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Associations of cumulative exposure and dynamic trajectories of the C-reactive protein-triglyceride-glucose index with incident cardiovascular disease in middle-aged and older Chinese adults: a nationwide cohort study

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Abstract

Objective This study aimed to explore the relationships between cumulative C-reactive protein-triglyceride-glucose index (cuCTI) and CTI changes and the risk of new-onset cardiovascular disease (CVD) in middle-aged and older Chinese individuals.

Methods This longitudinal study employed data from the China Health and Retirement Longitudinal Study. To evaluate the association between the cuCTI index and CVD risk, we conducted Cox regression analyses alongside restricted cubic spline (RCS) regression models. The participants were categorized into three groups on the basis of the dynamic changes in the CTI through K-means clustering. Subgroup analysis and sensitivity analysis were performed to confirm the robustness of the results.

Results A total of 4157 participants were included in the study, of whom 609 (13.5%) were diagnosed with CVD. The incidence risk of CVD increased with increasing cuCTI. In fully adjusted Model 3, the Cox regression results indicated that, compared with those in Q1, participants in Q2 had a significantly greater risk of developing CVD (HR, 1.53 [1.22, 1.92], $P_{\text{adj}} < 0.001$); similarly, participants in Q3 had a 1.36 [1.07, 1.74] increased risk ($P_{\text{adj}} = 0.014$). RCS analysis revealed a linear association between cuCTI and the risk of CVD ($P_{\text{adj}} < 0.05$). K-means clustering identified three groups of CTI trajectory changes. Compared with participants with consistently low CTI levels, those with persistently high and increasing CTI levels had a significantly elevated risk of developing CVD (HR, 1.31 [95% CI 1.01–1.70], $P_{\text{adj}} = 0.041$). Subgroup and interaction analyses revealed no statistically significant differences across all subgroups (all $p > 0.05$).

Conclusion This study revealed that cuCTI and changes in CTI are independently associated with the risk of CVD among middle-aged and elderly individuals with elevated cuCTI levels, particularly those with sustained high

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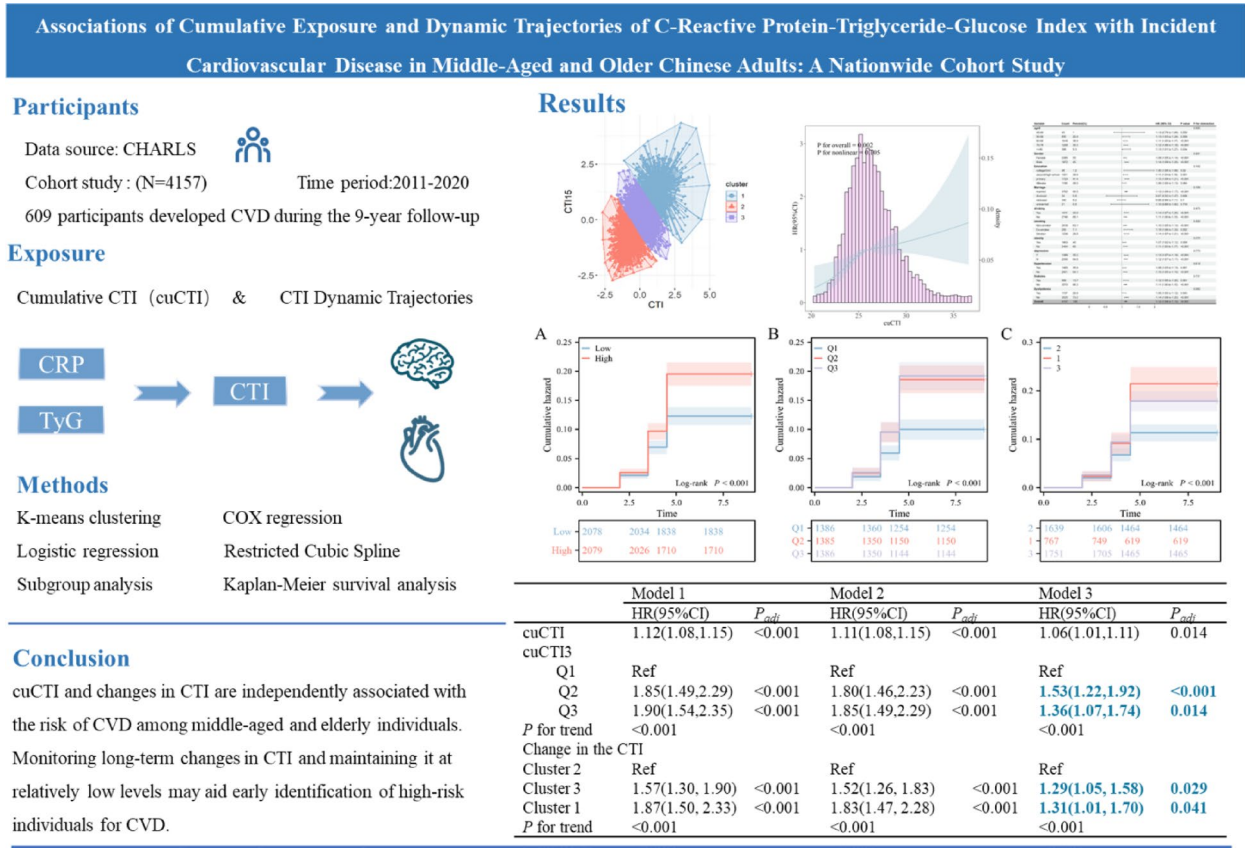


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CTI levels, exhibited a significantly higher risk of CVD. As a cost-effective and accessible tool, cuCTI may provide supplementary information for assessing CVD risk. Monitoring long-term changes in the CTI and maintaining it at relatively low levels may aid early identification of individuals at high risk for CVD.

Keywords Cardiovascular diseases, C-reactive protein-triglyceride-glucose index, Dynamic changes, K-means clustering, Inflammation, Insulin resistance

Graphical abstract



Introduction

Cardiovascular disease (CVD) remains the primary threat to global public health, causing approximately 17.9 million deaths annually and accounting for 32% of all deaths worldwide [1]. In China, the burden of CVD is particularly severe [2]. According to the *China Cardiovascular Health and Disease Report*, the current prevalence of CVD has reached 330 million cases. CVD mortality ranks first among all causes of death, accounting for 44% of total mortality, with an annual incidence growth rate of 7.6% [3, 4]. Despite progress in preventing and managing traditional risk factors, the incidence of CVD in populations with residual risk remains high [5], highlighting the urgent need to develop novel biomarkers to optimize risk stratification systems.

Current studies demonstrate that the synergistic interplay between inflammation and insulin resistance (IR) represents a fundamental mechanism driving residual CVD risk [6]. Inflammation promotes atherosclerotic plaque instability, endothelial damage, and thrombus formation by activating the NF- κ B signaling pathway, which plays a pivotal role in CVD progression and pathogenesis [7]. C-reactive protein (CRP), a classical inflammatory biomarker, is recognized as a potential indicator of residual CVD risk [8], serving as a promising biomarker for multiple CVD risk assessments [9] and holding promise for stratified management of CVD [10]. The triglyceride-glucose (TyG) index, a well-validated biomarker of insulin resistance, shows strong associations with poor CVD events [11, 12]. Notably, evidence suggests a significant interactive effect between inflammation and IR [13], implying that single-marker assessments may have biological pathway bias. Integrative evaluation of TyG and CRP could therefore improve cardiovascular risk re-stratification [14].

In this context, the C-reactive protein-triglyceride glucose index (CTI) has emerged as a dual-dimensional biomarker that integrates inflammation and metabolism [15]. Previous studies have confirmed associations between traditional CTI (CRP $\times$ TG/FBG) and cardiovascular risk in specific populations. For example, cross-sectional studies have shown that each 1-unit increase in CTI is associated with a 35.7% higher risk of CHD [16] and a 19% higher risk of stroke [17]. Tang et al. [18] reported that the CTI predicts stroke risk in hypertensive individuals (HR = 1.21, 95% CI 1.08–1.37), and Cui et al. [19] demonstrated that a concurrently high TyG index and hsCRP were associated with increased cardiovascular disease risk (aHR = 1.300, 95% CI 1.155–1.462). However, no study has explored the associations between the cumulative exposure/dynamic trajectories of cuCTI and CVD risk in the general population. However, existing evidence is primarily based on single-time point measurements and overlooks the dynamic evolution

characteristics of metabolic-inflammatory burden, lacking longitudinal evaluation of the cumulative effects of CTI (cuCTI). Cumulative indicators and dynamic trajectory patterns derived from multi-timepoint measurements may better capture the synergistic effects of chronic inflammation and metabolic dysregulation. For example, Ren et al. demonstrated that cumulative TyG-waist-to-height ratio (TyG-WHtR) exposure improved CVD prediction efficiency (AUC = 0.596), a ~5% improvement over the single-time-point TyG-WHtR [20]; Wu et al. reported that changes in TyG predicted stroke incidence in the general population aged > 45 years [21]. However, longitudinal research on CTI remains limited, and the associations of both cumulative CTI (cuCTI) and dynamic CTI trajectories with CVD risk have yet to be fully elucidated. Therefore, it is essential to assess the relationships between cuCTI and longitudinal CTI changes and the risk of CVD.

This study uses national cohort data from the China Health and Retirement Longitudinal Study (CHARLS) and multiwave follow-up data (2011–2020) to assess the predictive value of cuCTI exposure and CTI trajectories for incident CVD risk in middle-aged and elderly populations. By constructing restricted cubic spline (RCS) models, this study explores the dose-response relationship of metabolic-inflammatory burden offering new evidence for precision prevention.

Methods

Study design and participants

This study utilized data from the China Health and Retirement Longitudinal Study (CHARLS), a nationally representative longitudinal survey employing multistage stratified sampling. The initial national baseline survey (Wave 1) was conducted in 2011, enrolling 17,708 middle-aged and older adults across 450 villages from 150 districts in 28 Chinese provinces. Demographic and clinical information was collected via standardized questionnaires. Follow-up surveys were conducted biennially to triennially thereafter to monitor health outcomes. No additional interviews were conducted for this analysis. The study incorporated five waves of existing CHARLS data (2011, 2013, 2015, 2018, and 2020). The detailed methodologies and data collection procedures for CHARLS have been previously described [22]. Ethical approval was granted by the Peking University Biomedical Ethics Review Committee (IRB00001052-11015), and all participants provided written informed consent.

Fasting status, blood glucose, and triglyceride levels were obtained from blood samples collected during Waves 1 and 3. The exclusion criteria were as follows: (1) age $\leq$ 45 years; (2) prior CVD event or missing CVD data before Wave 3 (2015); (3) nonfasting status; (4) missing data for age, sex, C-reactive protein (CRP), fasting

blood glucose (FBG), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), or total cholesterol (TC); and (5) missing or abnormal waist circumference measurements (defined as values exceeding three standard deviations from the mean). The detailed inclusion and exclusion process is outlined in Fig. 1. The final analysis cohort comprised 4157 participants.

Assessment of CTI changes

The TyG index, CTI, and cumulative CTI (cuCTI) were calculated via the following formulas: TyG index = $\ln [\text{triglycerides (mg/dL)} \times \text{glucose (mg/dL)} / 2]$; $\text{CTI} = 0.412 \times \ln(\text{CRP [mg/L]}) + \ln(\text{TG [mg/dL]} \times \text{FPG [mg/dL]}) / 2$ [15].

The cumulative CTI (cuCTI) was calculated via a linear model as the product of the mean CTI values from 2012 and 2015 and the time interval, following the formula: $\text{cuCTI} = (\text{CTI}_{2012} + \text{CTI}_{2015}) / 2 \times \text{time interval (2015 - 2012)}$. CTI_{2012} and CTI_{2015} denote CTI measurements from 2012 (Wave 2) and 2015 (Wave 3), with a 3-year interval between measurements. The mean of these two time points was computed to reflect the average exposure level, then multiplied by the time duration to calculate long-term cumulative exposure. This approach adheres to the methodology for cumulative metabolic indices in the CHARLS cohorts, which is consistent with the approach described by Zou [23] and Lu [24].

Assessment of incident CVD

The presence of heart disease was determined by asking, “Have you been doctor-diagnosed with heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems? Or have you been doctor-diagnosed with stroke?” CVD was defined as self-reported heart disease and stroke. CVD determination was consistent with prior studies using CHARLS data [20]. Time to CVD onset was determined as the period between the last study interview and the first documented CVD event.

Covariates

Covariates included sociodemographic characteristics (age, sex, marital status, education level, smoking status, alcohol consumption), health indicators (systolic blood pressure [SBP], diastolic blood pressure [DBP], hypertension, diabetes, dyslipidemia), and laboratory parameters (C-reactive protein [CRP], fasting blood glucose [FBG], total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], glycated hemoglobin [HbA1c]. Hypertension was defined as $\text{SBP} \geq 140$ mmHg, $\text{DBP} \geq 90$ mmHg, or self-reported hypertension. Diabetes was defined as $\text{FBG} \geq 7.0$ mmol/L, $\text{HbA1c} \geq 6.5\%$ or self-reported diabetes diagnosis. Dyslipidemia was defined as $\text{TC} \geq 240$ mg/dL, $\text{TG} \geq 150$ mg/dL, $\text{LDL-C} \geq 160$ mg/dL, or self-reported dyslipidemia.

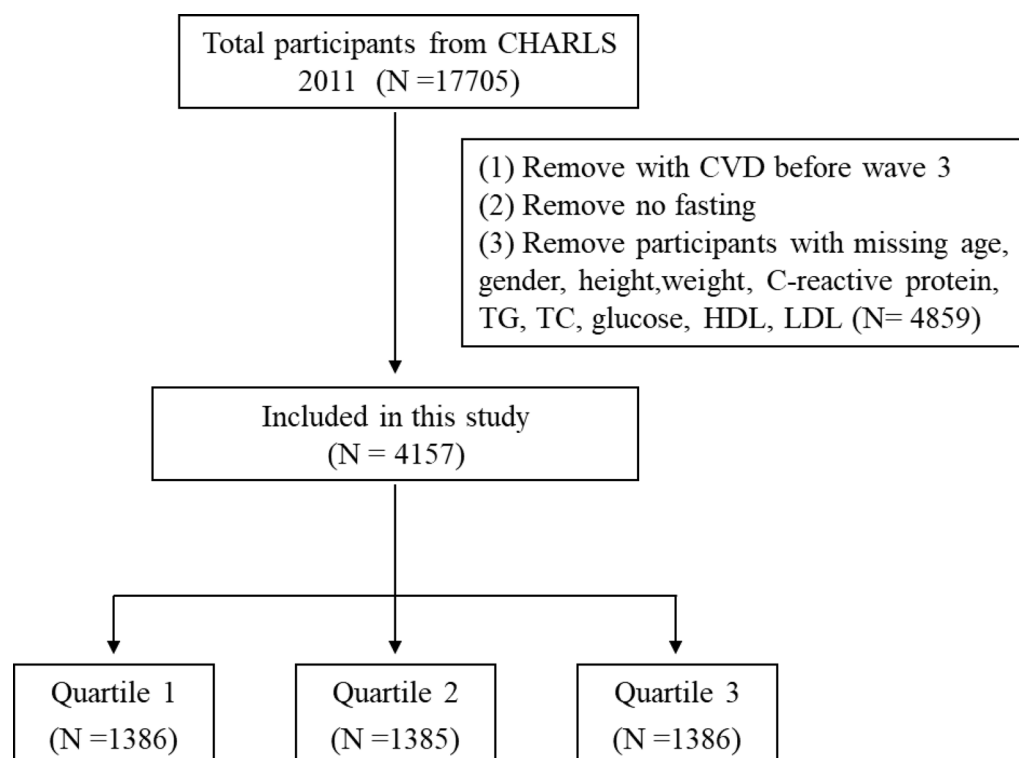


Fig. 1 Flowchart of the study population.

Covariates included sociodemographic characteristics (age, sex, marital status, education, smoking, and drinking status), health status (systolic blood pressure (SBP), diastolic blood pressure (DBP), hypertension, diabetes, and dyslipidemia), and laboratory measurements (CRP, FBG, TG, TC, HDL-C, LDL-C).

Statistical analysis

Data analysis was performed via R Studio. Two-tailed P values <0.05 were considered statistically significant. Continuous variables with a normal or approximately normal distribution are presented as the means $\pm$ standard deviations (SDs), whereas nonnormally distributed variables are reported as medians (interquartile ranges). Categorical variables are presented as frequencies and percentages. Baseline characteristics were compared across groups via analysis of variance (ANOVA) or the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables. Three multivariable models were constructed to evaluate associations between cuCTI and incident CVD: Model 1: unadjusted; Model 2: adjusted for sex, age, marital status, and education level; Model 3: further adjusted for BMI, drinking status, smoking status, depression, hypertension, dyslipidemia, diabetes, antihypertensive medication, antidiabetic medication, and lipid-lowering medication. The Benjamini–Hochberg method was used to correct for multiple comparisons, controlling the false discovery rate (FDR) to reduce false-positive results. Kaplan–Meier survival analysis was used to estimate cumulative CVD risk by cuCTI categories. Mediation analysis was performed to explore interactions between the CRP and TyG components of the CTI. A four-knot restricted cubic spline (RCS) model was used to assess nonlinear dose–response relationships between cuCTI and CVD risk. Subgroup analyses were conducted stratified by age, sex, marital status, education level, BMI, hypertension, dyslipidemia, and diabetes via Cox proportional hazards regression. Sensitivity analyses were performed to validate the robustness of the findings: logistic regression models were used to evaluate associations between cuCTI and CVD incidence. Participants were clustered into subgroups on the basis of CTI trajectory patterns via K-means clustering, followed by logistic regression analysis. Analyses were repeated after excluding deceased participants. Participants in the 2020 follow-up were excluded from analysis to prevent potential COVID-19 pandemic effects on data reliability and endpoint event reporting.

Results

Baseline characteristics

A total of 4157 participants were included in this study, including 2285 males (55.0%) and 1872 females (45.0%),

with a mean age of 58.10 ± 8.40 years. Participants were stratified into tertiles on the basis of cuCTI levels. Significant increases were observed across rising cuCTI tertiles for fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), diastolic blood pressure (DBP), and systolic blood pressure (SBP), along with elevated proportions of female participants, dyslipidemia, hypertension, and prevalent CVD. Conversely, high-density lipoprotein cholesterol (HDL-C) levels and the proportion of males decreased with increasing cuCTI. Incident CVD occurred in 609 participants (14.6%), with prevalence rates of 9.8%, 16.9%, and 17.4% in cuCTI tertiles Q1, Q2, and Q3, respectively, indicating a dose-dependent association between cuCTI and CVD risk (Table 1).

K-means cluster analysis of CTI trajectories

Using k-means clustering with the elbow method, participants were grouped into three distinct CTI trajectory patterns on the basis of measurements from 2012 and 2015 (Fig. 2, Table S1): Cluster 1 ($n=767$): High-stability CTI, with values increasing from 9.78 in 2012 to 10.09 in 2015 (cuCTI=29.805). This group presented the highest CVD incidence (19.3%; 148 events). Cluster 2 ($n=1639$): A low-stable CTI, ranging from 8.00 to 8.12 (cuCTI=24.18), was associated with the lowest CVD incidence (11.3%; 185 events). Cluster 3 ($n=1751$) exhibited a moderate-increasing CTI trajectory, ascending from 8.82 to 9.01 (cuCTI=26.75, and demonstrated intermediate CVD incidence (260 events; 14.9%).

Associations among cuCTI, CTI trajectories, and incident CVD risk

Three Cox proportional hazards models were constructed to evaluate the associations between cuCTI/CTI trajectories and CVD risk (Table 2). Across all the models, the cuCTI was positively associated with CVD risk ($P<0.001$). In fully adjusted Model 3, each 1-unit increase in cuCTI conferred a 5% higher CVD risk (HR=1.06, 95% CI 1.01–1.11). Compared with those in Q1, participants in the highest cuCTI tertile (Q3) had a 53% increased risk of CVD (HR=1.36, 95% CI 1.07–1.74; $P=0.029$). Compared with Cluster 2 (low-stable CTI), Cluster 1 (high-stable CTI) and Cluster 3 (moderate-increasing CTI) presented significantly greater CVD risk in Model 3 (HR=1.31, 95% CI 1.01–1.70; and HR=1.29, 95% CI 1.05–1.58, respectively).

Restricted cubic spline (RCS) analysis

To investigate the association between cuCTI and new-onset CVD risk a four-knot RCS model was applied based on Model 3 to model the association. The analysis demonstrated a statistically significant overall association between cuCTI and CVD risk ($P<0.001$), confirming that higher cuCTI levels consistently predict increased

Table 1 Baseline characteristics of the study population based on new-onset CVD

Characteristic	Overall (n = 4157)	cuCTI Q1 (n = 1386)	cuCTI Q2 (n = 1385)	cuCTI Q3 (n = 1386)	p
Age (mean (SD))	58.1 (8.4)	57.8 (8.6)	58.3 (8.5)	58.0 (8.1)	0.278
Age5 (%)					0.01
45–49	43 (1.0)	19 (1.4)	17 (1.2)	7 (0.5)	
50–59	850 (20.4)	318 (22.9)	270 (19.5)	262 (18.9)	
60–69	1618 (38.9)	505 (36.4)	557 (40.2)	556 (40.1)	
70–79	1258 (30.3)	423 (30.5)	397 (28.7)	438 (31.6)	
> = 80	388 (9.3)	121 (8.7)	144 (10.4)	123 (8.9)	
Gender (%)					< 0.001
Female	2285 (55.0)	695 (50.1)	779 (56.2)	811 (58.5)	
Male	1872 (45.0)	691 (49.9)	606 (43.8)	575 (41.5)	
Education (%)					0.501
Illiterate	1185 (28.5)	389 (28.1)	401 (29.0)	395 (28.5)	
Primary	1723 (41.4)	570 (41.1)	592 (42.7)	561 (40.5)	
Second/high school	1201 (28.9)	406 (29.3)	380 (27.4)	415 (29.9)	
College/higher	8 (1.2)	21 (1.5)	12 (0.9)	15 (1.1)	
Marriage (%)					0.289
Divorced	34 (0.8)	12 (0.9)	12 (0.9)	10 (0.7)	
Married	3762 (90.5)	1253 (90.4)	1244 (89.8)	1265 (91.3)	
Unmarried	21 (0.5)	12 (0.9)	5 (0.4)	4 (0.3)	
Widowed	340 (8.2)	109 (7.9)	124 (9.0)	107 (7.7)	
Drinking (%)					0.002
No	2746 (66.1)	870 (62.8)	919 (66.4)	957 (69.0)	
Yes	1411 (33.9)	516 (37.2)	466 (33.6)	429 (31.0)	
Smoking (%)					0.013
Ex-smoker	295 (7.1)	86 (6.2)	101 (7.3)	108 (7.8)	
Nonsmoker	2618 (63.1)	837 (60.4)	898 (64.8)	883 (63.9)	
Smoker	1239 (29.8)	462 (33.4)	386 (27.9)	391 (28.3)	
Depression (%)					0.005
No	2556 (64.8)	809 (61.9)	852 (64.6)	895 (67.9)	
Yes	1389 (35.2)	499 (38.1)	467 (35.4)	423 (32.1)	
Hypertension (%)					< 0.001
No	2651 (64.1)	1026 (74.4)	900 (65.3)	725 (52.7)	
Yes	1483 (35.9)	353 (25.6)	478 (34.7)	652 (47.3)	
Diabetes (%)					< 0.001
No	3570 (86.3)	1308 (94.8)	1246 (90.3)	1016 (73.7)	
Yes	569 (13.7)	130 (9.4)	283 (20.6)	694 (50.4)	
Dyslipidemia (%)					< 0.001
No	3025 (73.2)	1251 (90.6)	1092 (79.4)	682 (49.6)	
Yes	1107 (26.8)	130 (9.4)	283 (20.6)	694 (50.4)	
CVD (%)					< 0.001
No	3548 (85.4)	1254 (90.5)	1150 (83.0)	1144 (82.5)	
Yes	609 (14.6)	132 (9.5)	235 (17.0)	242 (17.5)	
BMI (mean (SD))	23.5 (3.8)	22.1 (3.0)	23.4 (3.8)	25.1 (3.9)	< 0.001
Waist (mean (SD))	85.0 (9.7)	80.7 (8.2)	84.7 (9.1)	89.6 (9.6)	< 0.001
SBP (mean (SD))	128.5 (20.3)	124.0 (18.9)	128.2 (19.8)	133.2 (21.0)	< 0.001
DBP (mean (SD))	75.2 (11.8)	72.5 (11.4)	75.3 (11.4)	77.9 (11.9)	< 0.001
CRP (mean (SD))	2.4 (6.8)	0.8 (1.0)	1.9 (4.2)	4.4 (10.7)	< 0.001
FBG (mean (SD))	6.0 (1.7)	5.5 (0.8)	5.8 (1.1)	6.7 (2.4)	< 0.001
HbA1c (mean (SD))	5.3 (0.8)	5.1 (0.5)	5.2 (0.6)	5.5 (1.1)	< 0.001
TG (mean (SD))	1.4 (1.0)	0.8 (0.3)	1.2 (0.5)	2.1 (1.4)	< 0.001
TC (mean (SD))	5.0 (1.0)	4.8 (0.9)	5.0 (0.9)	5.3 (1.0)	< 0.001
HDL (mean (SD))	1.3 (0.4)	1.5 (0.4)	1.4 (0.4)	1.1 (0.3)	< 0.001

Table 1 (continued)

Characteristic	Overall (n = 4157)	cuCTI Q1 (n = 1386)	cuCTI Q2 (n = 1385)	cuCTI Q3 (n = 1386)	p
LDL (mean (SD))	3.0 (0.9)	2.9 (0.8)	3.1 (0.8)	3.1 (1.0)	< 0.001
CTI12(mean (SD))	8.7 (0.8)	8.0 (0.4)	8.6 (0.4)	9.5 (0.7)	< 0.001
CTI15 (mean (SD))	8.9 (0.9)	8.0 (0.5)	8.8 (0.4)	9.7 (0.7)	< 0.001

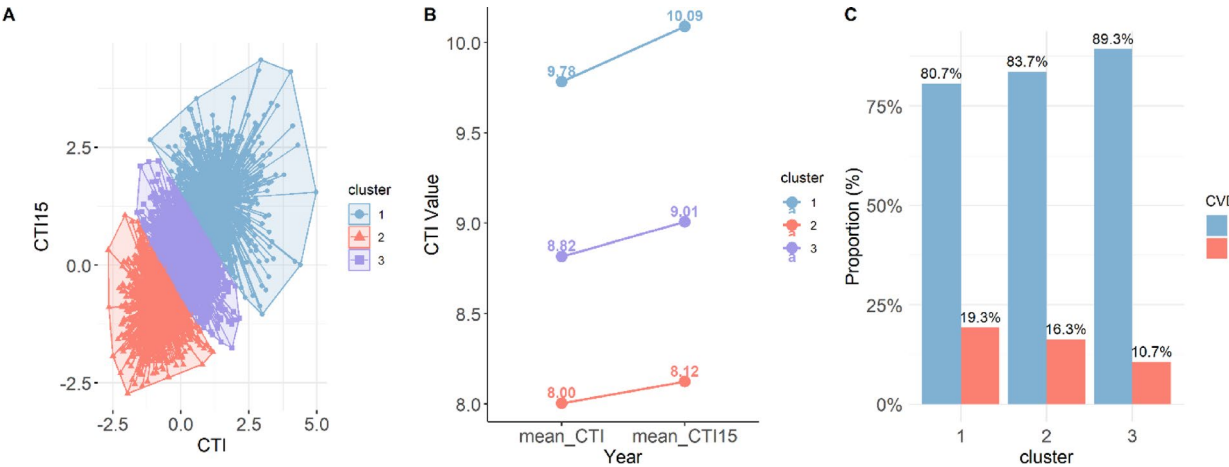


Fig. 2 Clustering of the change in the CTI from 2012–2015. **A** Three clusters were found via the K-means method with Euclidean distance. **B** Change in the CTI from 2012–2015. **C** Onset of CVD in three clusters

Table 2 Multivariate Cox regression of the relationships between cuCTI, different clusters of CTI and the risk of new-onset CVD

	Model 1		Model 2		Model 3	
	HR(95%CI)	P _{adj}	HR(95%CI)	P _{adj}	HR(95%CI)	P _{adj}
cuCTI	1.12(1.08,1.15)	< 0.001	1.11(1.08,1.15)	< 0.001	1.06(1.01,1.11)	0.014
cuCTI3						
Q1	Ref		Ref		Ref	
Q2	1.85(1.49,2.29)	< 0.001	1.80(1.46,2.23)	< 0.001	1.53(1.22,1.92)	< 0.001
Q3	1.90(1.54,2.35)	< 0.001	1.85(1.49,2.29)	< 0.001	1.36(1.07,1.74)	0.014
P for trend	< 0.001		< 0.001		< 0.001	
Change in the CTI						
Cluster 2	Ref		Ref		Ref	
Cluster 3	1.57(1.30, 1.90)	< 0.001	1.52(1.26, 1.83)	< 0.001	1.29(1.05, 1.58)	0.029
Cluster 1	1.87(1.50, 2.33)	< 0.001	1.83(1.47, 2.28)	< 0.001	1.31(1.01, 1.70)	0.041
P for trend	< 0.001		< 0.001		< 0.001	

Model 1: unadjusted for any covariates
Model 2: adjusted for sex, age, marital status, and education level
Model 3: adjusted for sex, age, BMI, marital status, education level, smoking status, drinking status, hypertension, dyslipidemia, heart disease, hypertension medications, dyslipidemia medications, antihypertensive medication, antidiabetic medication, and lipid-lowering medication

CVD incidence. The nonlinearity test was nonsignificant ($P=0.105$), indicating a predominantly linear dose-response relationship without evidence of threshold effects (Fig. 3).

K–M survival and ROC curve analysis

The Kaplan–Meier cumulative incidence curve demonstrated progressively raised CVD incidence across ascending cuCTI quartiles (Q1–Q3), with statistically significant between-group differences (log-rank $P<0.001$; Fig. 4). Receiver operating characteristic (ROC) analysis

revealed that the cuCTI had the highest predictive value for CVD (AUC=0.589), followed by the baseline CTI (AUC=0.582), CTI 2015 (AUC=0.578), TyG index (AUC=0.573), and CRP (AUC=0.555) (Figure S1).

Subgroup analysis and interaction tests

To assess the reliability and stability of the association between cuCTI and CVD risk in the fully adjusted Model 3, subgroup analyses and interaction tests were performed. Stratified factors included sex, age, educational level, marital status, and comorbidities such as

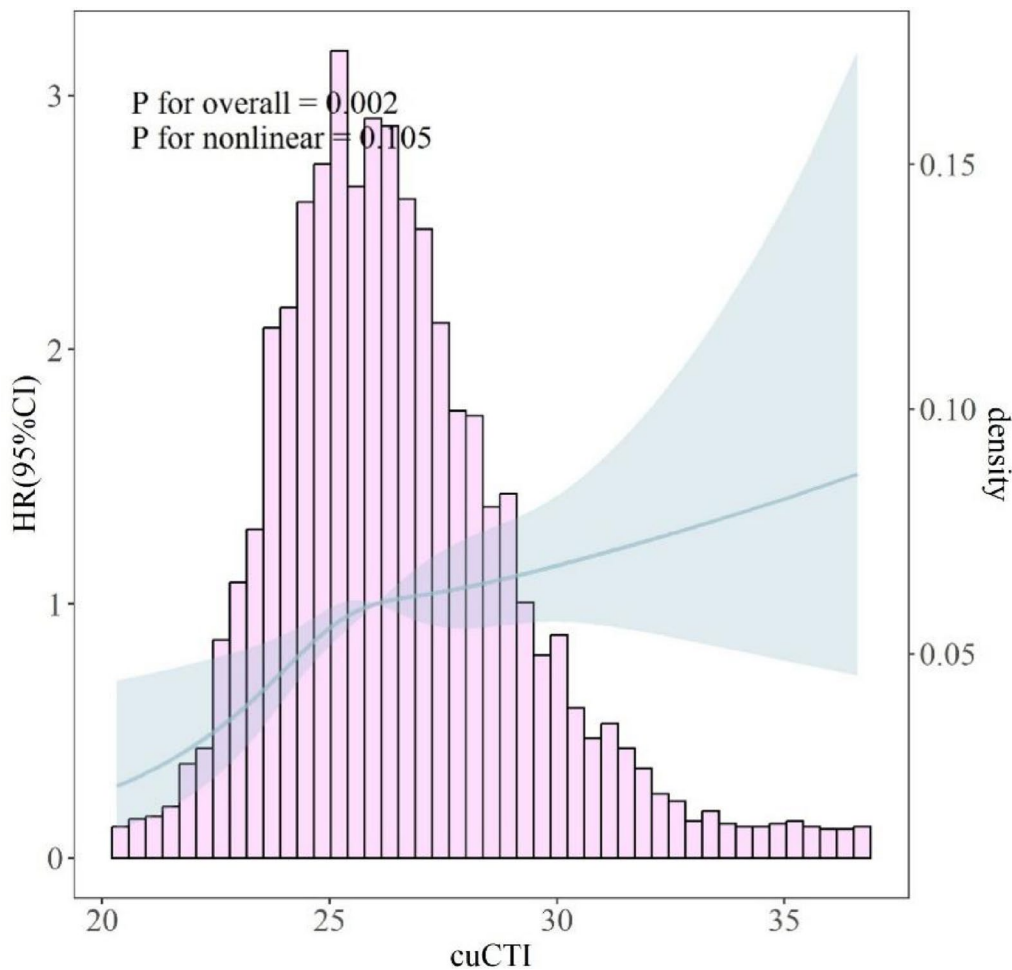


Fig. 3 RCS curve between cuCTI and CVD incidence

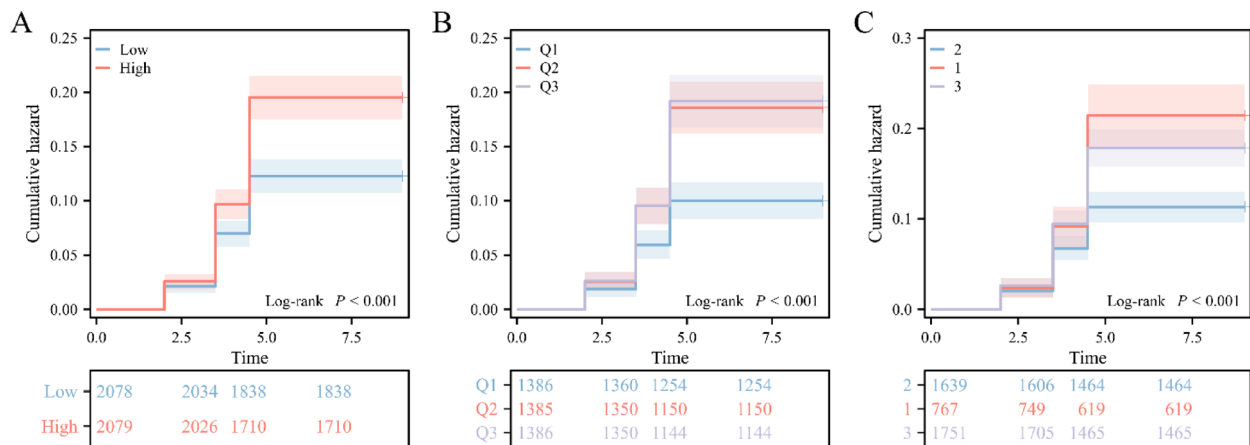


Fig. 4 K–M plot of CVD incidence according to cuCTI (A), cuCTI3 (B), and the cuCTI cluster (C)

hypertension, diabetes, and dyslipidemia. As shown in the forest plot (Fig. 5), a consistent positive correlation between the cuCTI and CVD incidence was observed across most stratified factors ($HR > 1$, $P < 0.05$). However, no significant associations were found in the 45–49 years age group or the divorced/unmarried/widowed marital status group ($P > 0.05$). These subgroups have small sample sizes (e.g., only 43 participants in the 45–49 years age group), which may lead to nonsignificant associations due to insufficient statistical power. Interaction tests

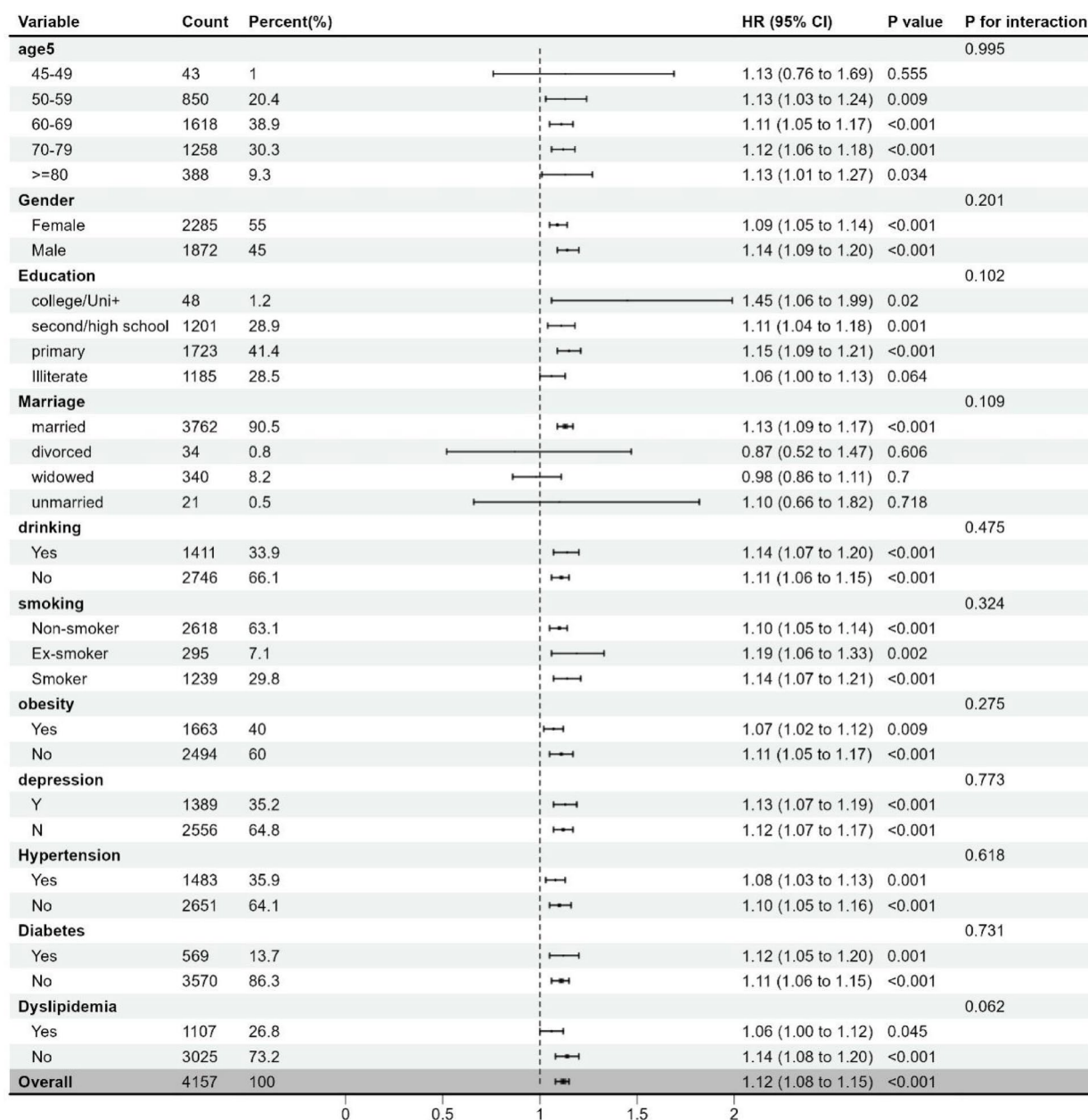


Fig. 5 Subgroup and interaction analyses of the associations between cuCTI and CVD risk. Adjusted for sex, age, residence, marital status, education level, smoking status, drinking status, hypertension, dyslipidemia, heart disease, hypertension medications, dyslipidemia medications, SBP, DBP, and BMI

across all subgroups revealed no statistically significant P values ($P > 0.05$).

Sensitivity analyses

A series of sensitivity analyses were conducted to verify the robustness of our results. First, logistic regression models were used to explore the relationship between cuCTI and the incidence of stroke (Model 3: OR, 1.39 (1.05–1.85), $P_{\text{adj}} = 0.021$). Second, we performed analyses on the CTI change clustering groups (Model 3: OR, 1.37 (1.03–1.83), $P_{\text{adj}} = 0.039$). Third, we reanalyzed the data after excluding all deceased participants (Model 3: OR,

1.39 (1.07–1.82), $P_{\text{adj}} = 0.014$), and participants from the 2020 follow-up were excluded (Model 3: OR, 1.45 (1.04–2.03), $P_{\text{adj}} = 0.041$); the results remained stable (Table 3).

Discussion

In this study, we investigated the relationships between cumulative exposure and dynamic trajectories of the CTI and CVD. Our findings revealed that individuals with moderately high-stable (cluster 1) and moderately-increasing CTI values (cluster 3) presented a significantly greater CVD risk than did those with persistently low CTI values (cluster 2). Notably, cuCTI demonstrated an

Table 3 Sensitivity analysis results of logistic regression analysis in different groups

	Model 1		Model 2		Model 3	
	OR(95%CI)	<i>P</i> _{adj}	OR(95%CI)	<i>P</i> _{adj}	OR(95%CI)	<i>P</i> _{adj}
<i>Cumulative CTI in all participants (N = 4157)</i>						
cuCTI	1.13(1.09, 1.18)	< 0.001	1.13(1.09, 1.17)	< 0.001	1.07(1.02, 1.13)	0.017
cuCTI3						
Q1	Ref		Ref		Ref	
Q2	1.94(1.55, 2.44)	< 0.001	1.90(1.51, 2.39)	< 0.001	1.60(1.26, 2.05)	< 0.001
Q3	2.01(1.60, 2.53)	< 0.001	1.95(1.56, 2.46)	< 0.001	1.39(1.05, 1.85)	0.022
<i>Change in the CTI in all participants (N = 4157)</i>						
Cluster 2	Ref		Ref		Ref	
Cluster 3	1.63(1.34, 2.00)	< 0.001	1.58(1.29, 1.94)	< 0.001	1.32(1.06, 1.65)	0.029
Cluster 1	2.00(1.58, 2.54)	< 0.001	1.97(1.55, 2.50)	< 0.001	1.37(1.03, 1.83)	0.039
<i>Cumulative CTI in alive participants(N= 4140)</i>						
cuCTI	1.13(1.09, 1.18)	< 0.001	1.13(1.09, 1.17)	< 0.001	1.07(1.02, 1.12)	0.012
cuCTI3						
Q1	Ref		Ref		Ref	
Q2	1.94(1.55, 2.45)	< 0.001	1.90(1.51, 2.39)	< 0.001	1.61(1.26, 2.05)	< 0.001
Q3	2.01(1.61, 2.53)	< 0.001	1.96(1.56, 2.47)	< 0.001	1.39(1.07, 1.82)	0.014
<i>Cumulative CTI (excluding 2020, N = 3880)</i>						
cuCTI	1.09(1.04, 1.15)	< 0.001	1.09(1.03, 1.14)	< 0.001	1.06(1.00, 1.13)	0.051
cuCTI3						
Q1	Ref		Ref		Ref	
Q2	1.72(1.29, 2.31)	< 0.001	1.66(1.24, 2.23)	< 0.001	1.55(1.14, 2.11)	0.016
Q3	1.73(1.29, 2.32)	< 0.001	1.64(1.23, 2.21)	< 0.001	1.45(1.04, 2.03)	0.041

Model 1: unadjusted for any covariates
Model 2: adjusted for sex, age, marital status, and education level
Model 3: adjusted for sex, age, BMI, marital status, education level, smoking status, drinking status, hypertension, dyslipidemia, heart disease, hypertension medications, dyslipidemia medications, antihypertensive medication, antidiabetic medication, and lipid-lowering medication

independent association with elevated CVD risk, with participants in ascending CVD risk tertiles showing progressively higher CVD risk. A chronically higher CTI or a higher cuCTI is associated with a higher incidence of CVD events. The ability of the CTI to assess CVD risk is superior to that of the CRP alone or the TyG alone, and the cuCTI, an indicator of dynamic changes in the CTI, has the best performance. Additionally, subgroup analyses and sensitivity analyses consistently supported the primary findings.

From a pathophysiological perspective, CRP promotes atherogenesis through three key mechanisms: (1) induction of endothelial dysfunction, (2) enhancement of oxidative lipoprotein accumulation, and (3) facilitation of leukocyte infiltration [25]. The TyG index, which reflects insulin resistance (IR), impairs peripheral glucose metabolism and directly damages the vascular endothelium through oxidative stress and lipotoxicity [26]. Both inflammation and IR have been established as independent risk factors for CVD, acting synergistically in CVD pathogenesis [27, 28]. Although CRP and the TyG index are well-established biomarkers of inflammation and IR respectively, previous research has primarily examined their individual associations with CVD, consistently reporting positive correlations [29–31]. Recent evidence

emphasizes the necessity of joint assessment and management of inflammation and atherogenic dyslipidemia in primary CVD prevention [32, 33], prompting recommendations for integrated evaluation of the TyG index and inflammatory biomarkers to refine cardiovascular risk stratification [19, 34]. The CTI integrates inflammation (CRP) and IR (TyG), capturing dual pathophysiological processes with promising predictive value for stroke and CHD. For example, Tang et al. [18] demonstrated that elevated CTI levels correlate with increased stroke risk in hypertensive Chinese adults, whereas Huo et al. [17] reported significant CTI-stroke associations in both normoglycemic and prediabetic populations. In U.S. cohorts, Xu et al. [35] reported a positive linear association between CTI and CHD, enhancing its utility for screening in the general population. However, previous research has focused mainly on single-time-point measurements of the CTI, overlooking its dynamic changes over time and lacking longitudinal assessments of the dynamic cumulative effect of the CTI (cuCTI), which may lead to potential regression dilution bias and impact the accuracy of the results.

Compared with previous studies, our study captures longitudinal changes in cuCTI, providing a more dynamic perspective for risk stratification: (1) focusing

on a national community cohort (CHARLS) rather than a single hypertensive population; (2) being the first to construct a cumulative cuCTI exposure model and analyze its dynamic trajectories (cluster analysis), revealing a significantly elevated CVD risk in the persistent high cuCTI subgroup (HR = 1.30). This study revealed that cuCTI, as a cumulative indicator reflecting long-term inflammatory-metabolic burden, was significantly and positively associated with incident CVD risk. According to the fully adjusted model, individuals in the highest cuCTI tertile (Q3) had a 36% increased CVD risk compared with those in the lowest tertile (Q1) (HR = 1.36, 95% CI 1.07–1.74). These findings demonstrate that sustained exposure to elevated CTI levels progressively aggravates vascular injury, aligning with established pathophysiological mechanisms in which chronic low-grade inflammation and metabolic dysregulation act synergistically to accelerate atherosclerotic progression." Additionally, cuCTI showed superior predictive performance compared with single-time CTI, the TyG index, and CRP, suggesting that by integrating multiple timepoint data, cuCTI more accurately captures the cumulative effects of inflammation and insulin resistance—which is consistent with studies on cumulative metabolic indices such as the atherogenic index of plasma (AIP) [36, 37], the TyG-BMI [38, 39], the TyG-WWI [40], and the METS-VF [41], where prolonged exposure correlates with increased CVD risk.

K-means clustering identified three CTI dynamic trajectories, with the "persistently high CTI group" (Cluster 1) exhibiting the highest CVD risk. This suggests that dynamic changes in the CTI better reflect disease progression than single measurements do: a persistently increasing trajectory may indicate the initiation of a vicious cycle between inflammation and metabolic disorders, whereas short-term fluctuations or mild elevations have relatively weaker effects. These findings align with those of Wu et al. [21], who demonstrated that dynamic changes in the TyG index predict stroke risk, validating the value of trajectory analysis in capturing disease deterioration trends. Ren et al. [20] reported that changes in the TyG-WHtR are independently associated with the risk of CVD. Additionally, RCS analysis revealed a significant positive linear relationship between cuCTI levels and CVD event incidence: higher cuCTI levels are associated with higher CVD risk, providing a basis for reducing risk by controlling cuCTI levels in clinical practice. Subgroup analyses confirmed the stable association between cuCTI and CVD across most populations, with nonsignificant results in small subgroups, likely due to limited statistical power. The reliability of these conclusions was substantiated through sensitivity analyses, which demonstrated their stability and confirmed they were unaffected by model selection or data bias.

Clinically, CTI serves as a practical complementary tool for risk stratification. Targeting individuals with elevated cuCTI demonstrates efficient intervention potential, with an NNT of 13 (preventing one CVD event per 13 persons treated) and a population-attributable risk (PAR%) of 10.7%. Utilizing low-cost routine tests (approximately \$15 USD), CTI enables precision prevention in resource-limited primary care settings, though future studies should validate its cost-effectiveness across diverse populations.

This study has several limitations. First, self-reported CVD events may lead to an underestimation of risk due to missed diagnoses of asymptomatic cases. Future studies could use electronic medical records or imaging, but self-reports were used here because of cohort design constraints. Second, limited CRP and TyG measurements may not capture full variability, and acute-phase CRP reactions (e.g., from infections) may bias baseline values. Third, residual confounders such as dietary patterns and genetic susceptibility may influence the results. Fourth, potential batch differences in blood index measurements across CHARLS waves (e.g., TG, FBG) could introduce systematic errors in cuCTI calculations. Fifth, the loss to follow-up might bias the results, as lost participants likely had higher baseline CVD risk or uncontrolled metabolic disorders. Sixth, the study's focus on middle-aged and older adults limits extrapolation to younger populations. Future research should validate the cuCTI in more diverse age groups. While this study highlights the epidemiological association of cuCTI, the underlying mechanism of "inflammation-metabolism synergy" requires further verification in future studies via basic experiments or more appropriate statistical methods such as structural equation modeling.

Conclusion

This CHARLS-based study revealed that over 9 years of follow-up, cuCTI and its dynamic changes are significantly linked to new-onset CVD risk. Individuals exhibiting both elevated cuCTI levels and sustained high CTI trajectories demonstrate a substantially increased risk of CVD, with hazard ratios exceeding 1.30. Owing to its low cost and easy accessibility, cuCTI can effectively identify middle-aged and older adults at high risk of CVD, offering a window for timely individualized interventions to prevent CVD events.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12933-025-02869-4>.

Supplementary Material 1

Supplementary Material 2

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Author contributions

Conceptualization, M-Xj; Methodology, Z-Cj and M-Xj; Formal analysis, M-Xj and M-Xd.; Investigation, M-Xj; Writing, Z-Cj and M-Xj; Supervision, M-Xd, W-Yl and Q-G. All authors have read and agreed to the published version of the manuscript.

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Data availability

The data supporting the findings of this study are available on the CHARLS website (<http://charls.pku.edu.cn/>).

Declarations

Ethics approval and consent to participate

CHARLS was approved by the Institutional Review Board of Peking University (approval number: IRB00001052-11015 for the household survey and IRB00001052-11014 for blood samples), and all participants provided written informed consent.

Competing interests

The authors declare no competing interests.

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