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Cumulative C-reactive protein-triglyceride glucose index and its longitudinal trajectory in relation to incident cardiometabolic multimorbidity: the mediating role of body roundness index in middle-aged and older adults

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Research Article

Keywords: Cardiometabolic multimorbidity, cumulative C-reactive protein-triglyceride glucose index, longitudinal trajectory, cohort study, risk prediction, CHARLS, cumulative CTI, BRI, mediation

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Running title

Cumulative CTI, trajectory, BRI, and cardiometabolic multimorbidity

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Keywords:

Cardiometabolic multimorbidity; cumulative C-reactive protein-triglyceride glucose index; longitudinal trajectory; cohort study; risk prediction; CHARLS

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Ethics approval:

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board of Peking University (IRB00001052-11015). All participants provided written informed consent prior to enrollment.All participants provided written informed consent to participate in this study.

Conflict of interest:

The authors declare that they have no conflicts of interest.

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Abstract

Background: Cardiometabolic multimorbidity (CMM) represents a major public health challenge worldwide, particularly in aging populations. The C-reactive protein-triglyceride glucose index (CTI), a composite biomarker integrating inflammation and metabolic dysregulation, has been linked to cardiometabolic outcomes. However, the associations of cumulative CTI burden and longitudinal CTI trajectories with incident CMM remain unclear, and the underlying mechanisms are poorly understood.

Methods: This prospective cohort study included 8,464 participants free of CMM at baseline from the China Health and Retirement Longitudinal Study (CHARLS) 2011–2018. CTI in 2011 and 2015 was calculated using a validated formula incorporating C-reactive protein, triglycerides, and fasting plasma glucose. CuCTI was computed as the average of CTI 2011 and CTI 2015 multiplied by 4. Longitudinal CTI trajectories were identified using group-based trajectory modeling. Cox proportional hazards models and restricted cubic splines were performed to evaluate the associations. Mediation analysis was conducted to assess the mediating effect of Body Roundness Index (BRI) on incident CMM.

Results: During a median follow-up of 7 years, 481 incident CMM cases occurred. In fully adjusted models, per 1-unit increment in cuCTI was associated with a 6% higher risk of incident CMM (HR 1.06, 95% CI 1.03–1.09, P<0.001). Compared with the lowest quartile, the highest cuCTI quartile showed a 69% increased risk (HR 1.69, 95% CI 1.22–2.35, P=0.002), with a linear dose–response relationship. High-persistent CTI trajectory was associated with elevated CMM risk. BRI significantly mediated the association between cuCTI and incident CMM, accounting for 7.0% of the total effect.

Conclusions: Higher cuCTI and unfavorable longitudinal CTI trajectory are independently associated with an increased risk of incident CMM.

The association is partially mediated by BRI. Monitoring cuCTI and improving body fat distribution may help prevent incident CMM.

Keywords: Cardiometabolic multimorbidity; cumulative CTI; longitudinal trajectory; BRI; mediation; CHARLS

Research insights

What is currently known about this topic?

Cardiometabolic multimorbidity (CMM) constitutes a growing global health threat associated with poor quality of life, heavy medical burden, and excess mortality. Traditional cardiometabolic risk assessment relies predominantly on single-time-point measurements, which fail to capture long-term cumulative burden or dynamic longitudinal changes in metabolic health. C-reactive protein-triglyceride glucose index (CTI) is a validated composite marker integrating inflammation, dyslipidemia, and hyperglycemia, but the associations of its cumulative exposure and longitudinal trajectories with incident CMM remain unclear. Body Roundness Index (BRI) reflects abdominal fat distribution more accurately than BMI and may participate in cardiometabolic risk pathways; however, no prior study has explored its mediating role between cumulative CTI and CMM.

What is the key research question?

1. Are cumulative C-reactive protein-triglyceride glucose index (cuCTI) and longitudinal CTI trajectory independently associated with incident cardiometabolic multimorbidity (CMM) risk?

2. Does Body Roundness Index (BRI) mediate the association between cuCTI and incident CMM?

What is new?

To our knowledge, this is the first prospective cohort study to simultaneously evaluate cumulative CTI burden and longitudinal CTI trajectories in relation to incident CMM.Higher cuCTI was associated with an increased risk of CMM in a linear dose–response manner, independent of conventional confounders.A persistently high CTI trajectory conferred the highest risk of incident CMM.BRI partially mediates the association between cuCTI and incident CMM, explaining approximately 7.0% of the total effect, revealing a novel mechanistic pathway.

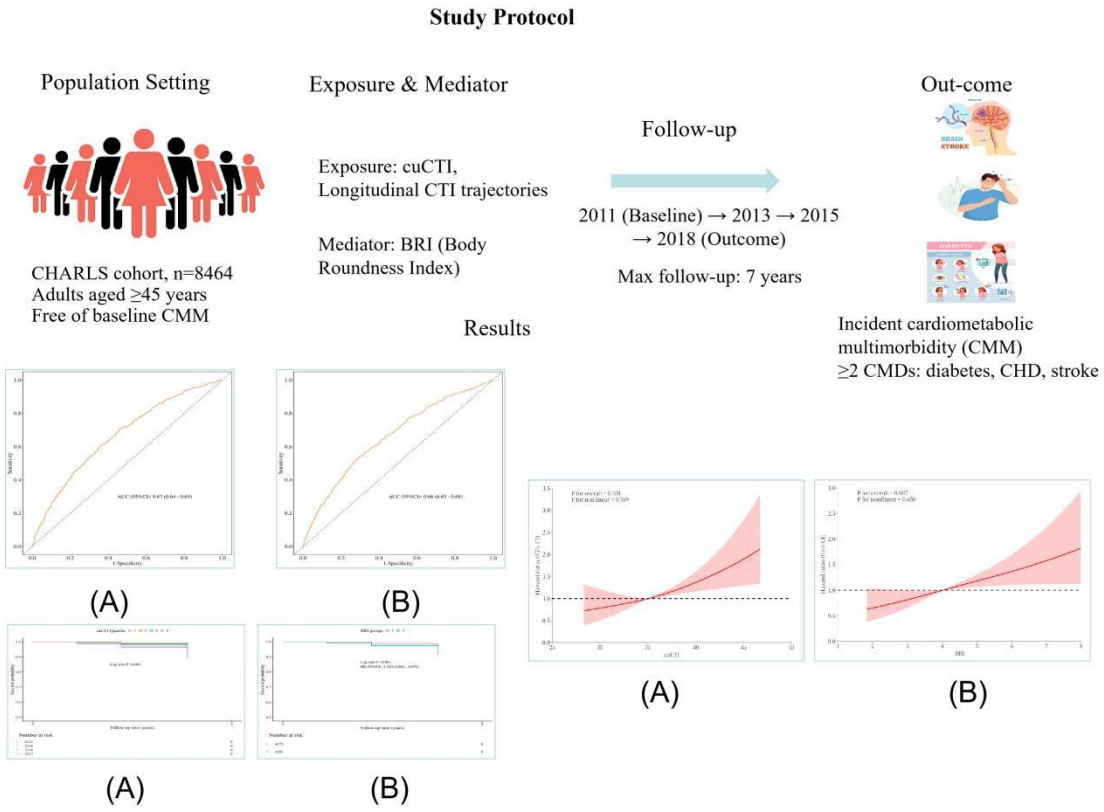
How might this study influence clinical practice?

Supports the use of cumulative and longitudinal cardiometabolic risk assessment rather than single-time-point measurements for CMM risk stratification.

Provides a simple, clinically practical composite index (cuCTI) to identify high-risk individuals before multimorbidity onset.

Highlights BRI and abnormal body fat distribution as modifiable intervention targets for reducing CMM risk.

Informs population-level public health strategies for early prevention of cardiometabolic multimorbidity in middle-aged and older adults.



Introduction

The global prevalence of cardiometabolic multimorbidity (CMM), defined as the coexistence of two or more interrelated cardiometabolic conditions including type 2 diabetes, hypertension, coronary heart disease, and stroke, has risen continuously alongside population aging[1, 2]. Unlike isolated chronic diseases, CMM represents a progressive clinical phenotype driven by long-standing metabolic disturbance, systemic low-grade inflammation, and impaired vascular homeostasis, leading to

substantial impairments in functional status, increased healthcare utilization, and excess mortality risk[3, 4].

Conventional risk assessment for cardiometabolic diseases has long relied on single-time-point measurements of individual risk factors[5–7], which fail to capture the cumulative burden or dynamic changes of metabolic health over time. Emerging evidence indicates that sustained metabolic dysregulation plays a more critical role in the pathogenesis of complex multimorbidity than transient fluctuations. However, clinically applicable tools for evaluating cumulative and longitudinal cardiometabolic risk remain limited[5, 8, 9].

The C-reactive protein-triglyceride glucose index (CTI), a composite indicator integrating C-reactive protein (CRP), triglycerides (TG), and fasting plasma glucose (FPG), has emerged as a practical tool to assess integrated cardiometabolic health status[10–12]. Compared with single biomarkers, CTI reflects systemic low-grade inflammation, lipid disorders, and glucose dysregulation simultaneously and has been linked to adverse cardiometabolic outcomes[7, 13, 14]. However, most previous studies focused on single-time-point CTI measurements, neglecting long-term cumulative burden and dynamic longitudinal changes in cardiometabolic health. Previous studies[15, 16] have shown that CTI is closely associated with the onset and progression of cardiovascular diseases, chronic kidney disease, and diabetes. Furthermore, when used

for early risk stratification, the CTI has demonstrated superior predictive performance compared to its individual components. While current research[5, 17] suggests that exposure assessments based on cumulative and disease-course trajectories can accurately reflect the long-term adverse effects of persistent cardiometabolic abnormalities, it has not been established whether the BRI plays a role in this context.

Body Roundness Index (BRI), a novel anthropometric index derived from waist circumference and height, reflects body fat distribution more accurately than traditional BMI[18]. BRI is strongly associated with insulin resistance, chronic inflammation, and multiple cardiometabolic disorders[19–21]. Recent evidence suggests that abnormal body fat distribution may lie on the causal pathway linking cumulative cardiometabolic risk to the development of complex diseases. Nevertheless, whether BRI serves as a mediating pathway connecting cumulative and longitudinal cardiometabolic risk to incident CMM has not been previously investigated.

Using data from a nationwide prospective cohort (CHARLS), we aimed to: (1) examine the associations of cumulative CTI (cuCTI) and longitudinal CTI trajectory with incident CMM; (2) explore the dose–response relationship; and (3) determine the mediating effect of BRI. We hypothesized that higher cuCTI and unfavorable CTI trajectory are

associated with increased risk of incident CMM, and that BRI partially mediates these associations.

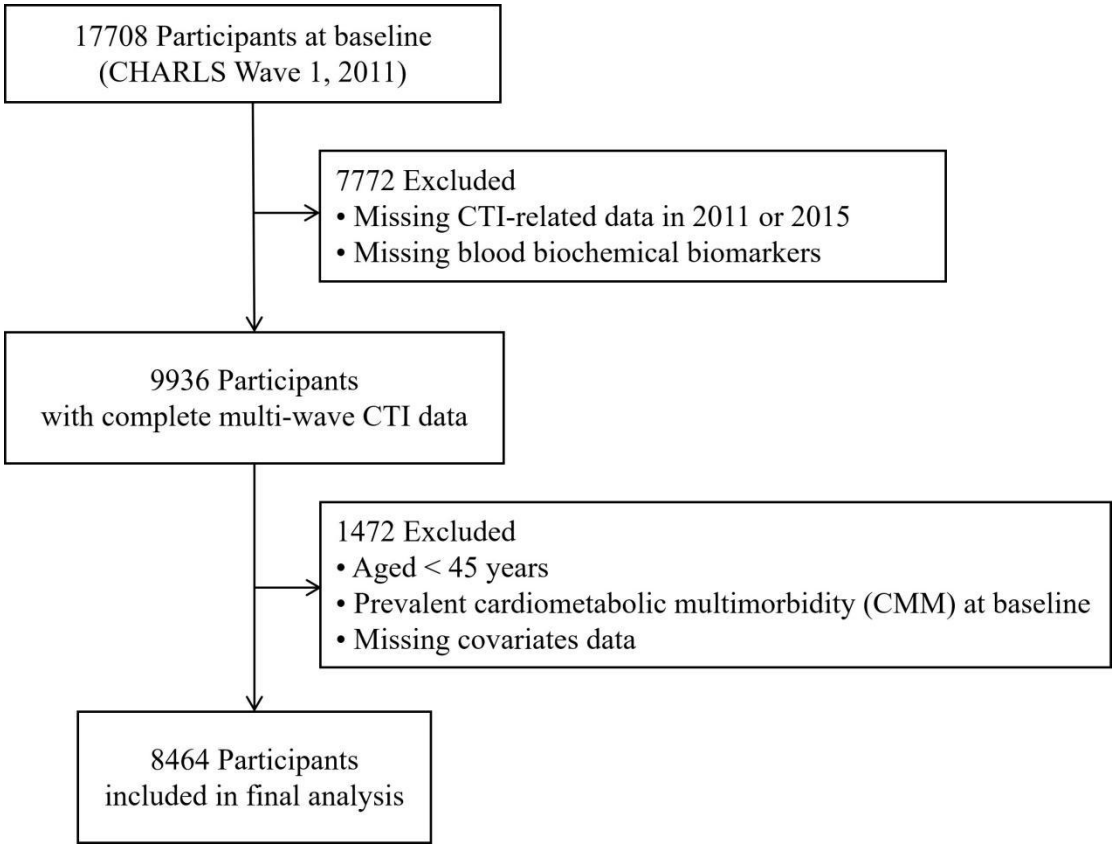
Methods

Study Design and Population

This prospective cohort study used data from the China Health and Retirement Longitudinal Study (CHARLS), a nationally representative survey of community-dwelling adults aged ≥45 years in China[22]. The baseline survey was conducted in 2011, with follow-up surveys in 2013, 2015, and 2018. The study protocol was approved by the Institutional Review Board of Peking University, and all participants provided written informed consent, and the study protocol received approval from the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015), adhering to the principles of the Declaration of Helsinki. The study was carried out in compliance with the Declaration of Helsinki. The CHARLS dataset is publicly accessible at http://charls.pku.edu.cn[23].

Participants were included if they: (1) aged ≥45 years at baseline; (2) had complete data on key variables at 2011 and 2015; (3) were free of CMM (defined as <2 cardiometabolic diseases) at baseline. Participants were excluded if they had missing data for CTI, BRI, or main covariates. Finally, 8,464 participants were included in the analytical sample. The participant flow diagram is presented in Figure 1.

Fig. 1 Flowchart of participant enrollment in the present study



Follow-up period and outcome ascertainment

The present study used a prospective cohort design with baseline enrollment in 2011 and follow-up through 2018. Participants with prevalent cardiometabolic multimorbidity (CMM≥2conditions) at baseline (2011) were excluded to ensure all participants were free of CMM at study entry. The follow-up period began at the time of the 2011 baseline survey and continued until the earliest occurrence of:(1) incident CMM, defined as the first diagnosis of ≥2 cardiometabolic diseases during follow-up;(2) death;(3) loss to follow-up; or (4) the end of the study period (2018 wave). Given the interval-censored nature of the CHARLS data, exact dates of disease onset were unavailable.

Therefore, the time to event was assigned as the midpoint between the last follow-up wave with no reported CMM and the first wave with documented incident CMM, consistent with standard methods for interval-censored longitudinal cohort data.

Assessment of CTI Index /the change in CTI/ Longitudinal CTI Trajectories

C-reactive protein-triglyceride glucose index（CTI）: CTI at each wave was calculated using the formula: CTI = 0.412 × Ln(CRP) + Ln((TG × FPG) / 2), where CRP is C-reactive protein (mg⁄L), TG is triglycerides (mg⁄dL), and FPG is fasting plasma glucose (mg⁄dL)[24]**.** CuCTI = (value_2011+value_2015)/2 × (2015-2011)[9].

Identification of CTI Trajectory: Group-based trajectory modeling (GBTM) was applied to identify distinct longitudinal CTI trajectories from 2011 to 2015. The optimal number of trajectory groups was determined based on Bayesian information criterion (BIC), model plausibility, and group size. Three trajectory groups were identified: low-level stable Trajectory 1, moderate-level stable Trajectory 2, and high-level persistent Trajectory 3[8].

Measurement of BRI

BRI was calculated as: $BRI = 364.2\text{-}365.5\times \sqrt{1-(\frac{WC/2\pi}{0.5*height})2}$,

Waist circumference and height were measured at baseline using standardized procedures[25–27].

Ascertainment of Incident CMM

CMM was defined as having two or more of the following conditions: diabetes, heart disease, or stroke. Incident CMM was defined as new onset of ≥2 conditions during follow-up among participants with <2 conditions at baseline[28, 29]. Diabetes was diagnosed if participants reported a physician-confirmed diagnosis, were using glucose-lowering medications, or presented with fasting blood glucose (FBG) levels ⩾ 126 mg/dL. Heart disease (including coronary heart disease, angina, myocardial infarction, and heart failure) and stroke were ascertained using standardized self-reported questions administered at baseline and each follow-up wave. Participants were classified as having a condition if they answered “yes” to being diagnosed by a physician[30, 31].

Covariates

Potential confounding variables were selected based on prior epidemiologic evidence and clinical relevance. All covariates were assessed at baseline (2011) and classified into five domains: sociodemographic characteristics, lifestyle factors, anthropometric measures, laboratory biomarkers, and baseline medical conditions. Sociodemographic variables included age, sex, residential location (rural/urban), marital status (married/other), and educational level (primary school or below/secondary school or above). Lifestyle factors included current smoking (yes/no) and current alcohol drinking (yes/no).

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2) using standardized measurements. Laboratory biomarkers included triglycerides (TG), fasting plasma glucose (FPG), and high-sensitivity C-reactive protein (CRP). Baseline medical conditions included hypertension, diabetes, heart disease, and stroke[32].

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR) as appropriate. Categorical variables were summarized as frequencies and percentages.

Statistical Analysis

All statistical analyses were performed using R software (version 4.5.0) and SPSS (version 27.0). All tests were two-sided, and $P < 0.05$ was considered statistically significant. The normality of continuous variables was examined using the Shapiro–Wilk test. Normally distributed continuous variables are presented as mean ± standard deviation (SD), and non-normally distributed variables as median and interquartile range (IQR). Categorical variables are expressed as frequencies and percentages. Between-group differences were evaluated using the chi-square test or Fisher's exact test for categorical variables, and independent-samples t-test, Mann–Whitney U test, one-way ANOVA, or Kruskal–Wallis test for continuous variables, as appropriate.

Group-based trajectory modeling (GBTM) was used to identify distinct longitudinal CTI trajectories from 2011 to 2015. Participants were categorized into quartiles of cumulative CTI (cuCTI): Q1 (lowest), Q2, Q3, and Q4 (highest). The cumulative incidence of CMM across cuCTI quartiles and trajectory groups was estimated using Kaplan–Meier curves and the log-rank test.

Multivariate Cox proportional hazards regression models were applied to evaluate the independent associations of cuCTI and CTI trajectories with incident CMM. Three progressive models were constructed: Model 1: Unadjusted; Model 2: Adjusted for age, sex, residence, marital status, and educational level; Model 3: Fully adjusted model, further adjusted for smoking, alcohol consumption, BMI, baseline hypertension, diabetes, heart disease, and stroke.

The proportional hazards assumption was verified using the Schoenfeld residual test. Restricted cubic spline (RCS) regression with three knots was performed to explore potential non-linear associations between continuous cuCTI and incident CMM.

Subgroup analyses stratified by age, sex, residence, smoking, alcohol consumption, hypertension, and diabetes were conducted to test the robustness of the main findings. Likelihood ratio tests were used to examine interaction effects.

Results

Baseline characteristics of the study population

Baseline characteristics of the 8,464 participants stratified by quartiles of cumulative Cardiometabolic Index (cuCTI) are presented in Table 1. The median age of the total population was 58.00 years, and 47.06% were male. Levels of CRP 2011, TG 2011, FPG 2011, BRI 2011, and BMI 2011 all increased significantly across ascending cuCTI quartiles (all P<0.001). Participants in higher cuCTI quartiles were more likely to be female, physically inactive, and to have hypertension, diabetes, or heart disease at baseline (all P<0.001). The proportion of single baseline cardiometabolic multimorbidity (CMM) increased markedly from the lowest to the highest cuCTI quartile (13.48% to 50.31%, P<0.001). The incidence of incident CMM showed a clear graded increase across cuCTI quartiles: 2.41%, 4.06%, 5.95%, and 10.30% in Q1 to Q4, respectively (P<0.001).

Table 1. Baseline characteristics of the study population stratified by quartiles of cumulative CTI (cuCTI).

Variables	Total (n = 8464)	1 (n = 2115)	2 (n = 2116)	3 (n = 2116)	4 (n = 2117)	*P*
Age, M (Q_1, Q_3)	58.00 (52.00, 65.00)	58.00 (51.00,64.00)	58.00 (52.00,65.00)	58.00 (52.00,65.00)	58.00 (52.00,64.00)	0.018
CRP 2011, M (Q_1, Q_3)	1.07 (0.56, 2.41)	0.56 (0.37,0.94)	0.91 (0.55,1.69)	1.34 (0.74,2.61)	2.50 (1.15,7.19)	<.001
Tg 2011, M (Q_1, Q_3)	107.08 (76.11,	73.46 (57.53,93.81)	96.46 (74.34,125.01)	121.25 (92.93,157.53)	184.96 (129.21,278.77)	<.001

	157.53)					
Fpg 2011, M (Q_1, Q_3)	102.24 (94.32, 112.32)	97.20 (90.90,104.76)	100.08 (92.88,108.18)	103.14 (95.58,112.50)	111.06 (100.62,130.86)	<.001
BRI 2011, M (Q_1, Q_3)	4.02 (3.22, 5.02)	3.48 (2.87,4.28)	3.88 (3.13,4.80)	4.23 (3.38,5.17)	4.65 (3.80,5.53)	<.001
BMI 2011, M (Q_1, Q_3)	23.07 (20.87, 25.56)	21.78 (20.03,23.74)	22.61 (20.51,24.88)	23.46 (21.26,25.94)	24.60 (22.32,27.15)	<.001
Marriage, n(%)						0.337
Yes	7479 (88.36)	1885 (89.13)	1849 (87.38)	1868 (88.28)	1877 (88.66)	
No	985 (11.64)	230 (10.87)	267 (12.62)	248 (11.72)	240 (11.34)	
Gender, n(%)						<.001
Male	3983 (47.06)	1088 (51.44)	1000 (47.26)	943 (44.57)	952 (44.97)	
Female	4481 (52.94)	1027 (48.56)	1116 (52.74)	1173 (55.43)	1165 (55.03)	
Drinking status, n (%)						0.002
No	5208 (61.53)	1228 (58.06)	1312 (62.00)	1339 (63.28)	1329 (62.78)	
Yes	3256 (38.47)	887 (41.94)	804 (38.00)	777 (36.72)	788 (37.22)	
Physical Activity, n(%)						<.001
No	2764 (32.66)	696 (32.91)	704 (33.27)	755 (35.68)	609 (28.77)	
Yes	5700 (67.34)	1419 (67.09)	1412 (66.73)	1361 (64.32)	1508 (71.23)	
Basal Hypertension, n(%)						<.001
No	5156 (60.92)	1531 (72.39)	1383 (65.36)	1198 (56.62)	1044 (49.32)	
Yes	3308 (39.08)	584 (27.61)	733 (34.64)	918 (43.38)	1073 (50.68)	
Basal Diabetes,						<.001

n(%)						
No	7147 (84.44)	2005 (94.80)	1930 (91.21)	1846 (87.24)	1366 (64.53)	
Yes	1317 (15.56)	110 (5.20)	186 (8.79)	270 (12.76)	751 (35.47)	
Basal heart disease, n (%)						<.001
No	7666 (90.57)	1962 (92.77)	1940 (91.68)	1924 (90.93)	1840 (86.92)	
Yes	798 (9.43)	153 (7.23)	176 (8.32)	192 (9.07)	277 (13.08)	
Basal stroke, n (%)						0.280
No	8343 (98.57)	2093 (98.96)	2085 (98.53)	2085 (98.53)	2080 (98.25)	
Yes	121 (1.43)	22 (1.04)	31 (1.47)	31 (1.47)	37 (1.75)	
New-onset multimorbidity, n(%)						<.001
No	7983 (94.32)	2064 (97.59)	2030 (95.94)	1990 (94.05)	1899 (89.70)	
Yes	481 (5.68)	51 (2.41)	86 (4.06)	126 (5.95)	218 (10.30)	
Baseline CMM status, n(%)						<.001
No baseline CMM	6228 (73.58)	1830 (86.52)	1723 (81.43)	1623 (76.70)	1052 (49.69)	
Single baseline CMM	2236 (26.42)	285 (13.48)	393 (18.57)	493 (23.30)	1065 (50.31)	
Smoke, n(%)						0.056
Yes	6209 (73.36)	1506 (71.21)	1552 (73.35)	1576 (74.48)	1575 (74.40)	
No	2255 (26.64)	609 (28.79)	564 (26.65)	540 (25.52)	542 (25.60)	
Education, n(%)						0.054
Below high school	7649 (90.37)	1898 (89.74)	1934 (91.40)	1927 (91.07)	1890 (89.28)	
High school or above	815 (9.63)	217 (10.26)	182 (8.60)	189 (8.93)	227 (10.72)	

Residence, n(%)						<.001
Agricultual	7149 (84.46)	1843 (87.14)	1799 (85.02)	1798 (84.97)	1709 (80.73)	
Non-Agricultual	1315 (15.54)	272 (12.86)	317 (14.98)	318 (15.03)	408 (19.27)	
Marriage, n (%)						0.337
Yes	7479 (88.36)	1885 (89.13)	1849 (87.38)	1868 (88.28)	1877 (88.66)	
No	985 (11.64)	230 (10.87)	267 (12.62)	248 (11.72)	240 (11.34)	

Note: Data are presented as median (interquartile range) for continuous variables with skewed distribution, or n (%) for categorical variables.

P-values were derived from the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables.

cuCTI, cumulative Cardiometabolic Index; IQR, interquartile range; BMI, body mass index; BRI, Body Roundness Index; FPG, fasting plasma glucose; TG, triglycerides; CRP, C-reactive protein; CTI, Cardiometabolic Index; CMM, cardiometabolic multimorbidity..

Associations of cuCTI and CTI trajectory with incident CMM

The results of Cox proportional hazards regression models are presented in Table 2. In Model 1 (unadjusted), each 1-unit increment in cuCTI was associated with a 19% higher risk of incident CMM (HR=1.19, 95%CI: 1.16–1.22, P<0.001). After adjustment for demographic confounders (Model 2), the association remained virtually unchanged. In the fully adjusted model (Model 3), cuCTI remained independently associated with incident CMM (HR=1.06, 95%CI: 1.03–1.09, P<0.001). Compared with the lowest quartile (Q1), the highest quartile (Q4) of

cuCTI conferred a 69% increased risk of incident CMM (HR=1.69, 95%CI: 1.22–2.35, P=0.002), with a clear dose–response relationship.

For CTI change, a significant inverse association was observed in Model 1 and Model 2 (HR=0.82 and 0.81, both P<0.001), but this association was attenuated to non-significance in Model 3 (HR=0.95, 95%CI: 0.88–1.02, P=0.157). Regarding CTI trajectory groups, compared with Cluster 2 (reference), Cluster 1 and Cluster 3 showed elevated risks in unadjusted and demographically adjusted models. After full adjustment, these associations were attenuated but remained marginally significant (Cluster 1: HR=1.23, P=0.079; Cluster 3: HR=1.23, P=0.075).

Table 2. Associations of cumulative CTI (cuCTI) and CT trajectory with incident cardiometabolic multimorbidity.

Variables	Model1		Model2		Model3	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
cuCTI	1.19 (1.16 ~ 1.22)	<.001	1.19 (1.15 ~ 1.22)	<.001	1.06 (1.03 ~ 1.09)	<.001
Quartiles of cuCTI						
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	1.70 (1.20 ~ 2.40)	0.003	1.65 (1.16 ~ 2.33)	0.005	1.30 (0.92 ~ 1.84)	0.141
Q3	2.48 (1.79 ~ 3.43)	<.001	2.38 (1.72 ~ 3.30)	<.001	1.52 (1.09 ~ 2.12)	0.013
Q4	4.36 (3.21 ~ 5.91)	<.001	4.16 (3.06 ~ 5.64)	<.001	1.69 (1.22 ~ 2.35)	0.002
CTI Change	0.82 (0.75 ~ 0.88)	<.001	0.81 (0.75 ~ 0.88)	<.001	0.95 (0.88 ~ 1.02)	0.157
CHG trajectory groups						
Cluster 2	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Cluster 1	1.27 (1.01 ~ 1.61)	0.043	1.26 (1.00 ~ 1.59)	0.054	1.23 (0.98 ~ 1.56)	0.079
Cluster 3	1.59 (1.27 ~ 1.99)	<.001	1.59 (1.27 ~ 1.99)	<.001	1.23 (0.98 ~ 1.54)	0.075

Note: Model 1: unadjusted.

Model 2: adjusted for age, sex, residence, marital status, and educational level.

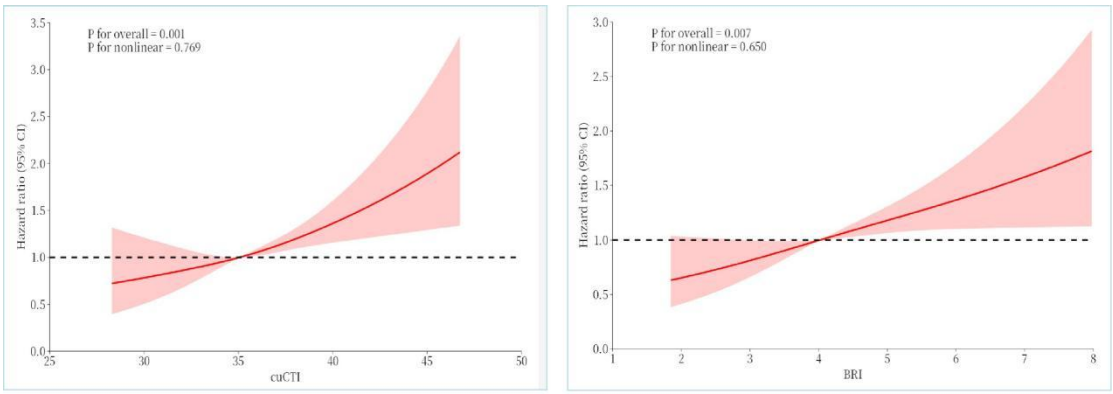
Model 3: fully adjusted model, further adjusted for smoking, alcohol consumption, BMI, baseline hypertension, diabetes, heart disease, and stroke.

HR, hazard ratio; CI, confidence interval; cuCTI, cumulative Cardiometabolic Index; CTI, Cardiometabolic Index; CMM, cardiometabolic multimorbidity.

Dose-response relationship between cuCTI, BRI and incident CMM

Restricted cubic spline regression was performed to examine potential non-linear associations between continuous cuCTI, BRI and incident CMM(Figure 2A, Figure 2B). As shown in the spline curves, there was a significant linear positive association between cuCTI and incident CMM risk (P for overall = 0.001, P for nonlinearity = 0.769). The hazard ratio increased gradually with higher cuCTI levels, consistent with the graded risk observed across cuCTI quartiles. Similarly, BRI also showed a linear association with incident CMM risk (P for overall = 0.007, P for nonlinearity = 0.650), with higher BRI values associated with an increased hazard ratio for CMM.

Figure. 2 Dose–response relationship between cuCTI/BRI and incident CMM.



(A) (B)

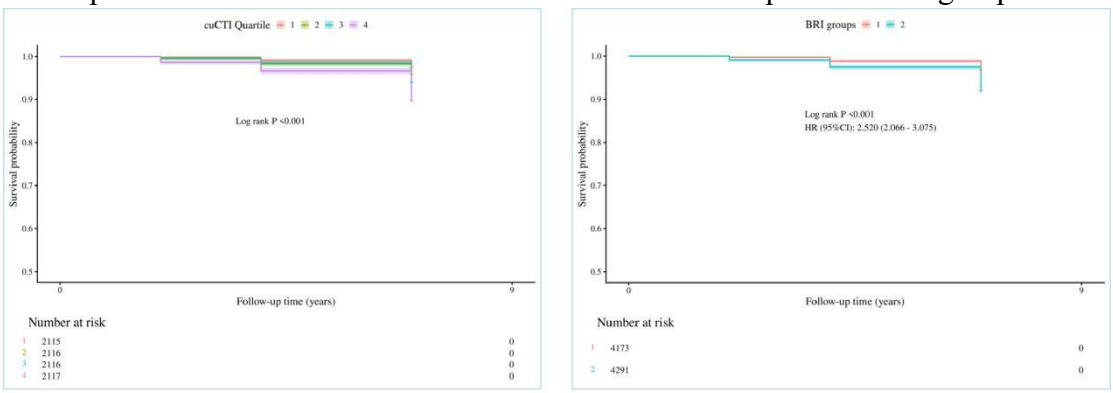
Figure 2A. Dose-response relationship between cuCTI and incident CMM.

Figure 2B. Dose-response relationship between BRI and incident CMM.
Hazard ratios(solid line)and 95%confidence intervals(shaded area)are presented.BRI,Body Roundness Index;CMM,cardiometabolic multimorbidity.

Kaplan－Meier survival analysis

Kaplan–Meier curves were used to estimate the cumulative incidence of CMM across cuCTI quartiles and BRI groups[9](Figure 3A, Figure 3B). Participants in the highest cuCTI quartile had the lowest CMM-free survival probability compared with those in lower quartiles (Log-rank P<0.001). Similarly, participants with higher BRI levels showed a significantly lower CMM-free survival probability (Log-rank P<0.001, HR=2.520, 95%CI: 2.066–3.075).

Figure. 3 Kaplan–Meier curves for incident CMM across cuCTI quartiles/BRI groups.



(A) (B)

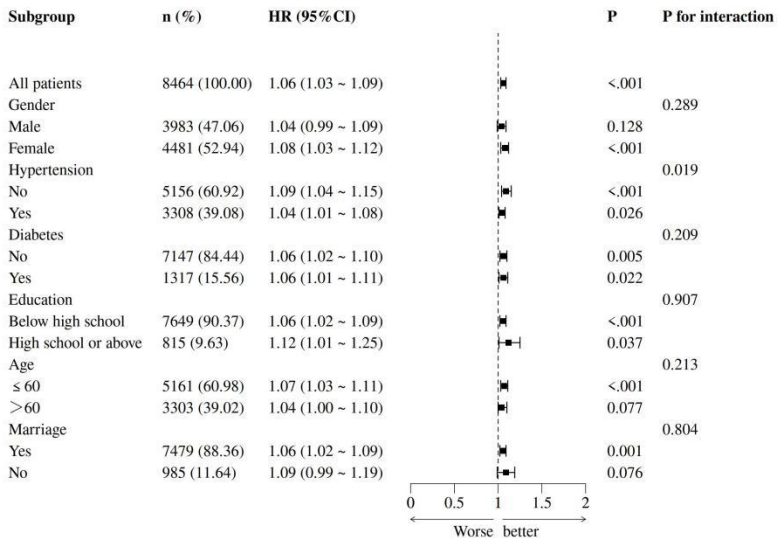
Figure 3A. Kaplan–Meier curves for incident CMM across cuCTI quartiles.
Figure 3B. Kaplan–Meier curves for incident CMM across BRI groups.
Log-rank test was used to compare survival distributions. HR, hazard ratio; CI, confidence interval; BRI, Body Roundness Index; CMM, cardiometabolic multimorbidity.

Subgroup and interaction analyses

Subgroup analyses were conducted to assess the robustness of the

association between cuCTI and incident CMM across different strata(Figure 4). The positive association between cuCTI and CMM risk remained consistent across most subgroups, including sex, age, education, smoking, alcohol consumption, and diabetes status. A significant interaction was observed only in the hypertension subgroup (P for interaction=0.019). Specifically, the association was stronger in participants without baseline hypertension (HR=1.09, 95%CI: 1.04–1.15) compared with those with hypertension (HR=1.04, 95%CI: 1.01–1.08). No significant interactions were found for other subgroups (all P for interaction > 0.05).

Figure 4. Forest plot of subgroup analyses for cuCTI and incident CMM.



Predictive performance of cuCTI and BRI for incident CMM

The predictive abilities of cuCTI and BRI for incident CMM were

evaluated using time-dependent receiver operating characteristic (ROC) curves(Figure 5A, Figure 5B). The AUC was 0.67 (95% CI: 0.64–0.69) for cuCTI and 0.66 (95% CI: 0.63–0.68) for BRI, indicating moderate predictive performance for identifying individuals at higher risk of developing CMM.

Figure 5. Time-dependent ROC curve of cuCTI/BRI for incident CMM.

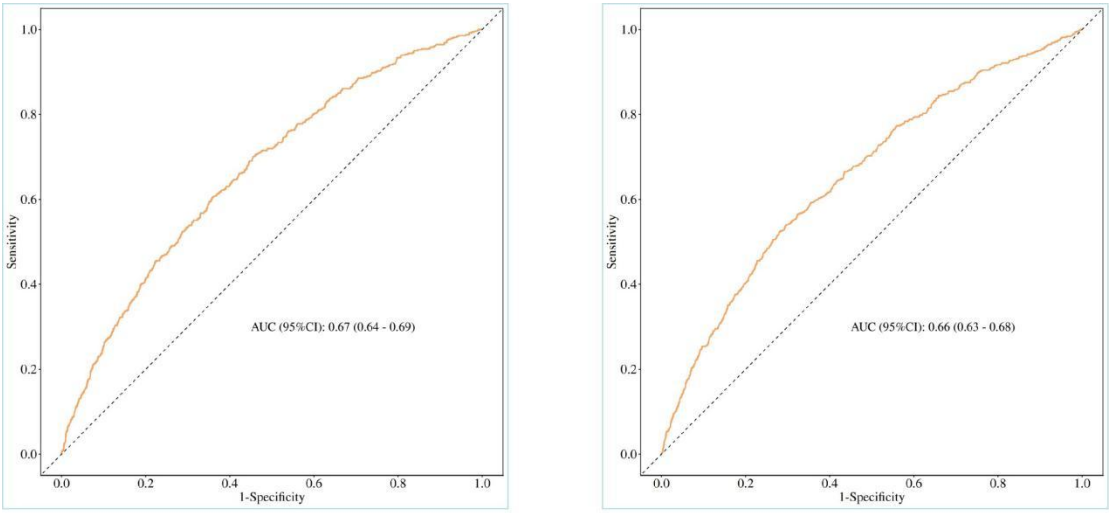


Figure 5A. Time-dependent ROC curve of cuCTI for incident CMM.

Figure 5B. Time-dependent ROC curve of BRI for incident CMM.

AUC and 95% confidence interval are presented. ROC, receiver operating characteristic; AUC, area under the curve; BRI, Body Roundness Index; CMM, cardiometabolic multimorbidity.

Mediation effect of BRI

Mediation analysis was performed using the percentile bootstrap method with 5000 resamples to examine whether BRI mediated the association between cuCTI and incident CMM (Table 3). The total effect of cuCTI on CMM was significant (β=0.0004, 95%CI:0.0003-0.0006, P<0.01). The direct effect remained significant after adjustment for

BRI(β=0.0004, 95%CI:0.0002-0.0006, P<0.01). The indirect effect through BRI was significant (indirect effect=0.00003,95%bootstrap CI:0.0001-0.0014, not crossing zero).

Path a (cuCTI→BRI) was positively significant (β=0.042,95%CI:0.036 – 0.048,P<0.001), and path b(BRI→CMM)was also significant(β=0.007,95%CI:0.001-0.014,P<0.05). BRI exerted a partial mediating effect,accounting for 7.0% of the total association between cuCTI and incident CMM.

Table 3. Mediation analysis of the association between cumulative CTI (cuCTI) and incident cardiometabolic multimorbidity (CMM) mediated by Body Roundness Index (BRI).

Pathway	Coefficient	95% Bootstrap CI*	p-value
Total effect (c)	0.0004	0.0003–0.0006	<0.01
Direct effect (c')	0.0004	0.0002–0.0006	<0.01
Indirect effect (a×b)	0.00003	0.0001–0.0014	—
Path a (cuCTI → BRI)	0.042	0.036–0.048	<0.001
Path b (BRI → CMM)	0.007	0.001–0.014	<0.05

*Note: Percentile bootstrap method with 5000 resamples was used to estimate the 95% confidence intervals (CI) for the indirect effect. The indirect effect (a×b) was considered statistically significant if the 95% CI did not include zero. The mediating effect of BRI accounted for approximately 7.0% of the total effect (a×b / c).

Discussion

In this prospective, population-based cohort study of middle-aged and older Chinese adults, we demonstrated that elevated cumulative C-reactive protein-triglyceride glucose index (cuCTI) and a persistently

high CTI trajectory were independently associated with an increased risk of incident cardiometabolic multimorbidity (CMM). Importantly, BRI partially mediated the association between cuCTI and CMM, explaining 7.0% of the total effect. To our knowledge, this is the first prospective study to simultaneously evaluate cumulative cardiometabolic burden, longitudinal trajectory patterns, and the mediating role of body fat distribution in the development of CMM.

Consistent with emerging evidence emphasizing the limitations of single-time-point measurements, our findings underscore the superiority of cumulative and longitudinal metabolic assessment over single-time-point measurements. Traditional cardiometabolic risk assessment typically relies on cross-sectional values of individual biomarkers[33–36], which fail to reflect the sustained imbalance among inflammation, glucose metabolism, and lipid profiles over time. In contrast, cuCTI integrates repeated assessments of C-reactive protein (CRP), triglycerides (TG), and fasting plasma glucose (FPG), thereby comprehensively capturing long-term low-grade inflammation, insulin resistance, dyslipidemia, and glycemic dysregulation[8, 37].

The biological plausibility of our findings is further strengthened by the synergistic pathophysiological mechanisms underlying the C-reactive protein-triglyceride glucose index. CTI integrates two core and interconnected pathways involved in cardiometabolic damage: systemic

444 inflammation represented by CRP, and metabolic dysregulation reflected
445 by the triglyceride-glucose (TyG) index[38–41]. Elevated CRP promotes
446 endothelial dysfunction, enhances oxidative modification of lipoproteins,
447 and facilitates leukocyte infiltration into the vascular wall, thereby
448 triggering and accelerating atherogenesis. Meanwhile, the TyG
449 component serves as a robust marker of insulin resistance, which impairs
450 peripheral glucose utilization, induces lipotoxicity, and generates
451 excessive oxidative stress, further impairing vascular homeostasis.
452 Inflammation and insulin resistance act synergistically, forming a vicious
453 cycle that aggravates systemic metabolic disturbance and vascular
454 damage. Unlike single biomarkers that capture only one aspect of risk,
455 CTI provides a unified measure of inflammatory-metabolic dysfunction,
456 offering a more comprehensive reflection of overall cardiometabolic
457 health. Furthermore, cumulative CTI (cuCTI) advances this framework
458 by quantifying long-term, sustained exposure rather than transient
459 fluctuations. Continuously elevated cuCTI indicates prolonged
460 inflammatory and metabolic stress, which gradually disrupts pancreatic
461 function, promotes ectopic fat deposition, damages vascular integrity, and
462 ultimately drives the co-occurrence of multiple cardiometabolic diseases.

463 The linear dose-response relationship observed in our study-where
464 the risk of CMM rose progressively with increasing cuCTI
465 quartiles-further supports the cumulative damage hypothesis: persistent

metabolic disturbances rather than transient fluctuations drive the pathological progression leading to the co-occurrence of multiple cardiometabolic diseases. These findings align with recent reports [17, 32, 37]indicating that cumulative metabolic indices improve risk stratification beyond conventional single-time indicators.

Longitudinal trajectory analysis showed that the persistently high CTI group carried the highest CMM risk, supporting the importance of sustained metabolic control. Although statistical significance was attenuated after full adjustment, the direction and magnitude remained biologically plausible.

A novel mechanistic finding is that BRI partially mediates the cuCTI – CMM pathway (7.0%). Prolonged elevated cuCTI promotes abdominal adiposity and abnormal fat distribution. Compared with BMI, which reflects general obesity, BRI more sensitively captures central adiposity and visceral fat accumulation[42–44]—core drivers of insulin resistance, chronic inflammation, endothelial dysfunction, and ectopic fat deposition in the liver, pancreas, and vasculature. Visceral adipose tissue secretes large amounts of pro-inflammatory cytokines and free fatty acids, which further impair insulin signaling, promote lipid disorders, and damage vascular function. This vicious cycle ultimately accelerates the co-development of hypertension, type 2 diabetes, cardiovascular disease, and stroke[44–46]. By demonstrating that BRI acts as an intermediate

phenotype, our study identifies abnormal body fat distribution as a modifiable target to interrupt the pathogenic pathway from cumulative cardiometabolic risk to CMM.

This study has several major strengths. First, the prospective design and large, nationally representative sample from CHARLS minimize selection bias and enhance generalizability to middle-aged and older Chinese adults. Second, repeated measurements of key metabolic and anthropometric indicators enable robust evaluation of cumulative exposure and longitudinal trajectories. Third, mediation analysis clarifies a biologically plausible mechanism, improving the translational potential of our findings for clinical practice.

Several limitations should be acknowledged. First, CMM and its components were identified using self-reported physician diagnoses, which may introduce minor misclassification. However, standardized data collection in CHARLS helps reduce this bias. Second, residual confounding from unmeasured factors, such as dietary intake, genetic susceptibility, and medication adherence, cannot be fully excluded. Third, the study population was restricted to Chinese adults aged 45 years and older, limiting extrapolation to younger or other ethnic populations. Finally, the marginal significance of CTI trajectories after full adjustment requires validation in cohorts with more waves of measurement and longer follow-up.

Conclusions

In conclusion, elevated cumulative C-reactive protein-triglyceride glucose index and unfavorable longitudinal CTI trajectory are independently associated with a higher risk of incident cardiometabolic multimorbidity in middle-aged and older Chinese adults. The association between cumulative cardiometabolic burden and CMM is partially mediated by Body Roundness Index, indicating that abnormal central body fat distribution plays an important intermediate role. These findings support the use of cumulative and longitudinal metabolic monitoring in clinical practice and highlight the importance of improving body fat distribution for the early prevention of cardiometabolic multimorbidity.

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