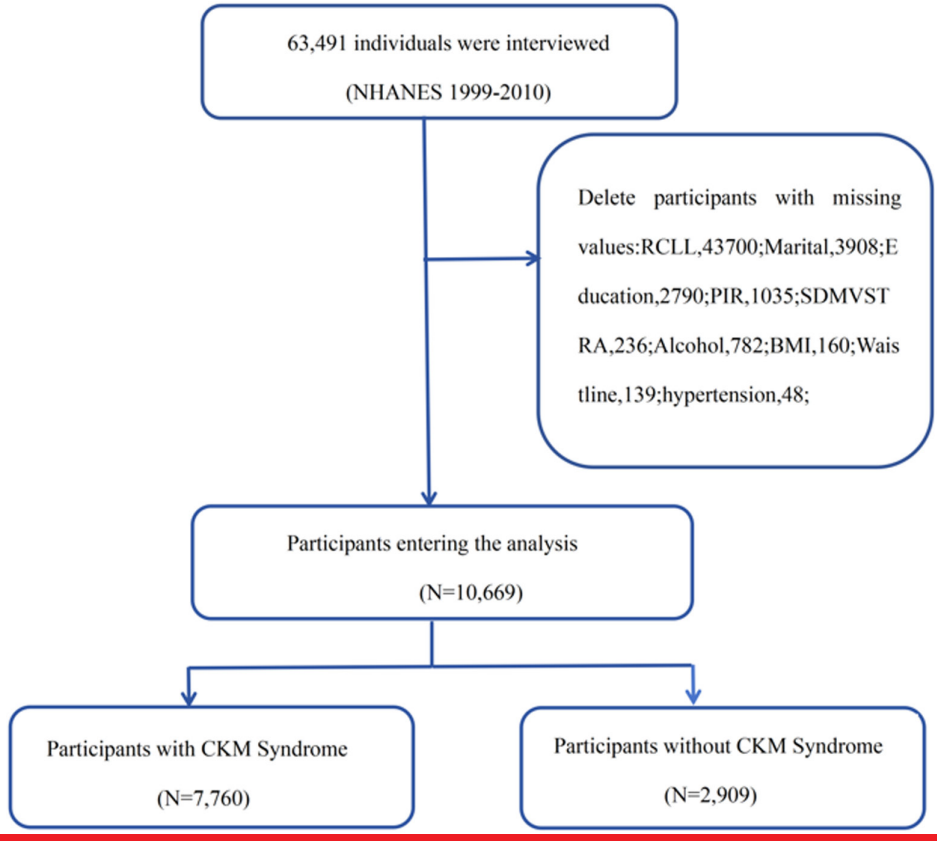

Figure 1. Screening process in the National Health and Nutrition Examination Survey (NHANES).

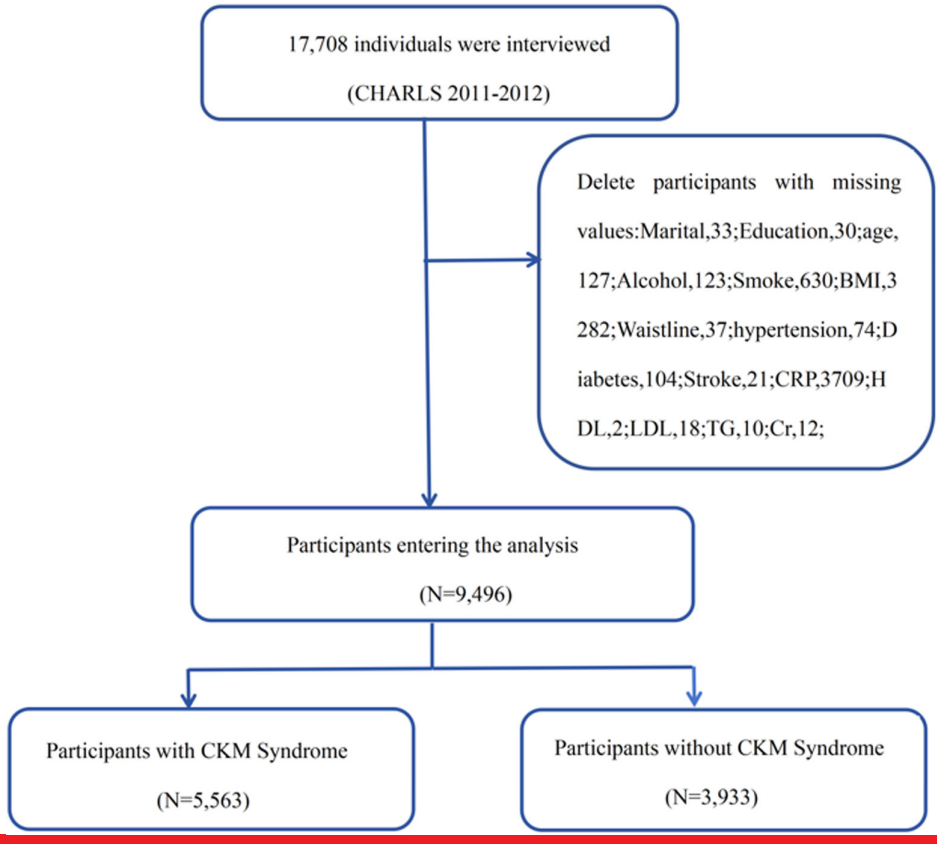

Figure 2. Screening flow of respondents in the China Health and Retirement Longitudinal Study (CHARLS).

4. Elevated blood pressure: Systolic pressure ≥ 130 mm Hg, diastolic pressure ≥ 85 mm Hg, or using antihypertensive medication
5. Hyperglycemia: Fasting plasma glucose (FPG) ≥ 100 mg/dL or currently using antidiabetic medication

Anthropometric measurements (WC, weight, and height) were obtained using standardized protocols and blood pressure measurement was done on the average of 4 measurements. Certified laboratories measured serum TG and HDL levels, as well as plasma FPG levels. CKD was defined by an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 or a urine albumin-creatinine ratio of >30 mg/g.[16,17] The eGFR calculation was done using the CKD-EPI 2009 creatinine (Cr) equation.[18,19] Individuals with CKM stage ≥ 2 were classified as having CKM, based on previous evidence indicating that stage ≥ 2 is associated with more pronounced metabolic disturbances and greater cardiorenal risk.[20,21]

RC and RCII Calculation

RC (mg/dL) was determined by subtracting HDL and low density lipoprotein (LDL) sum from total cholesterol (TC). For the CHARLS cohort, based on the study by Chen et al[22] RCII was calculated as:

RCII = (RC × hsCRP [mg/L])/10

In the NHANES cohort, because CRP was measured in mg/dL rather than hsCRP in mg/L, the formula was:

RCII = RC × CRP [mg/dL]

Statistical Analysis

This study used data from NHANES and CHARLS. Initial descriptive analyses were conducted to summarize the baseline attributes of the study participants. Group differences were assessed using a chi-square test for categorical variables and an independent-sample *t*-test for continuous variables. Regression, subgroup, and restricted cubic spline (RCS) analyses were performed to determine the associations of interest, with the results displayed in forest plots. Three regression models with increasing adjustments were established: Model 1 was unadjusted; Model 2 included adjustments for race, marital status, educational level, sex, and age; and Model 3 incorporated subsequent adjustments for behavioral functions including nicotine addiction status, ethanol intake, poverty income ratio (PIR), and body mass index (BMI). Statistical analyses were conducted using R software (v4.5.1), with a 2-sided $P < .05$ indicating significance.

RESULTS

Baseline Characteristics

Baseline characteristics of participants from NHANES and CHARLS were stratified by the presence or absence of CKM (Tables 1 and 2). In the NHANES cohort (n = 10,669), participants with CKM were older (50.35 vs. 37.58 yr, $P < .001$), more likely to be male (52% vs. 41%, $P < .001$), displayed lower education (≥high school: 24% vs. 33%, $P < .001$), higher smoking prevalence (51% vs. 44%, $P < .001$), and lower alcohol consumption (73% vs. 79%, $P < .001$). Clinically, they exhibited significantly higher BMI, WC, blood pressure, FBG, uric acid (UA), Cr, TG, and CRP levels, along with decreased HDL levels (all $P < .001$). Interestingly, the CKM group (RC: 29.98 vs. 16.43 mg/dL, RCII: 14.55 vs. 4.91; $P < .001$) was found to exhibit the higher level of RC and RCII. Cardiovascular–kidney–metabolic participants were older (61.15 vs. 56.57 years, $P < .001$), with lower alcohol consumption rates (30% vs. 36%, $P < .001$) and tobacco use (27% vs. 31%, $P = .004$). They also exhibited significantly higher WC, CRP, TG, UA, and RCII values (all $P < .001$).

Interaction Between RCII and CKM

Three logistic regression models were constructed to evaluate the RCII–CKM association in both cohorts:

Model 1: Unadjusted

Model 2: Adjusted for demographic variables

NHANES: age, sex, race, education level, marital status

CHARLS: age, sex, education level, marital status

Model 3: Additionally adjusted for socioeconomic and lifestyle variables

NHANES: Model 2 + PIR, smoking, alcohol use, and BMI

CHARLS: Model 2 + smoking, alcohol use, and BMI

NHANES Findings (Table 3)

RCII showed a significant association with CKM. As a continuous variable, each 1-unit increment in RCII was associated with a 4% increase in CKM risk (Model 3: OR = 1.04, 95% CI: 1.03-1.06, $P < .001$). In a quartile-based analysis, unlike Q1, the OR for CKM in Q2, Q3, and Q4 were 0.55 (0.39-0.71), 1.00 (0.86-1.20), and 1.80 (1.60-2.00), respectively (P for trend < 0.001), indicating a nonlinear dose-response relationship.

CHARLS Findings (Table 4)

There were similar associations in the CHARLS data. Each 1-unit increment in RCII was related to a 3% escalation in CKM risk (Model 3: OR = 1.03, 95% CI: 1.02-1.05, $P < .001$). Unlike Q1, the ORs in Q2-4 were 2.26 (1.91-2.67), 5.08 (4.18-6.18), and 9.60 (7.83-11.80), respectively (P for trend < .001), which indicates a strong and consistent dose-response effect across increasing RCII levels.

Subgroup Analysis and Interaction Effects

Subgroup analyses (Figures 3 and 4) were done to determine whether the interaction between RCII and CKM varied across demographic and clinical subpopulations. For NHANES, the positive association remained robust across sex, age groups, BMI categories, nicotine intake level, ethanol intake, HTN, and diabetes mellitus (DM) subgroups. No notable interaction was evident in these strata (all interaction $P > .05$), suggesting consistent effects across the populations. The only significant heterogeneity was observed in race/ethnicity (interaction $P = .000$). This association was significant among Mexican Americans, Non-Hispanic Whites/Blacks, and multi-racial participants (OR range: 1.02-1.07), but not among other Hispanics (OR = 1.01).

For CHARLS, no prominent interaction was found across sex, education, or alcohol consumption (interaction $P > .05$); however, significant heterogeneity was detected in subgroups of HTN ($P = .000$), DM ($P = .000$), stroke ($P = .002$), and smoking

Table 1. Baseline Attributes of NHANES Participants Categorized by Their Cardiovascular–kidney–metabolic Syndrome (CKM) Status

Characteristic	n	Overall (%)	Non-CKM (%)	CKM (%)	*P*
Age (years)	10 669	46.18 ± (16.39)	37.58 ± (12.64)	50.35 ± (16.38)	<.001
Sex, n (%)	10 669				<.001
Male		5,171 ± (48)	1,212 ± (41)	3,959 ± (52)	
Female		5,498 ± (52)	1,697 ± (59)	3,801 ± (48)	
PIR	10 669	3.10 ± (1.61)	3.20 ± (1.60)	3.04 ± (1.61)	<.001
Race, n (%)	10 669				.11
Mexican American		2,155 ± (7.6)	602 ± (8.4)	1,553 ± (7.2)	
Other Hispanic		607 ± (3.9)	179 ± (4.4)	428 ± (3.6)	
Non-Hispanic White		5,588 ± (74)	1,480 ± (73)	4,108 ± (74)	
Non-Hispanic Black		1,907 ± (10.0)	539 ± (10)	1,368 ± (9.9)	
Other Race - Including Multi-Racial		412 ± (5.0)	109 ± (4.5)	303 ± (5.3)	
Marital Status, n (%)	10 669				<.001
Married		6,002 ± (60)	1,521 ± (56)	4,481 ± (61)	
Widowed		920 ± (5.3)	44 ± (1.0)	876 ± (7.4)	
Divorced		1,055 ± (9.6)	245 ± (8.5)	810 ± (10)	
Separated		312 ± (2.4)	77 ± (2.1)	235 ± (2.5)	
Never married		1,594 ± (16)	740 ± (23)	854 ± (12)	
Living with a partner		786 ± (7.5)	282 ± (8.8)	504 ± (6.8)	
Education level, n (%)	10 669				<.001
<9th grade		1,342 ± (6.0)	206 ± (3.5)	1,136 ± (7.1)	
9th–11th grade (Includes 12th grade with no diploma)		1,676 ± (12)	410 ± (10)	1,266 ± (13)	
High school graduate/GED or equivalent		2,519 ± (25)	617 ± (22)	1,902 ± (27)	
Some college or AA degree		2,925 ± (30)	909 ± (32)	2,016 ± (30)	
College graduate or above		2,197 ± (27)	766 ± (33)	1,431 ± (24)	
Alcohol, n (%)	10 669				<.001
Yes		7,523 ± (75)	2,176 ± (79)	5,347 ± (73)	
No		3,146 ± (25)	733 ± (21)	2,413 ± (27)	
Smoke, n (%)	10 669				<.001
Yes		5,151 ± (49)	1,217 ± (44)	3,934 ± (51)	
No		5,518 ± (51)	1,692 ± (56)	3,826 ± (49)	
BMI, kg/m^2	10 669	28.35 ± (6.38)	25.62 ± (5.00)	29.68 ± (6.56)	<.001
WC, cm	10 669	97.37 ± (15.91)	88.84 ± (12.80)	101.51 ± (15.63)	<.001
HTN, n (%)	10 669				<.001
Yes		3,589 ± (29)	0 ± (0)	3,589 ± (44)	
No		7,068 ± (70)	2,906 ± (100)	4,162 ± (56)	
DM, n (%)	10 669				<.001
Yes		1,025 ± (6.7)	0 ± (0)	1,025 ± (10.0)	
No		9,470 ± (92)	2,892 ± (99)	6,578 ± (88)	
Borderline		168 ± (1.4)	16 ± (0.6)	152 ± (1.8)	
Stroke, n (%)	10 669				<.001
Yes		358 ± (2.4)	0 ± (0)	358 ± (3.6)	
No		10,298 ± (97)	2,909 ± (100)	7,389 ± (96)	
CRP, mg/dL	10 669	4.15 ± (8.34)	2.79 ± (6.26)	4.82 ± (9.11)	<.001
HDL, mg/dL	10 669	53.79 ± (15.59)	58.47 ± (14.80)	51.51 ± (15.45)	<.001
TC, mg/dL	10 669	197.52 ± (39.73)	186.74 ± (35.20)	202.76 ± (40.74)	<.001
LDL, mg/dL	10 669	118.19 ± (35.13)	111.84 ± (32.02)	121.28 ± (36.14)	<.001
TG, mg/dL	10 669	127.74 ± (67.50)	82.16 ± (25.63)	149.90 ± (70.36)	<.001
RCII	10 669	11.39 ± (24.66)	4.91 ± (12.22)	14.55 ± (28.30)	<.001
RC	10 669	25.55 ± (13.50)	16.43 ± (5.13)	29.98 ± (14.08)	<.001
UA, mg/dL	10 669	5.44 ± (1.39)	4.90 ± (1.22)	5.71 ± (1.39)	<.001
Cr, μmol/L	10 669	0.87 ± (0.34)	0.82 ± (0.17)	0.90 ± (0.39)	<.001

Continuous data: Mean ± SE; weighted *T*-test-calculated *P*-values. Categorical data: n (%); weighted chi-square test-calculated *P*-value.
BMI, body mass index; CKM, cardiovascular–kidney–metabolic syndrome; Cr, Creatinine; CRP, C-reactive protein; DM, diabetes mellitus; HDL, high-density lipoprotein; HTN, hypertension; LDL, low-density lipoprotein; Model 1, No adjustment; Model 2, Adjusted for age, sex, race, education level, and marital status; Model 3, Further adjusted for PIR, smoking status, alcohol consumption, and BMI; PIR, poverty income ratio; RC, remnant cholesterol; RCII, residual cholesterol inflammatory index.

Table 2. Baseline Attributes of CHARLS Participants Categorized by CKM Status

Characteristic	n	Overall (%)	Non-CKM (%)	CKM (%)	*P*
Age (years)	9 496	59.27 ± (10.04)	56.57 ± (9.18)	61.15 ± (10.19)	<.001
Sex, n (%)	9 496				.131
Male		5 157 ± (55)	2 096 ± (54)	3 061 ± (55)	
Female		4 339 ± (45)	1 837 ± (46)	2 502 ± (45)	
Marital Status, n (%)	9 496				<.001
Married		1161 ± (14)	382 ± (9.9)	779 ± (16)	
Unmarried		8 335 ± (86)	3 551 ± (90)	4,784 ± (84)	
Education level, n (%)	9 496				.082
Illiteracy		4 581 ± (46)	1 871 ± (46)	2 710 ± (47)	
Completed primary education		2 100 ± (22)	851 ± (21)	1 249 ± (23)	
Middle school		1 902 ± (21)	827 ± (23)	1 075 ± (20)	
High school and above		913 ± (10)	384 ± (10)	529 ± (10)	
Drinking	9 496	3 063 ± (32)	1 401 ± (36)	1 662 ± (30)	<.001
Smoking	9 496	2 830 ± (29)	1 249 ± (31)	1 581 ± (27)	.004
BMI, kg/m^2	9 496	24.69 ± (45.62)	24.80 ± (69.99)	24.61 ± (10.91)	<.001
WC, cm	9 496	84.43 ± (12.73)	80.53 ± (11.92)	87.14 ± (12.57)	<.001
HTN, n (%)	9 496				<.001
No		6 998 ± (73)	3,933 ± (100)	3,065 ± (55)	
Yes		2 498 ± (27)	0 ± (0)	2,498 ± (45)	
DM, n (%)	9 496				<.001
No		8 911 ± (94)	3,933 ± (100)	4,978 ± (89)	
Yes		585 ± (6.3)	0 ± (0)	585 ± (11)	
Stroke, n (%)	9 496				<.001
No		9,254 ± (97)	3,933 ± (100)	5,321 ± (95)	
Yes		242 ± (2.7)	0 ± (0)	242 ± (4.7)	
CRP, mg/L	9 496	2.73 ± (7.48)	2.35 ± (7.61)	3.00 ± (7.38)	<.001
HDL, mg/dL	9 496	50.49 ± (15.04)	55.75 ± (14.17)	46.82 ± (14.54)	<.001
LDL, mg/dL	9 496	115.74 ± (34.71)	114.80 ± (31.39)	116.40 ± (36.83)	.129
TC, m/dL	9 496	132.17 ± (94.61)	87.78 ± (28.93)	163.10 ± (110.80)	<.001
RCII	9 496	7.61 ± (43.50)	3.74 ± (14.34)	10.31 ± (55.23)	<.001
RC	9 496	26.06 ± (24.48)	15.63 ± (9.46)	33.34 ± (28.74)	<.001
UA, mg/dL	9 496	4.51 ± (1.30)	4.20 ± (1.12)	4.73 ± (1.37)	<.001
Cr, μmol/L	9 496	0.79 ± (0.25)	0.75 ± (0.18)	0.82 ± (0.28)	<.001

(*P* = .030). In individuals without these comorbidities, RCII exhibited a positive association with CKM (OR range: 1.01-1.04), whereas the association was attenuated or became nonsignificant in those with existing metabolic or vascular disease (OR ≈ 1.00).

Taken together, the predictive RCII value may be more pronounced in metabolically "at-risk but not yet overtly diseased" individuals, underscoring the importance of considering clinical context and population heterogeneity in risk interpretation.

Table 3. Multivariate Logistic Regression Analysis of the RCII–CKM Relationship in the NHANES Cohort

	Models					
	1		2		3	
Characteristic	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Continuous RCII	0.07 (0.05, 0.08)	<.001	1.07 (1.05, 1.09)	<.001	1.04 (1.03, 1.06)	<.001
RCII-Q1	Ref		Ref		Ref	
RCII-Q2	0.97 (0.82, 1.1)	<.001	0.74 (0.58, 0.90)	<.001	0.55 (0.39, 0.71)	<.001
RCII-Q3	1.5 (1.4, 1.7)	<.001	1.4 (1.2, 1.5)	<.001	1.0 (0.86, 1.2)	<.001
RCII-Q4	2.4 (2.2, 2.5)	<.001	2.4 (2.2, 2.6)	<.001	1.8 (1.6, 2.0)	<.001
P for trend		<.001		<.001		<.001

Table 4. Multivariate Logistic Regression Analysis of RCII–CKM Relationship in the CHARLS Cohort

	Models					
	1		2		3	
Characteristic	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Continuous RCII	1.05 (1.03, 1.06)	<.001	1.04 (1.03, 1.06)	<.001	1.03 (1.02, 1.05)	<.001
RCII-Q1	Ref		Ref		Ref	
RCII-Q2	1.95 (1.69, 2.25)	<.001	1.93 (1.68, 2.23)	<.001	2.26 (1.91, 2.67)	<.001
RCII-Q3	4.35 (3.70, 5.12)	<.001	4.24 (3.63, 4.96)	<.001	5.08 (4.18, 6.18)	<.001
RCII-Q4	8.40 (6.97, 10.1)	<.001	8.19 (6.83, 9.81)	<.001	9.60 (7.83, 11.8)	<.001
P for trend		<.001		<.001		<.001

Nonlinear Association: RCS Analysis

The RCS models have been demonstrated Figure 5 and 6 which displayed the non-linear relationship between the RCII and CKM values obtained from both cohorts. The graphical curves showed the progressive increment in the CKM risk factor at low levels of RCII, followed by a steeper rise at higher RCII values without any noticeable plateau or inflection point. These results exhibited the continuous and accelerating risk elevations which support the biomarker capability of RCII for CKM risk sensation.

Summary

The present investigation focused on the link assessment between RCII and CKM utilizing 2 extensive nationally representative cohorts. The results indicate that RCII independently contributes to CKM risk and shows a significant dose-response correlation. Furthermore, the consistent association across various population subgroups indicates the potential of RCII as a novel inflammatory biomarker for cardiorenal-metabolic risk stratification.

Table 1-4 & Figure 3-6.

DISCUSSION

In the present study, 2 extensive, nationally representative population databases, China's CHARLS and the US NHANES, were analyzed enabling the first systematic assessment of the relationship between RCII and CKM. The results were consistent across both cohorts and indicated that increased RCII levels markedly increased the risk of CKM. Overall, RCII may be a sensitive and universal marker for assessing multisystem metabolic impairment.

The present revealed several important findings. First, previous studies on RCII primarily focused on predicting cardiovascular event risk. Residual cholesterol is an independent risk factor for CVD and correlates with systemic inflammation. For instance, in the EPIC-Norfolk study, each 1 mmol/L increment in RC corresponded to a 29.5% increase in hsCRP levels, underscoring the strong linkage between RC and systemic inflammation.[22,23] The elevated RC levels are directly linked to major cardiovascular events.[24] The establishment of RC as an independent predictor of cardiovascular death has been recognized by the NHANES-based analysis, which exhibited the linear correlation between RC and cardiovascular mortality.[25] RCII is a composite index of RC and hsCRP and shows higher prognostic value for cardiovascular risk prediction. Residual cholesterol inflammatory index was used to evaluate stroke risk in the CHARLS cohort, and higher stroke incidence was associated with increased RCII levels.[26] The present investigation extended this framework to CKM with particular emphasis on the identification of RCII for investigation of comorbidity risk in the heart, kidney, and metabolic system by the CKM.

The outcome generalizability was magnanimously enhanced by the broad population coverage through incorporation of CHARLS and NHANES in the investigation. The meticulous analytical model adjustment was carried out on broad spectrum variables including demographic, socioeconomic, lifestyle, and BMI confounders. The non-linear associations and dose-dependent relationships were validated through quartile analysis and RCS modeling. The sysregulated lipid metabolism and systemic inflammation exhibited dependency on the 2 major variables including RC and hsCRP. Their levels were associated with the extent of coronary artery disease even for individuals having normal LDL level.[26] These factors into a single composite index offers a tool for evaluating cardiovascular risk and disease severity. C-reactive protein contributes to atherosclerotic progression by promoting oxidative stress and plaque instability as well as associated with lipoprotein metabolism, particularly under hypertriglyceridemic and low HDL conditions, and exhibits an interactive role in CKM pathogenesis.[27,28] RC exacerbates atherosclerosis[23,24] by accumulating within macrophages, which promotes foam cell generation and endothelial dysfunction, which in turn intensifies vascular inflammation.[29-32] Further amplification of vascular inflammation can be triggered by the RC crystal upon activation of the NLRP3 inflammasome.[33] The increment in the level of RC and CRP in the CKM group with noticeably higher RCII values compared with the non-CKM group (NHANES: 14.55 vs. 4.91; CHARLS: 10.31 vs. 3.74; all $P < .001$) suggests the synergistic activation of lipid-inflammatory imbalance by the RCII.[26,34] The non-linear RCII–CKM risk interaction by the RCS analysis with a rapid risk escalation at higher RCII levels indicates the potential clinical "acceleration threshold" for risk stratification. Subgroup analyses indicated that, in NHANES, the RCII–CKM association remained consistent across age, sex, smoking, alcohol use, HTN, and DM subgroups, except for notable heterogeneity across racial groups, which suggests broad population applicability. In contrast, within CHARLS, HTN, DM, stroke, and smoking appeared to modulate the

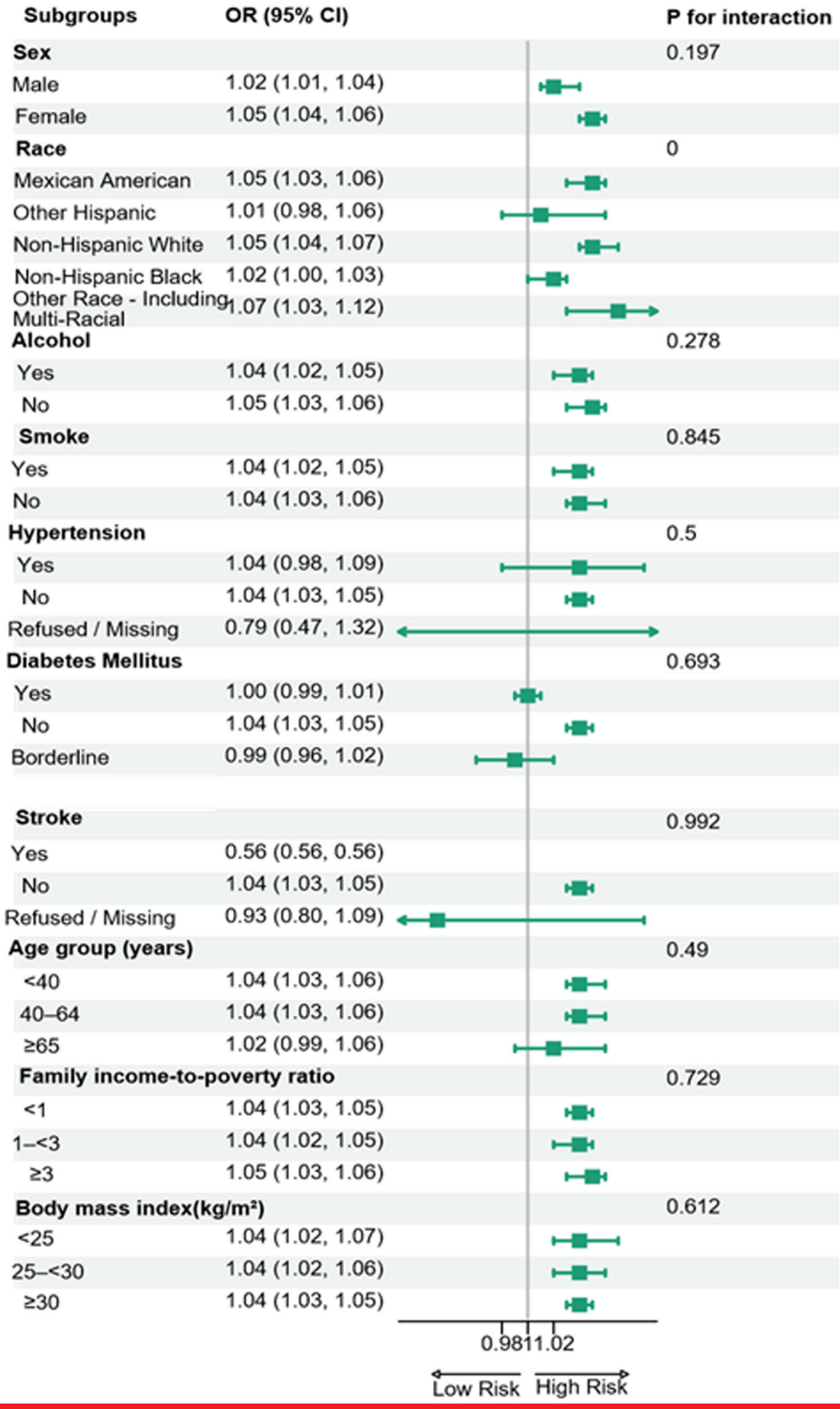

Figure 3. Forest plots: Subgroup analyses of the RCII–CKM relationship in the NHANES study

strength of the RCII–CKM relationship, suggesting that underlying disease states may affect the biomarker's predictive magnitude. Previous studies have indicated that cholesterol deposition within atherosclerotic plaques drives disease progression and correlates with plaque vulnerability,[35] which warrants clinical attention in risk management.

Despite several outcome-based results of the present investigation, it also carries some limitations. The first one includes that the cross-sectional design did not permit causal inference. Second, CHARLS lacked detailed data on diet, medication use, and renal function parameters (e.g., eGFR, proteinuria, etc.), introducing potential residual

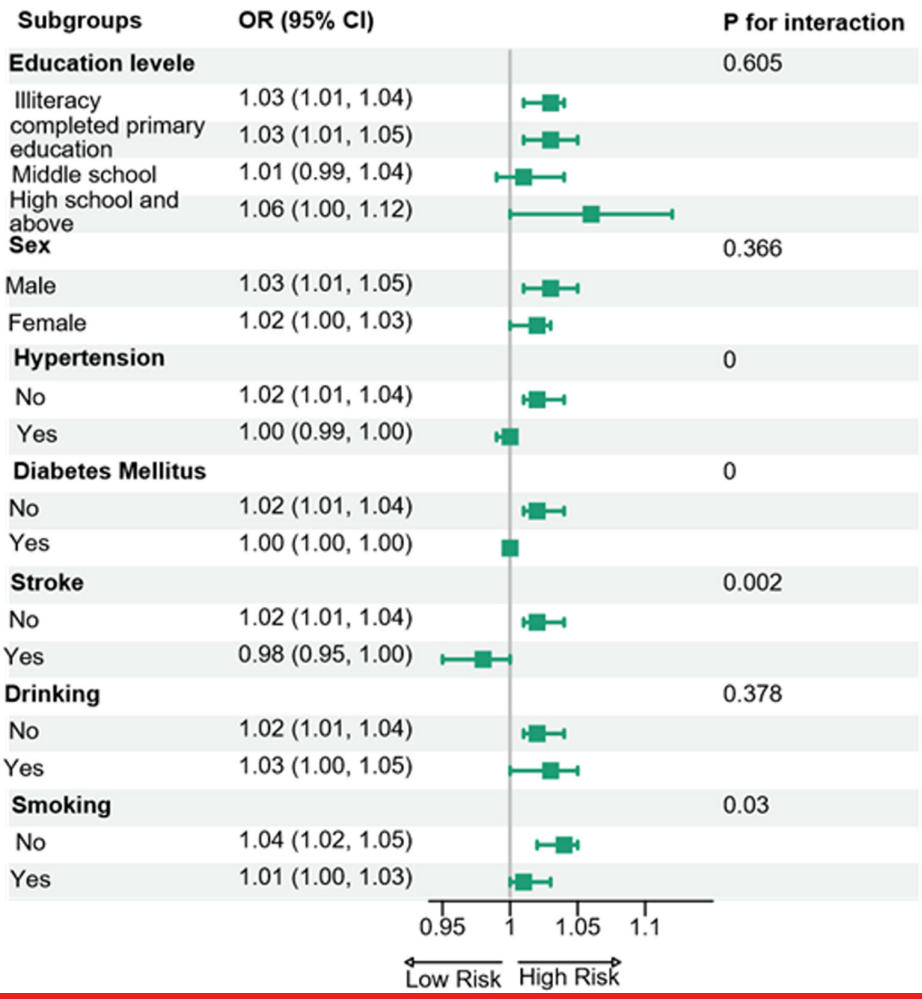

Figure 4. Forest plots: Subgroup analyses of the RCII–CKM relationship in CHRALS

confounding. Lifestyle factors were primarily self-reported, which may have resulted in information bias. Finally, although 3 progressively adjusted models were constructed, the effects of unmeasured confounders cannot be entirely excluded. Future investigations are required to clarify the causal mechanism by examining the temporal dynamics of

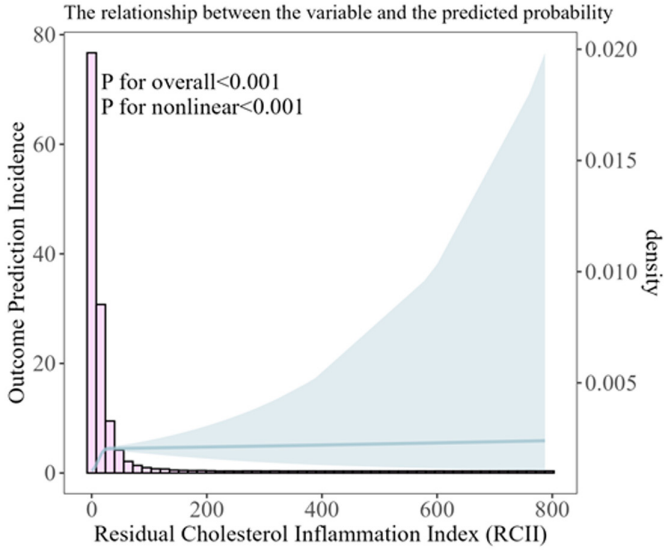

Figure 5. Nonlinear relationship of RCII with cardiorenal-metabolic syndrome incidence (NHANES data).

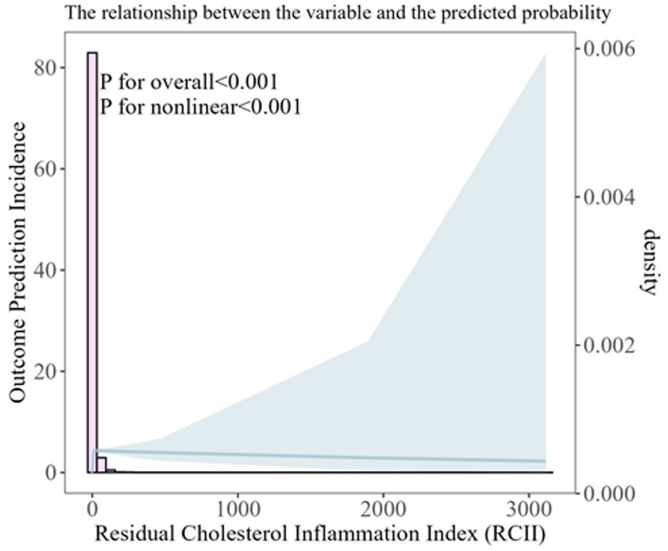

Figure 6. Nonlinear relationship of RCII index with cardiorenal-metabolic syndrome incidence (CHRALS data).

RCII relative to CKM onset and progression through prospective cohorts or interventional analysis.

CONCLUSION

The present investigation represents the significant interaction between increased RCII levels and elevated CKM risk, which has been established by utilizing 2 large national cohorts from China and the US that represent the dose-responsive relationship and model stability among the variables. Residual cholesterol inflammatory index potentially serves as an integrative biomarker that bridges inflammatory and lipid-metabolic pathways, offering a potential indicator for preliminary risk recognition and assessment of metabolic comorbidities. Although the cross-sectional design constrains causal inference, the results suggest that maintaining lower RCII levels might help mitigate CKM risk. Future studies should examine its predictive performance, mechanistic pathways, and response to interventions, offering novel tools and perspectives for preventing and managing CKM.

Data Availability Statement: The data used in this study were obtained from publicly accessible repositories. Data from the National Health and Nutrition Examination Survey (NHANES), provided by the US Centers for Disease Control and Prevention (CDC; https://www.cdc.gov/nchs/nhanes/), are openly available to the public. Data from the China Health and Retirement Longitudinal Study (CHARLS), conducted (http://charls.pku.edu.cn/), can be accessed upon registration and approval through the official data portal. No additional data were generated or used during the current study.

Ethics Committee Approval: National Health and Nutrition Examination Survey and CHARLS received ethical approval from their respective review boards, with NHANES authorized by the National Center for Health Statistics (NCHS) Ethics Review Board. Appropriate sampling weights were applied to ensure that the estimates could be generalized to the national populations of each country. The study was conducted in accordance with the Declaration of Helsinki.

Artificial Intelligence Usage Statement: During the preparation of this work, the author(s) used [CHATGPT] in order of GRAMMATICAL CORRECTION. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Informed Consent: Informed consent was obtained from all participants in the original CHARLS and NHANES studies. The present study used publicly available, de-identified data; therefore, no additional informed consent was required.

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