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C-reactive protein-triglyceride glucose index in evaluating cardiovascular disease and all-cause mortality incidence among individuals across stages 0–3 of cardiovascular–kidney–metabolic syndrome: a nationwide prospective cohort study

Huiwen Ou¹, Miaomiao Wei¹, Xin Li^{1*} and Xiaoshuang Xia^{1*}

Abstract

Objective The American Heart Association (AHA) developed the notion of cardiovascular–kidney–metabolic (CKM) syndrome, which emphasizes the interconnection of heart, kidney, and metabolic illnesses. The C-reactive protein–triglyceride–glucose (CTI) represents a potential indicator to assess the resistance to insulin and an inflammatory response. However, the connection among CTI, cardiovascular disease (CVD) incidence, and overall mortality rates remains uncertain, particularly among individuals at CKM stages 0–3.

Methods The China Health and Retirement Longitudinal Study (CHARLS) enrolled 17,705 middle-aged and elderly people. The primary outcome was the occurrence of CVD and overall mortality rates. The CTI was obtained by $0.412 * \ln(\text{CRP [mg/L]}) + \ln(\text{TG [mg/dL]} \times \text{FPG [mg/dL]})/2$. The correlation among CTI and CVD incidence and overall mortality was assessed via Cox proportional hazard models, Kaplan–Meier curves and restricted cubic spline (RCS) analysis. To improve the study results, a stratified analysis evaluated the influence of varying socio-demographic characteristics.

Results This study involved 5723 participants for CVD and 5847 participants for all-cause mortality in the CKM syndrome stages 0–3. RCS analysis revealed a notable non-linear association between CTI and CVD occurrence, as well as a linear association between CTI and all-cause death. After comprehensive multivariate adjustment, the data showed a striking 111% increase in overall mortality risk for every 1-unit rise in continuous CTI measurements.

Conclusions Findings show that higher CTI level significantly associated with CVD and death risk, highlighting its potential as a biomarker for individuals with CKM stages 0–3.

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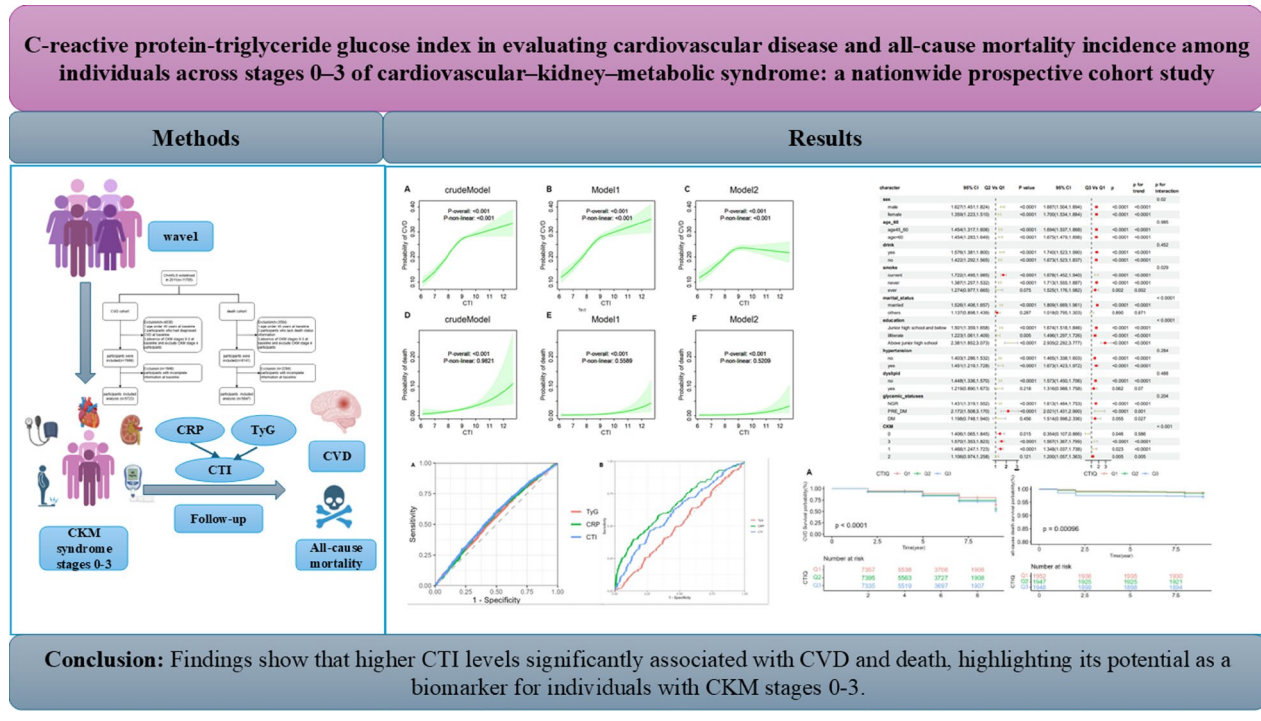
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Keywords C-reactive protein-triglyceride glucose index, Cardiovascular diseases, All-cause mortality, Cardiovascular–kidney–metabolic syndrome

Graphical abstract



Research insights

What is currently known about this topic?

- Previous study has shown CTI as a measure of resistance to insulin resistance and inflammatory response.

What is the key research question?

- How do CTI correlate with CVD occurrences and all-cause death in the individuals with stages 0–3 CKM syndrome?

What is new?

- This research represents the first comprehensive large-scale analysis examining the link between CTI and both CVD occurrence and overall death in individuals with CKM syndrome (stages 0–3), while also evaluating the relationship based on age, gender and glucose condition.

How might this study influence clinical practice?

- This study confirmed a notable curvilinear association between CTI and CVD occurrence, as well as a linear association between CTI and overall mortality. To reduce CVD risk and all-cause death, various strategies should be implemented for monitoring CTI levels, considering age, gender and glucose condition.

Introduction

Cardiovascular disease (CVD) ranks as the primary cause of mortality across the globe, accounting for 523 million instances in 2021, nearly twice the number in 1990 [1, 2]. The overall mortality rate refers to the proportion of deaths from all causes within a specified period compared to the normal cohort [3]. For example, a total of 19.8 million deaths worldwide were ascribed to CVD, highlighting the critical need to address all-cause mortality in 2022 [4].

Several studies have shown the complicated and intimate link between CVD, chronic kidney disease (CKD), and metabolism disturbances [5, 6]. Patients with CVD frequently present with coexisting hypertension, renal dysfunction, and metabolic imbalances—all sharing common pathological pathways—and these comorbidities significantly influence the risk of developing

CVD and determining outcomes [7]. Diabetes impacts approximately one-fifth of individuals with heart failure, heightening their likelihood of developing cardiovascular problems by two to four times. It is well-established that diabetes is the primary driver behind both CKD and the progression to end-stage renal disease [8]. Furthermore, roughly half of those with heart failure are affected by CKD [9]. Consequently, to curb the progression of CVD and lessen its substantial clinical burden, the AHA stresses the importance of dedicated research targeting the earliest, preclinical phases of CKM syndrome (Stages 0–3).

Insulin resistance denotes the diminished physiological efficacy of insulin, a prevalent pathological mechanism underlying several metabolic disorders, and is intricately correlated with the onset and progression of atherosclerosis [10, 11]. Insulin resistance may precipitate arterial rigidity as well as CVD due to increased inflammation, oxidative pressure, and impaired functional endothelial cells [12]. The triglyceride-glucose (TyG) ration effectively measures insulin sensitivity and is extensively utilized in clinical settings [13]. Increasing data suggests a substantial association between the TyG index and atherosclerosis, stroke, and worse CVD outcomes [14, 15]. Moreover, inflammation is regarded as a key underlying cause of stroke [16]. Inflammation has been found to markedly elevate stroke risks through facilitating the development of arterial stiffness, impairing blood vessel endothelial integrity, and augmenting blood clots [17]. C-reactive protein (CRP) is markedly correlated with stroke risk and has proven as a practical marker for assessing stroke events [18].

Insulin resistance and vascular inflammation account for the main causes of atherosclerosis, which is the main risk factor for CVD [19, 20]. The C-reactive protein-triglyceride glucose index (CTI), first proposed by Ruan et al. [21], adeptly combines insulin resistance and inflammation, thereafter achieving widespread application in clinical investigations. CTI demonstrates considerable prognostic significance for cancer cachexia outcomes across the whole individuals, and heart attacks risk [22, 23]. However, the connection between CTI and the CVD incidence and overall death, especially in persons who have CKM syndrome in the stage of 0–3, remains ambiguous.

We analyzed the China Health and Retirement Longitudinal Study (CHARLS) data to evaluate the complicated connections among CTI, CVD and mortality within CKM syndrome in order to fill in these important research gaps and provide more proof that CTI can be used in real-world situations.

Methods

Study design and population

Data were obtained from the China Health and Retirement Longitudinal Study (CHARLS), encompassing participants over the age of 45. Previous papers have provided detailed specifications of the research design and inclusion criteria [24]. The study data comprises baseline and following data obtained via standardized questionnaire and clinical assessments, which are based on a series of social, demographic, health status, and habitual behavior. The research complied with the Declaration of Helsinki and obtained approval from the Biomedical Ethics Review Board of Peking University (IRB 00001052-11015). All subjects provided written informed permission prior to being included in the study. More information on CHARLS is accessible on its official website (<http://charls.pku.edu.cn/en>).

The CHARLS nationwide baseline survey was performed from June 2011 to March 2012, with participants receiving face-to-face follow-up interviews every 2 years. The interviews were done by trained professionals using computer-assisted ways to make sure that all the data was collected in the same way [25]. In this study, individuals interviewed between 2011 and 2012 were classified as part of the baseline cohort, with follow-up data obtained in 2013, 2015, 2018, and 2020. The flowchart depicts the strict inclusion and exclusion criteria (Fig. 1). 17,707 respondents were included in the 2011 baseline survey and we excluded for the following reasons: (1) Age below 45 years at baseline; (2) absence of CKM stages 0–3 at baseline; (3) incomplete data on anthropometric, health-related, sociodemographic, or other biomarkers at baseline; (4) For CVD cohort: presence of CVD, heart disease, or stroke at baseline; (5) For death cohort: lack of death status information. Consequently, a total of 5723 and 5847 participants were incorporated into the final analysis to assess the association between CVD incidence and all-cause mortality. The distribution of variables with missing data in study shows on Table S1.

Calculation of CTI

The CTI index is calculated according to this formula [21]: $CTI = 0.412 \times \ln(CRP [mg/L]) + \ln(TG [mg/dL] \times FPG [mg/dL])/2$.

Definition of CKM syndrome stages 0–3

The AHA Presidential Advisory Statement [5] lists the stages of CKM syndrome as follows: Stage 0: Absence of CKM risk factors. Stage 1: overweight or dysfunctional adiposity. Stage 2: Presence of metabolic disorders, including hypertension, diabetes and elevated triglycerides, or CKD. Stage 3: Subclinical CVD in the context of CKM syndrome [26]. Table S2 details the concrete stage criteria for CKM syndrome.

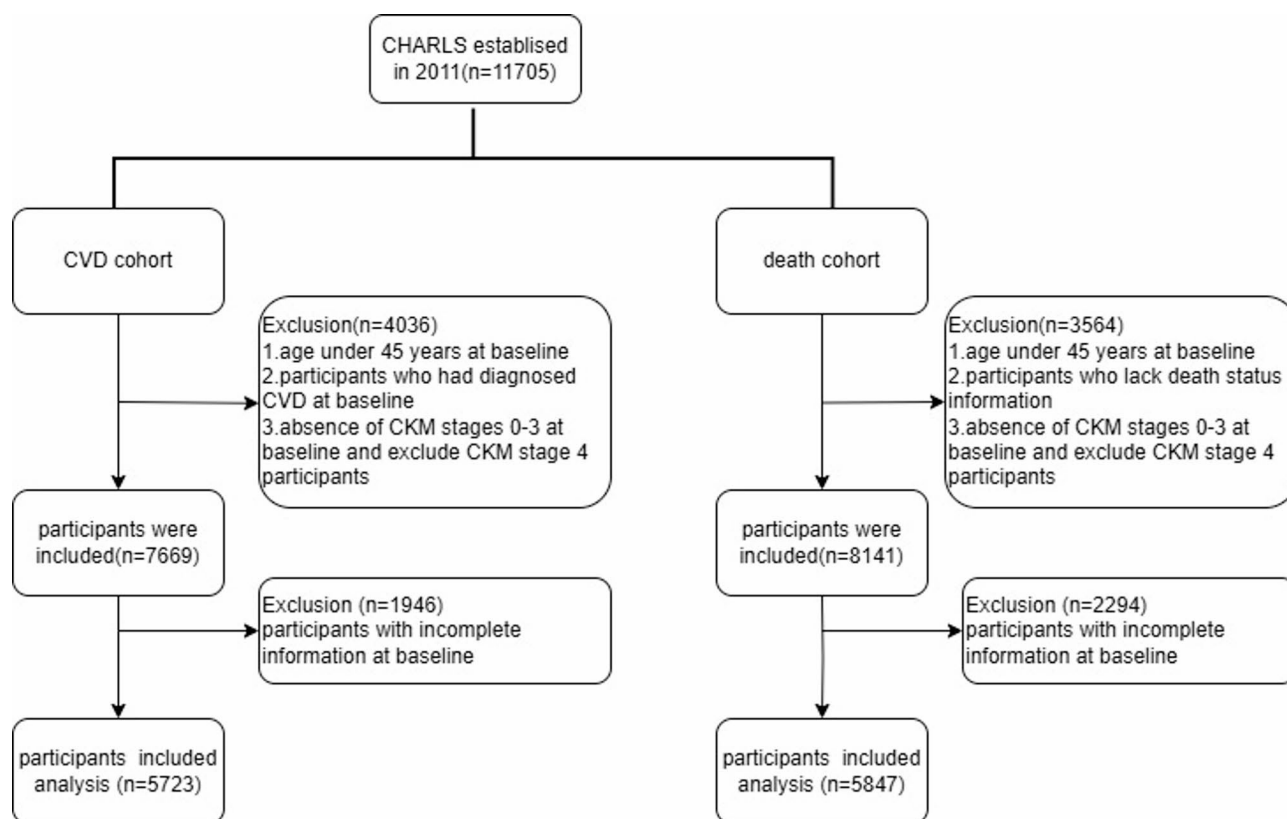


Fig. 1 Flow chart of study subjects

Ascertainment of outcomes

We chose the event of CVD and all-cause death as outcome indicators in people with 0–3 stages of CKM syndrome. The main endpoint CVD, encompassing heart disease and stroke, based on self-reported data. Individuals verified that they had obtained the accurate diagnosis of CVD through physicians, in accordance with established standards [27]. The CVD outcomes were defined as new instances occurring throughout the duration of observation, regardless of which happened early. The database team adopted stringent criteria to assure the precision and credibility of the data [24]. Deaths were determined from death certificates, medical records, or interviews with relatives in waves 2–5, but the exact time of death was only available in waves 2 and 5. The time-to-event was found by measuring the time between baseline and the last interview wave for participants.

Data collection

The CHARLS researchers collected variables based on previously established criteria. This study used the following sociodemographic and health data on baseline: Sociodemographic information included sex, age, educational attainment, marital condition, systolic blood pressure (SBP), diastolic blood pressure (DBP), and body mass index (BMI). Lifestyle information included smoking and

drinking habits. Physicians diagnosed diseases such as hypertension, glucose conditions (diabetes, prediabetes, and normal glucose regulation), dyslipidemia, and CVD and whether they were using medicine for hypertension, diabetes, and dyslipidemia. Furthermore, laboratory tests including triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), serum creatinine (Cr), estimated glucose disposal rate (eGFR), fasting blood glucose (Fglu), and HbA1c (Hb). Table S3 details the specific definitions of various diseases.

Statistical analysis

For quantitative variables that follow a normal distribution, results are presented as means and standard errors. Differences between groups are assessed using analysis of variance (ANOVA). For quantitative variables that do not conform to a normal distribution, we provide the median and interquartile range, evaluating differences among groups with the Kruskal–Wallis test. Categorical variables are described using counts and percentages, with statistical evaluations conducted using the Chi-square test. CTI tertiles were used to divide participants into three groups. To strengthen the study's credibility, CTI was evaluated both as a categorical and continuous measure. Multivariate Cox proportional hazards regression models were developed to explore the hazard ratios

(HRs) and 95% confidence intervals (CIs) for the correlation among CTI and CVD incidence as well as all-cause mortality. Proportional hazard assumptions for these Cox regression models were confirmed by the Schoenfeld residual. Model 1 was unadjusted, Model 2 adjusted for age, sex, smoking status, drinking status, marital status and educational level, and Model 3 contained additional adjustments for BMI, eGFR, hypertension, dyslipidemia, diabetes, Hypertension treatment, Diabetes treatment and dyslipidemia treatment. Restricted cubic splines (RCS) models with three nodes at the 10th, 50th and 90th percentiles of the CTI variable were applied to account for potential nonlinear associations.

A piecewise Cox proportional hazards regression model was applied to examine the correlation among the CTI index and CVD incidence as well as all-cause death. Additionally, K–M curves and log-rank tests were also employed to assess CVD risk and all-cause mortality with CTI. To assess the potential impact of CTI, CRP and TyG index for CVD risk and all-cause mortality, receiver operating characteristic (ROC) curves were developed. The area under the ROC curve (AUC) was employed to assess the increased value of CTI. In addition, for a more in-depth analysis of these relationships, subgroup analyses and interaction assessments were performed. Above analyses included stratification by various items, including sex, age (45–60 years and ≥ 60 years), alcohol consumption, smoking condition, marital status, educational level, hypertension, dyslipidemia, glucose levels (NGR, Pre-DM, and DM) and CKM 0–3 stages.

Results

Baseline characteristics

Table 1 displays baseline CVD risk factors stratified by CTI index tertiles. Finally, the final analysis included 5723 participants for CVD and 5847 participants for all-cause mortality. Individuals in the highest CTI tertile exhibit marked differences versus the lowest on various indicators. People in the top CTIs were the elderly and had high levels of BMI, SBP, DBP, fast blood glucose, HbA1c, LDL-C, TG, TC, serum creatinine, TyG, CRP, CTI. In addition, the prevalence of comorbidities such as hypertension, dyslipidemia, and diabetes was notably higher in people with elevated CTI levels. Baseline characteristics were compared between participants with and without CVD and all-cause death in Tables S4 and S5, while the detailed baseline characteristics comparison.

Association of CTI index with CVD and total mortality in CKM syndrome patients

As shown in Table 2, multivariable-adjusted analysis revealed a graded cardiovascular risk profile associated with CTI. Among CKM stage 0–3 individuals, the highest CTIQ quartile (Q3) showed 52% increased CVD risk

versus Q1 in the crude model (HR 1.52, 95% CI (1.44, 1.59), $P < 0.0001$), which remained significant after adjusting for demographic (age, gender, smoking, drinking status, marital status) and clinical confounders (BMI, eGFR, hypertension, diabetes, dyslipidemia, Hypertension treatment, Diabetes treatment, dyslipidemia treatment), with 18% excess risk in Model 2 (HR 1.18, 95% CI 1.12, 1.24, $P < 0.0001$; P -trend < 0.001). Meanwhile, the highest quartile (Q3) showed adjusted hazard ratios of 1.35 for TyG (95% CI 1.26–1.44; $P < 0.001$) and 1.43 for standardized CRP values (CRP-SD) (95% CI 1.34–1.52; $P < 0.001$). Both were lower than the CTI's highest quartile HR of 1.52 (95% CI (1.44, 1.59), $P < 0.0001$) (Table S7). For all-cause mortality, each unit increase in continuous CTI corresponded to 60% higher risk (Model 2: HR 1.60, 1.29–1.99, $P < 0.0001$). Stratified analysis demonstrated a 111% mortality increase in Q3 versus Q1 (Model 2: HR 2.11, 1.35–3.30, $P = 0.001$), whereas Q2 showed non-significant association ($P = 0.52$), indicating a threshold effect of CTI.

RCS and threshold effect analysis

We performed RCS analysis and threshold analysis to verify the association of CTI and CVD prevalence and mortality rates. For CVD incidence, standard Cox regression revealed non-linear association between CTI and CVD incidence (HR 1.075–1.224, $P < 0.0001$) (Fig. 2). Two-piecewise linear regression revealed a critical inflection point at $CTI = 8.602$: Below this threshold, each unit increase in CTI significantly elevated CVD risk (Model 2: HR 1.153, 95% CI 1.060–1.254, $P < 0.001$). Conversely, above the IP, CTI showed no significant association with CVD incidence in the fully adjusted Model 2 (HR 0.997, 95% CI 0.954–1.042, $P = 0.89$). The log-likelihood ratio test ($P < 0.0001$) confirmed the superiority in segmented model, highlighting a nonlinear dose–response pattern between CTI and CVD risk (Table S8). For all-cause mortality, standard Cox regression showed a notable linear trend between CTI and overall mortality (HR 1.486–1.674, $P < 0.0001$) (Fig. 2). While two-piecewise linear regression suggested a potential risk transition at $CTI = 8.606$ (HR 1.427–1.779, $P \leq 0.021$ above the threshold; no significant association below the threshold, HR 1.245–1.443, $P \geq 0.345$), the log-likelihood ratio tests ($P \geq 0.829$ for all models) indicated no statistically significant improvement in model fit with segmentation. Thus, despite localized risk differences near the inflection point, the overall relationship predominantly aligns with a linear pattern (Table S9).

Kaplan–Meier (K–M) survival curves

The Kaplan–Meier (K–M) survival curves showed an elevated CVD incidence or overall mortality in the high CTI group. The log-rank test's P values for the Q2 and Q3

Table 1 Baseline characteristics of the study individuals in CVD incidence

Variable	Total (n=5723)	Q1 (n=1908)	Q2 (n=1908)	Q3 (n=1907)	P value
Age, year	57.00 (51.00, 63.00)	56.00 (49.00, 62.00)	57.00 (52.00, 64.00)	58.00 (52.00, 63.00)	<0.0001
Sex, n (%)					<0.0001
Female	3128 (54.66)	967 (50.68)	1063 (55.71)	1098 (57.58)	
Male	2595 (45.34)	941 (49.32)	845 (44.29)	809 (42.42)	
Smoke status, n (%)					<0.01
Current	1729 (30.21)	632 (33.12)	567 (29.72)	530 (27.79)	
Ever	424 (7.41)	123 (6.45)	146 (7.65)	155 (8.13)	
Never	3570 (62.38)	1153 (60.43)	1195 (62.63)	1222 (64.08)	
Drink status, n (%)					<0.0001
No	3757 (65.65)	1183 (62.00)	1259 (65.99)	1315 (68.96)	
Yes	1966 (34.35)	725 (38.00)	649 (34.01)	592 (31.04)	
Marital status, n (%)					0.48
Married	5174 (90.41)	1723 (90.30)	1715 (89.88)	1736 (91.03)	
Others	549 (9.59)	185 (9.70)	193 (10.12)	171 (8.97)	
Educational level, n (%)					0.12
Above junior high school	575 (10.05)	201 (10.53)	186 (9.75)	188 (9.86)	
Illiterate	1609 (28.11)	517 (27.10)	578 (30.29)	514 (26.95)	
Junior high school and below	3539 (61.84)	1190 (62.37)	1144 (59.96)	1205 (63.19)	
BMI, kg/m ²	23.53±3.75	22.22±3.13	23.44±3.73	24.92±3.86	<0.0001
SBP, mmHg	128.81±20.43	124.63±19.56	128.86±20.08	132.95±20.79	<0.0001
DBP, mmHg	75.42±11.87	73.24±11.57	75.44±11.77	77.59±11.89	<0.0001
Fglu, mg/dL	102.06 (94.41, 111.60)	97.02 (90.72, 104.40)	100.98 (94.50, 108.54)	109.26 (100.62, 125.19)	<0.0001
Hb, mg/dL	5.26±0.76	5.08±0.46	5.18±0.53	5.51±1.06	<0.0001
LDL, mg/dL	117.86±34.43	113.50±29.79	122.18±33.59	117.90±38.79	<0.0001
TG, mg/dL	101.78 (73.46, 148.68)	68.14 (55.76, 83.19)	106.20 (84.96, 132.75)	173.46 (126.56, 233.64)	<0.0001
TC, mg/dL	194.70±37.52	185.53±33.58	195.00±36.28	203.58±40.23	<0.0001
Cr, mg/dL	0.77±0.18	0.76±0.18	0.76±0.17	0.78±0.19	<0.001
eGER, mL/min·1.73 m ²	122.51±29.17	125.37±28.28	122.31±27.83	119.84±31.06	<0.0001
TyG	8.64±0.64	8.10±0.32	8.59±0.33	9.24±0.61	<0.0001
CRP	0.96 (0.53, 1.96)	0.51 (0.35, 0.76)	0.99 (0.62, 1.73)	2.10 (1.14, 4.14)	<0.0001
Hypertension, n (%)					<0.0001
No	4530 (79.15)	1661 (87.05)	1528 (80.08)	1341 (70.32)	
Yes	1193 (20.85)	247 (12.95)	380 (19.92)	566 (29.68)	
Dyslipidemia, n (%)					<0.0001
No	5307 (92.73)	1846 (96.75)	1789 (93.76)	1672 (87.68)	
Yes	416 (7.27)	62 (3.25)	119 (6.24)	235 (12.32)	
Diabetes, n (%)					<0.0001
No	5472 (95.61)	1878 (98.43)	1847 (96.80)	1747 (91.61)	
Yes	251 (4.39)	30 (1.57)	61 (3.20)	160 (8.39)	
CVD, n (%)					<0.0001
No	4302 (75.17)	1540 (80.71)	1408 (73.79)	1354 (71.00)	
Yes	1421 (24.83)	368 (19.29)	500 (26.21)	553 (29.00)	
Hypertension treatment, n (%)					<0.0001
No	4846 (84.68)	1750 (91.72)	1633 (85.59)	1463 (76.72)	
Yes	877 (15.32)	158 (8.28)	275 (14.41)	444 (23.28)	
Diabetes treatment, n (%)					<0.0001
No	5568 (97.29)	1887 (98.90)	1873 (98.17)	1808 (94.81)	
Yes	155 (2.71)	21 (1.10)	35 (1.83)	99 (5.19)	
Dyslipidemia treatment, n (%)					<0.0001
No	5493 (95.98)	1875 (98.27)	1845 (96.70)	1773 (92.97)	
Yes	230 (4.02)	33 (1.73)	63 (3.30)	134 (7.03)	
CKM					<0.0001

Table 1 (continued)

Variable	Total (n = 5723)	Q1 (n = 1908)	Q2 (n = 1908)	Q3 (n = 1907)	P value
0	503 (8.79)	351 (18.40)	132 (6.92)	20 (1.05)	
1	1106 (19.33)	603 (31.60)	394 (20.65)	109 (5.72)	
2	2229 (38.95)	571 (29.93)	828 (43.40)	830 (43.52)	
3	1885 (32.94)	383 (20.07)	554 (29.04)	948 (49.71)	
NGR, mg/dL					< 0.0001
No	631 (11.03)	85 (4.45)	162 (8.49)	384 (20.14)	
Yes	5092 (88.97)	1823 (95.55)	1746 (91.51)	1523 (79.86)	
PRE-DM, mg/dL					< 0.0001
No	5323 (93.01)	1838 (96.33)	1779 (93.24)	1706 (89.46)	
Yes	400 (6.99)	70 (3.67)	129 (6.76)	201 (10.54)	

Table 2 Multivariate cox regression for the correlation between CTI, CVD and overall mortality risk

CTI	Crude model		Model 1		Model 2	
	95% CI	P	95% CI	P	95% CI	P
CVD incidence						
Categories						
Q1	Ref		Ref		Ref	
Q2	1.35 (1.28, 1.42)	< 0.0001	1.3 (1.24, 1.37)	< 0.0001	1.19 (1.13, 1.26)	< 0.0001
Q3	1.52 (1.44, 1.59)	< 0.0001	1.45 (1.38, 1.53)	< 0.0001	1.18 (1.12, 1.24)	< 0.0001
All-cause mortality						
Continuous	1.49 (1.24, 1.79)	< 0.0001	1.6 (1.32, 1.94)	< 0.0001	1.67 (1.36, 2.06)	< 0.0001
Categories						
Q1	Ref		Ref		Ref	
Q2	1.24 (0.78, 1.96)	0.36	1.2 (0.76, 1.90)	0.44	1.17 (0.73, 1.86)	0.52
Q3	1.95 (1.28, 2.97)	0.002	2.02 (1.32, 3.09)	0.001	2.11 (1.35, 3.30)	0.001
P for trend		0.001		< 0.001		< 0.001

Crude model: unadjusted for covariates; model 1: age, gender, smoke status, drink status, marital status, education; model 2: age, gender, smoke status, drink status, marital status, educational level, BMI, eGFR, hypertension, dyslipidemia, diabetes, Hypertension treatment, Diabetes treatment, dyslipidemia treatment

groups, all below 0.05, confirm a higher risk compared to the Q1 group (Figure S1).

Subgroup analyses

To delve deeper into the connection between CTI and the likelihood of CVD or all-cause mortality, researchers conducted subgroup and interaction analyses on various variables, which include age, gender, tobacco use, alcohol consumption, marital status, education attainment, diabetes status, hypertension, dyslipidemia, glucose levels (including NGR, Pre-DM, and DM), and CKM syndrome (0–3 stages). For CVD incidence, sex stratification revealed markedly higher CVD risk in males (*HR* 1.627, 95% *CI* 1.451–1.824; *P* < 0.0001) compared to females (*HR* 1.359, 95% *CI* 1.223–1.510; *P* < 0.0001), with a pronounced interaction effect (*P* = 0.02). A dose–response relationship was evident, as higher CTIQ quartiles (Q3 vs. Q1) consistently correlated with elevated CVD risk across all strata (*P* for trend < 0.0001). Notably, smoking status (*P* = 0.029) and marital status (*P* < 0.0001) exhibited significant interactions, where current smokers (*HR* 1.722, Q2 vs. Q1) and married individuals (*HR* 1.809, Q3 vs. Q1) showed heightened vulnerability. Conversely, no interaction was

observed for age, hypertension, or dyslipidemia (*P* > 0.05). Education level further modulated risk, with individuals above junior high school education displaying the steepest CTIQ-associated risk gradient (*HR* 2.935, Q3 vs. Q1; *P* < 0.0001) (Figure S4, Table S12). For overall mortality, lower education (e.g., “Junior high school and below”: *HR* 1.656, *P* < 0.001) and non-drinkers (*HR* 1.774, *P* < 0.0001) showed elevated mortality. CTI consistently predicted mortality across most subgroups (e.g., males: *HR* 1.538; females: *HR* 1.628, both *P* < 0.01), despite nonsignificant interactions for sex (*P* = 0.783) and age (*P* = 0.658). Notably, pre-diabetic individuals exhibited a non-significant trend toward heightened risk (*HR* 1.497, *P* = 0.254), warranting further investigation. The most pronounced interaction emerged in CKM strata (*P* < 0.001), which revealed CKM = 0 individuals have an exceptionally high risk (*HR* 8.225, 95% *CI* 2.558–27.964, *P* < 0.001). Therefore, the future study assessed the connection between CTIQ and overall death in the 0–3 stage of CKM group: CKM Stage 0 exhibited an extreme hazard ratio (Q3 vs. Q1: *HR* 19.611, 95% *CI* 2.251–171.300, *P* = 0.004), but with wide confidence intervals (Figure S5, Table S13).

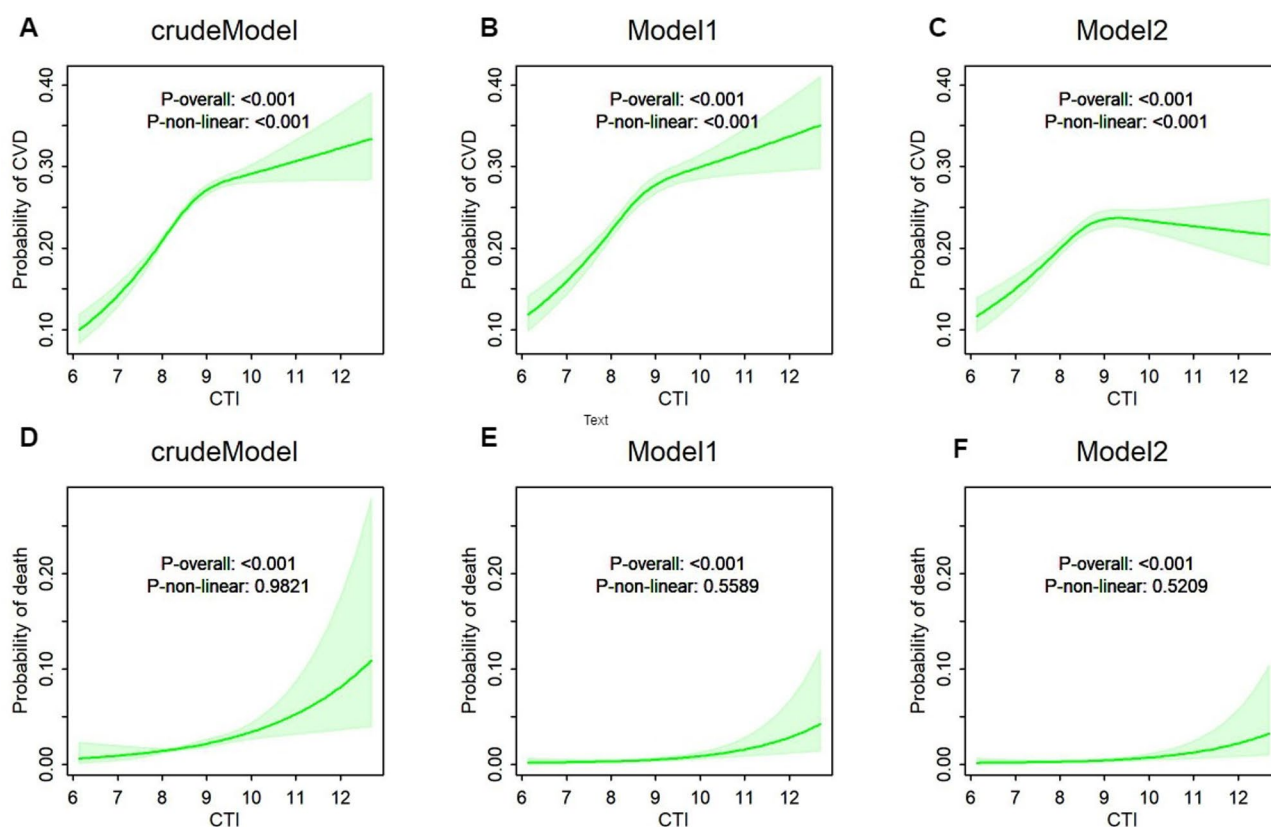


Fig. 2 RSC showing the connection between CTI, CVD incidence and all-cause death events. (A–C) cardiovascular disease. (D–F) All-cause mortality. Crude model: unadjusted for covariates; Model 1: Adjust for: age, gender, smoke, drink, marital status, education; Model 2: Adjusted for: age, gender, smoke, drink, marital status, education, BMI, eGFR, hypertension, dyslipidemia, diabetes, Hypertension treatment, Diabetes treatment, dyslipidemia treatment

AUC and ROC

For CVD risk, CRP and CTI retained comparable performance (AUC=0.66 and 0.61, respectively), whereas TyG again performed at chance level (AUC=0.5). Similarly, for all-cause mortality, CRP demonstrated moderate predictive utility (AUC=0.66, 95% CI 0.61–0.66), just ahead of CTI (AUC=0.61, 95% CI 0.56–0.61), while TyG showed no discriminative capacity (AUC=0.5, 95% CI 0.45–0.5). The findings indicate that CTI could outperformed CRP and the TyG index in assessing overall mortality risk stratification (Figure S6).

Sensitivity analyses

To check the stability of our findings, we conducted multiple sensitivity analyses. Firstly, in order to tackle the issue of missing data and to limit the possibility of bias, we employed multiple imputations. Subsequent analysis revealed that the correlation among CTI and CVD incidence and overall mortality was in accordance with the basic results (Table S10). Secondly, the application of logistic regression models to investigate the connection between CTI and CVD incidence, as well as all-cause mortality, yields consistent results. (Table S11). Thirdly,

the analysis of the piecewise Cox regression model confirmed result stability (Tables S12–S13). Fourthly, we also assessed the correlation among CTI and CVD incidence and overall mortality stratified by sex, age, and glucose level (grouped into NGR, Pre-DM, and DM). (Table S14). Furthermore, we explored additional analyses to analyze the associations of TyG and CRP standardized values (CRP-SD) with both CVD incidence and all-cause mortality, thereby validating the robustness of our primary findings (Table S7). Moreover, analyses stratified by sex and CKM stage (0–3) revealed consistent associations between CTI and adverse outcomes, as evidenced by Kaplan–Meier curves (all log-rank $P < 0.05$) (Figures S2 and S3). We excluded those individuals who died within 2 years of baseline to reduce potential bias from early terminal events (Table S6). Finally, RCS analyses (4 knots located at Harrell's recommended percentiles) were also adopted to further assess the nonlinear associations of CTI and the risk of CVD and death (Table Figure S7).

Discussion

We enrolled the subjects diagnosed with CKM syndrome across stages 0–3, categorizing them according to initial CTI evaluations. Using Cox proportional hazards models, we then analyzed how CTI levels correlated with both CVD occurrence and overall mortality rates. The main points of the study can be described in the following way: The dual role of CTI: a threshold-driven non-linear association with CVD incidence and a continuous linear predictor of all-cause mortality. Specifically, below an inflection point at 8.602, CTI was strongly associated with CVD risk, whereas the association attenuated above the inflection point. Notably, each 1-unit increment of continuous CTI was linked to a 111% excess overall mortality in completely adjusted analyses. These results not only support the therapeutic usefulness of CTI evaluation in older patients with CKM syndrome but also furnish critical data for precise risk classification in this demographic.

This index integrates CRP, an established inflammatory marker, with the TyG index reflecting insulin resistance. Substantial evidence links elevated TyG to increased CVD risk and mortality across populations, including specific subgroups such as hypertensive and diabetic patients [28–30]. Similarly, CRP independently predicts CVD outcomes, particularly stroke recurrence and diabetic complications [31]. Building on this evidence, CTI—combining both pathways—has shown predictive value for cardiovascular events in non-CKM contexts [32, 33]. Although the specific mechanism of CTI and CVD and overall mortality during the 0–3 CKM phase is still obscure, it can be elucidated by the following factors. Insulin resistance and chronic inflammation impair the integrity of the endothelium, reduce the body's ability to utilize nitric oxide effectively, disrupt healthy blood clotting mechanisms, and speed up the occurrence of atherosclerosis. All of these significantly increase CVD risk [34, 35]. Furthermore, inflammation may exacerbate insulin resistance, triggering tissue-derived inflammatory mediators and amplifying systemic inflammation. Inflammation and insulin resistance exhibit collaborative consequences that mutually promote and exacerbate each other, thereby increasing the risk of CVD [36]. Moreover, Atherosclerotic plaque stability undermined by inflammation and insulin resistance. This instability heightens rupture risk, potentially resulting in thrombosis and consequently contributing to the incidence of CVD and overall mortality [37]. Insulin resistant and inflamed patients often suffer from co-morbidities such as hypertension, diabetes, obesity, and metabolic syndrome. For metabolic syndrome, the processes of CVD risk and overall mortality essentially include lipid metabolism, Oxidative Stress, and inflammatory response [38].

The most significant difference between CKM syndrome and previous frameworks that emphasized CVD risk factors is the inclusion of CKD. The bidirectional relationship between CKD, metabolic dysfunction, and chronic inflammation creates a vicious cycle driving disease progression. Metabolic disorders like insulin resistance and ectopic lipid deposition promote kidney damage through oxidative stress and fibrosis, while CKD exacerbates these disturbances via toxin accumulation, hormonal imbalances, and sustained inflammation. Additionally, the “cardiorenal cross-worsening axis” highlights how CKD and CVD mutually reinforce each other: heart failure reduces renal perfusion, while CKD-induced volume overload and hypertension increase cardiac strain, contributing to the high cardiovascular mortality in advanced CKD patients [39]. Notably, our sensitivity analyses confirmed CTI's prognostic independence from baseline eGFR ($\Delta\text{HR} < 15\%$ after adjustment), suggesting it captures upstream drivers that concurrently target both cardiovascular and renal systems. Supporting this, eGFR progressively decreased across CKM stages (Stage 0: 126.34 ± 25.42 vs. Stage 3: 117.77 ± 31.41 mL/min/1.73 m², $P < 0.001$) (Table S15), yet CTI's risk stratification remained significant even within matched eGFR strata. The effect of CKD is substantial, yet awareness of the disease's effects at the population level is relatively low. Future studies should explore CTI's utility in monitoring renal trajectory within the CKM continuum.

Our study demonstrated that people with higher CTI may have more severe vascular damage, a higher incidence of CVD, and a higher death rate from all causes. The analysis of RCS demonstrated a complex, non-linear relationship correlation between CTI and CVD incidence, indicating that varying levels of CTI within the population experiencing 0–3 stages of CKM syndrome may exert dynamic effects: Below the threshold ($\text{CTI} < 8.602$), subclinical inflammation indicated by elevated CRP, along with developing insulin resistance reflected by an increased TyG index, may work together to activate pro-inflammatory pathways in vascular endothelial cells, such as NF- κ B signaling. This activation can enhance monocyte adhesion and foam cell formation through the regulation by modulating adhesion factors like VCAM-1 and ICAM-1, thus fostering the progression of early atherogenesis [40, 41]. Interventions aimed at suppressing inflammation, such as statins, or enhancing insulin sensitivity, such as GLP-1 receptor agonists, during this phase may produce optimal preventive results. Beyond the inflection ($\text{CTI} \geq 8.602$), chronic inflammation drives macrophage M1 polarization, releasing IL-6/TNF- α to activate MMP-9/MMP-2, degrading fibrous caps and increasing intraplaque neovascularization [42], while TyG-induced AGEs-RAGE signaling perpetuates mitochondrial dysfunction and

endothelial apoptosis, accelerating fibrosis even post-CTI reduction [43]. Simultaneously, persistent elevation of CTI interferes with intrinsic protective mechanisms via dual metabolic and inflammatory stress. This nonlinearity indicates a shift from reversible endothelial damage to irreversible vascular remodeling, underscoring the necessity for early dual pathway targeting.

While CTI's moderate AUC reflects inherent limitations of single biomarkers, its integration into existing models enhances risk stratification precision in CKM stages 0–3. Our analysis reveals a paradoxical association between CKM stage 0 (no overt cardiometabolic disease) and heightened all-cause mortality (P -interaction < 0.001). While counterintuitive, this finding may reflect limitations in current CKM stratification. First, classification misalignment is plausible: undiagnosed subclinical conditions (e.g., IR, vascular dysfunction) or non-traditional risk factors (chronic inflammation, epigenetic alterations) could drive mortality without meeting conventional diagnostic thresholds. Second, residual confounding occurs even after multivariable adjustments: socioeconomic inequalities, lifestyle heterogeneity (e.g., psychological stress, food habits), and competing hazards (e.g., cancer/trauma-related deaths) may disproportionately impact "apparently healthy" groups. Third, selection bias merits scrutiny: CKM stage 0 cohorts often exclude individuals with incomplete biomarker data, potentially inflating mortality estimates. Methodologically, we propose three validations: (1) Reclassification using extended biomarkers (e.g., coronary calcium scoring, urinary albumin-to-creatinine ratio) to detect occult disease; (2) Competing risk analysis differentiating between cardiovascular and non-cardiovascular causes; (3) Sensitivity analyses that include social determinants, such as neighborhood deprivation indices and healthcare access, are essential. If validated, this indicates a significant shift in understanding: "metabolically healthy" phenotypes may conceal underlying multiorgan dysregulation that necessitates the identification of new biomarkers, including mitochondrial DNA integrity and senescent cell burden. Meanwhile, this study also underscores the urgency of expanding multicenter cohorts to validate extreme risk estimates in CKM Stage 0 and resolve contradictions in intermediate phases. These results cast doubt on the CKM framework's capacity to identify dangers in their early stages. To improve preventative measures, we suggest using dynamic risk trajectories instead of static baseline staging.

These results give fresh perspectives for clinical treatment, implying that including CTI into routine examinations is a convenient, easily available technique for assessing individuals with CKM phases 0–3. Physicians can more accurately assess patients' metabolic health and create customized treatment plans by using dynamic

monitoring of CTI changes, which increases the accuracy and efficacy of illness management. Periodic CTI monitoring reduces the risk of negative outcomes and improves long-term survival rates by facilitating early diagnosis of disease development, supporting clinical decision-making, and enabling prompt interventions to avert deterioration.

Strength and limitation

There are some noteworthy advantages to the current investigation. First, it concentrates on the clinically significant but frequently disregarded person in CKM stages 0–3. This article is the earliest research to investigate the use of the CTI index in evaluating CVD incidence and overall mortality in people with 0–3 stages of CKM, offering considerable clinical significance and novelty. Secondly, the data included in this study employed a complicated method to finally choose 5723 qualifying individuals in CVD incidence and 5837 for mortality from a nationwide survey. The extensive dataset guarantees robust statistical significance. Furthermore, this research examines the connection among CTI, CVD incidence and overall mortality in people throughout 0–3 stages of CKM, which advances research in this area. Finally, we carried out thorough sensitivity analyses and strictly adjusted for potential contributors to guarantee the validity and dependability in our findings.

However, certain study constraints must be noted. Initially, the subjects consist exclusively of middle and elderly Chinese, thereby constraining the scope of the results' applicability. Secondly, the Framingham 10-year score for the risk of CVD was used for CKM syndrome staging instead of the most recent PREVENT equation, which may have an impact on staging accuracy. Thirdly, a restricted number of individuals were included in this research due to stringent exclusion criteria, which may have resulted in attrition bias for the participants. Fourthly, the accuracy of results is impacted by the reliance on self-reports for illness diagnosis, which may result in an underestimation of prevalence and an inability to differentiate between different forms of CVD or all-cause death. Fifthly, the possible impact of these alterations on mortality risk is unknown since the CTI index was merely evaluated at the initial assessment, and no analysis of fluctuations during the follow-up phase was conducted. In addition, the limitation of death ascertainment to waves 2–5, combined with our CKM 0–3 cohort's inherently healthier profile compared to general populations, could lead to underestimation of actual mortality rates. Future research should explore how changes in CTI across time affect CVD incidence and all-cause mortality. Furthermore, the use of Cox models without formal competing risk adjustment may overestimate CVD risk. Future studies with cause-specific

mortality data should apply Fine-Gray models. Finally, we were unable to do a Mendelian randomization study because there was insufficient genetic data for the CKM stages 0–3 cohort. To confirm the results and offer stronger support for research in related fields, more thorough investigation in additional substantial cohort studies and more multimodal prediction algorithms are required in the future.

Conclusions

In summary, this study employed the CHARLS database and an innovative integrated predictor of insulin resistance and inflammation, termed CTI, to significantly assess CVD incidence and all-cause death in the stage 0–3 CKM cohort. The results indicated the substantial connection among elevated CTI levels and a heightened CVD risk and all-cause mortality, implying that CTI may function as a predictive indicator in stages 0–3 of CKM subjects.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12933-025-02848-9>.

Supplementary Material 1

Author contributions

Huiwen Ou developed the study framework and drafted the manuscript. Huiwen Ou participated in the statistical analysis. Miaomiao Wei performed the literature review and compiled the illustrations. Xin Li and Xiaoshuang Xia conducted manuscript editing and review. All contributors endorsed the final draft.

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Data availability

The CHARLS has been cleared by Peking University Biomedical Ethics Review Board, with all individuals offering informed agreement. CHARLS data repository: <http://charls.pku.edu.cn/en>.

Declarations

Ethics approval and consent to participate

The CHARLS has been cleared by Peking University Biomedical Ethics Review Board, with all individuals offering informed agreement.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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