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# Association between the changes in the C-reactive protein-triglyceride-glucose index and future cardiometabolic multimorbidity risk: a nationwide cohort study

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## Abstract

# Background

Cardiometabolic multimorbidity (CMM) has become an escalating global public health concern. This study aimed to comprehensively investigate the associations of baseline CTI, cumulative CTI burden, and longitudinal CTI trajectories with the risk of incident CMM.

# Methods

A total of 4,425 participants from the China Health and Retirement Longitudinal Study (CHARLS) were included. CTI was calculated as 0.412 × ln[CRP (mg/L)] + ln[fasting triglycerides (mg/dL) × fasting glucose (mg/dL) / 2]. CTI exposure was assessed from three dimensions: baseline CTI, cumulative CTI(cuCTI), and longitudinal trajectory patterns. Associations were assessed using Cox regression analysis and restricted cubic spline (RCS) analyses. Predictive performance was evaluated using receiver operating characteristic (ROC) curves.

# Results

During the follow-up period, 423 participants (9.6%) developed CMM. Higher CTI levels were significantly associated with an increased risk of CMM. After full adjustment, participants in the highest quartile of baseline CTI had a 2.57-fold higher risk of CMM compared with those in the lowest quartile (HR 2.57, 95% CI 2.00–3.30). Similarly, individuals in the highest quartile of cuCTI exhibited an HR of 2.88 (95% CI 2.00–4.16). Trajectory analysis identified four distinct CTI patterns, and participants in the persistently high trajectory group demonstrating the greatest risk of CMM (HR 2.71, 95% CI 1.94–3.80). RCS analysis indicated a significant dose-response relationship between CTI and CMM risk. ROC analyses showed that CTI outperformed both the TyG index and CRP alone in predicting CMM, and cuCTI was demonstrated the highest predictive accuracy. These associations remained robust across subgroup and sensitivity analyses.

# Conclusion

Elevated cumulative CTI burden and persistently high CTI trajectories were independently and strongly associated with increased CMM risk. Dynamic monitoring of CTI may improve early risk stratification and serve as a promising tool for the primary prevention of cardiometabolic diseases.

## Introduction

Cardiometabolic diseases (CMDs), including diabetes, heart disease, and stroke, are leading causes of global morbidity and mortality [1]. Due to shared pathophysiological mechanisms, particularly insulin

resistance, chronic inflammation, and metabolic dysregulation, these conditions frequently cluster and co-occur within individuals, resulting in cardiometabolic multimorbidity (CMM), defined as the coexistence of two or more CMDs in the same individual [2]. Compared with a single CMD, CMM confers substantially higher risks of mortality, functional impairment, and diminished quality of life, imposing considerable burdens on healthcare systems [3]. With rapid population aging and prolonged exposure to adverse lifestyle factors, the prevalence of CMM has continued to increase. Therefore, identifying modifiable risk factors and improving early risk stratification, especially among middle-aged and older adults, is essential to reduce the incidence and adverse consequences of CMM.

The pathogenesis of CMM is complex; however, insulin resistance (IR) and inflammatory responses are considered two key pathophysiological mechanisms driving its onset and progression [4, 5]. Accumulating evidence indicates that the triglyceride-glucose (TyG) index is a validated surrogate marker of IR, with relatively high sensitivity and specificity, and it has substantial predictive value for CMDs [6, 7]. Likewise, C-reactive protein (CRP), a sensitive biomarker of systemic inflammation, possesses well-established clinical and prognostic value in cardiometabolic disorders [8–10]. Importantly, IR and inflammation interact bidirectionally and mutually reinforce each other during the progression of CMM [11]. Therefore, reliance on a single biomarker may not adequately capture the integrated metabolic–inflammatory risk profile. Combined assessment of TyG and CRP may improve risk stratification. In this context, the C-reactive protein-triglyceride-glucose index (CTI) has emerged as a novel composite biomarker that integrates inflammatory and metabolic information into a single metric [12]. Current studies have demonstrated associations between baseline CTI levels and CMM risk [13]. However, most evidence is based on single time-point measurements and does not account for the dynamic evolution of metabolic–inflammatory burden. Previous studies have demonstrated that cumulative indices and dynamic trajectory patterns derived from repeated measurements may better capture the synergistic effects of chronic inflammation and metabolic dysregulation [14–16]. Therefore, it is essential to systematically investigate the associations of cuCTI and longitudinal CTI changes with incident CMM in the general population.

This study uses nationally representative longitudinal data from CHARLS to systematically examine the associations of cumulative CTI exposure and its longitudinal trajectory patterns with incident CMM. By evaluating both the cumulative burden and the temporal evolution of CTI, this study aimed to provide more robust evidence for early risk identification and primary prevention of CMM.

## Methods

# Data Source and Study Population

The study population was derived from CHARLS, a nationally representative longitudinal survey initiated in 2011, targeting residents aged ≥ 45 years in China. Detailed information regarding the study design and enrollment criteria were reported in previous literature. Between 2011 and 2020, five waves of surveys were conducted. A multi-stage, stratified, probability proportional-to-size sampling strategy was

employed to recruit participants from 23 provinces across China. The national baseline survey was conducted in 2011, enrolling a total of 17,708 participants, followed by four waves of follow-up: Wave 2 (2013–2014), Wave 3 (2015–2016), Wave 4 (2017–2018), and Wave 5 (2019–2020) [17]. Data from Waves 1–5 were utilized in this study and were publicly available on the official CHARLS website (http://charls.pku.edu.cn).

Among the 17,708 participants initially enrolled, exclusions were applied sequentially as follows: (1) 434 individuals with pre-existing CMM at baseline; (2) 1,210 individuals with missing baseline CMM data or loss to follow-up; (3) 5,159 individuals lacking data required for CTI calculation at Wave 1; (4) 2,018 individuals with missing covariate information; and (5) 753 individuals in a non-fasting state. After these exclusions, 8,134 participants were included in the baseline CTI analysis. To further evaluate the associations of cuCTI and CTI trajectory patterns with incident CMM, additional exclusions were made: (1) 199 individuals developed CMM at or before Wave 3; (2) 1,185 individuals with missing CMM data at Wave 1 or Wave 3, or loss to follow-up; (3) 1,563 individuals with missing data required for cumulative CTI calculation; and (4) 762 individuals in a non-fasting state. Ultimately, 4,425 participants were included in the final analysis. The detailed participants selection process was presented in Fig. 1.

## Calculation of CTI and TyG index

The CTI was calculated as: 0.412 × Ln[CRP (mg/L)] + Ln[fasting triglycerides (mg/dL) × fasting glucose (mg/dL) / 2] [12]. The TyG index was defined as Ln[fasting triglycerides (mg/dL) × fasting glucose (mg/dL) / 2] [18]. The cumulative CTI was calculated as: (CTI 2012 + CTI 2015) / 2 × time (2015–2012). Similarly, the cumulative TyG was calculated as: (TyG 2012 + TyG 2015) / 2 × time (2015–2012). Venous blood samples were collected from participants by staff from the Chinese Center for Disease Control and Prevention after at least 8 hours of fasting. The samples were subsequently transported to Beijing, where relevant biomarkers were measured according to standardized protocols.

## Outcome variables

Outcome variables

The primary endpoint was incident CMM during the follow-up period. A CMM event was defined as the co-occurrence of at least two cardiometabolic diseases, including diabetes, heart disease, and stroke. Diagnoses of heart disease and stroke were confirmed based on self-reported physician diagnoses from questionnaire surveys. The relevant questions included: "Has a doctor ever told you that you were diagnosed with myocardial infarction, coronary heart disease, angina, congestive heart failure, or other heart problems?" or "Has a doctor ever told you that you were diagnosed with a stroke?". In addition to self-reported diabetes or current use of anti-hyperglycemic medications, participants were also classified as having diabetes if they met any of the following criteria: (1) fasting plasma glucose ≥ 7.0 mmol/L; or (2) glycated hemoglobin (HbA1c) ≥ 6.5%, based on the American Diabetes Association (ADA) diagnostic criteria [19]. The time of CMM onset was defined as the point when the second CMD was

diagnosed, that is, the first time an individual simultaneously met the criteria for two different types of CMD.

## Covariates

Baseline data of the participants were collected by trained interviewers using a structured questionnaire, encompassing sociodemographic characteristics (age, sex, marital status, educational level, residence), lifestyle factors (smoking, alcohol consumption), physical examination parameters (body mass index [BMI], waist circumference [WC], systolic blood pressure [SBP], diastolic blood pressure [DBP]), chronic conditions (dyslipidemia), and medication history (antihypertensive drugs, lipid-lowering drugs, glucose-lowering drugs). Marital status was categorized as married or other. Smoking and alcohol consumption status were defined as never or ever. Hypertension was defined as SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, self-reported hypertension, or current use of antihypertensive drugs. Dyslipidemia was defined as total cholesterol (TC) ≥ 240 mg/dL, triglycerides (TG) ≥ 150 mg/dL, low-density lipoprotein cholesterol (LDL-C) ≥ 160 mg/dL, or self-reported dyslipidemia.

# Statistical Analysis

Data analysis was performed using RStudio version 4.5.1. A two-sided P-value < 0.05 was considered statistically significant. First, participants were categorized into four groups based on the quartiles of cuCTI. Continuous variables with a normal or approximately normal distribution were presented as means ± standard deviations (SDs), while those with a non-normal distribution were presented as medians (interquartile ranges). Categorical variables were presented as frequencies and percentages. Comparisons of baseline characteristics among groups were performed using analysis of variance (ANOVA) or the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables. Second, K-means clustering analysis was applied to classify the trajectory of CTI changes from Wave 1 to Wave 3. In this study, the elbow method was used to determine the optimal number of clusters for the CTI trajectory. The K-means algorithm partitions data into K clusters by minimizing the sum of squared distances within each cluster, as illustrated in Fig. 2. The clustering process was conducted independently of the outcome variable to avoid analytical bias. The optimal number of clusters was determined to be K = 4 using the elbow method. Third, Cox proportional hazards models were employed to investigate the associations of baseline CTI, cuCTI, and longitudinal CTI trajectories with the risk of incident CMM. Three models were constructed: Model 1 was unadjusted; Model 2 was adjusted for age, sex, residence, marital status, and education level; Model 3 was further adjusted for smoking, alcohol consumption, BMI, WC, SBP, DBP, dyslipidemia, antihypertensive medication, hypoglycemic medication, and lipid-lowering medication. Subsequently, Kaplan-Meier survival analysis was used to estimate the cumulative risk of CMM across different baseline CTI, cuCTI, and trajectory groups. Fourth, restricted cubic spline (RCS) analysis was performed to explore potential nonlinear relationships between cumulative CTI, baseline CTI, and CMM risk. Fifth, to compare the predictive value of the CTI, TyG index, and CRP for CMM risk, receiver operating characteristic (ROC) analysis was

conducted. The DeLong test was used to compare the area under the curve (AUC).Sixth, to investigate whether the associations of cumulative CTI and baseline CTI with CMM risk differed across various populations, stratified subgroup analyses were performed. Finally, sensitivity analyses were conducted by repeating the primary analyses after excluding participants with any CMD at baseline.

## Results

# Baseline characteristics of the study population

As shown in Table 1, a total of 4,425 participants were included, with a mean age of 58.31 ± 8.75 years. Among them, 1,926 (43.5%) were male. Participants were categorized into quartiles (Q1–Q4) according to cuCTI levels. With increasing cuCTI quartiles, the proportions of females, urban residents, and individuals receiving antihypertensive, hypoglycemic, or lipid-lowering therapy increased significantly, as did the prevalence of dyslipidemia, heart disease, diabetes, and hypertension. Correspondingly, levels of fasting blood glucose (FBG), TC, TG, CRP, LDL-C, HbA1c, serum creatinine, cystatin C, uric acid (UA), WC, BMI, DBP, and SBP exhibited significant upward trends. In contrast, high-density lipoprotein cholesterol (HDL-C) levels and the proportions of smokers and alcohol drinkers decreased across higher cuCTI quartiles. Furthermore, similar baseline demographic and clinical patterns were observed when participants were grouped by baseline CTI quartiles (Table S1) and dynamic CTI trajectory classes (Table S2).

Table 1
Baseline characteristics of participants according to quartiles of cumulative CTI

| Characteristics | Overall | cuCTI | | | | p |
|---|---|---|---|---|---|---|
| | | Q1 | Q2 | Q3 | Q4 | |
| Participants, N | 4425 | 1107 | 1106 | 1106 | 1106 | |
| Age, years | 58.31 ± 8.75 | 57.73 ± 8.88 | 58.56 ± 8.87 | 58.53 ± 8.92 | 58.40 ± 8.32 | 0.089 |
| Male, n(%) | 1926 (43.5) | 549 (49.6) | 510 (46.1) | 447 (40.4) | 420 (38.0) | < 0.001 |
| Marital status,n(%) | | | | | | 0.319 |
| Married | 3957 (89.4) | 999 (90.2) | 978 (88.4) | 981 (88.7) | 999 (90.3) | |
| Others | 468(10.6) | 108(9.8) | 128(11.6) | 125(11.3) | 107(9.7) | |
| Residence, n(%) | | | | | | < 0.001 |
| Rural | 2950 (66.7) | 805 (72.7) | 769 (69.5) | 728 (65.8) | 648 (58.6) | |
| Urban | 1475(33.3) | 302(27.3) | 337(30.5) | 378(34.2) | 458(41.4) | |
| Educational level, n(%) | | | | | | 0.778 |
| Less than middle school | 4046 (91.4) | 1003 (90.6) | 1020 (92.2) | 1012 (91.5) | 1011 (91.4) | |
| High/Vocational school | 345 (7.8) | 93 (8.4) | 81 (7.3) | 85 (7.7) | 86 (7.8) | |
| College or above | 34 (0.8) | 11 (1.0) | 5 (0.5) | 9 (0.8) | 9 (0.8) | |
| Smoking, n(%) | | | | | | 0.034 |
| Ever | 1614 (36.5) | 438 (39.6) | 413 (37.3) | 380 (34.4) | 383 (34.6) | |
| Never | 2811(63.5) | 669(60.4) | 693(62.7) | 726(65.6) | 723(65.4) | |
| Drinking, n(%) | | | | | | 0.013 |
| Ever | 1793 (40.5) | 490 (44.3) | 450 (40.7) | 437 (39.5) | 416 (37.6) | |
| Never | 2632(59.5) | 617(55.7) | 656(59.3) | 669(60.5) | 690(62.4) | |

Abbreviations: CTI, C-reactive protein-triglyceride glucose index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; TG, triglyceride; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; CMM, cardiometabolic multimoribidity

| Characteristics | Overall | cuCTI | | | | p |
|---|---|---|---|---|---|---|
| | | Q1 | Q2 | Q3 | Q4 | |
| BMI, kg/m$^2$ | 23.27 [21.07, 25.82] | 21.62 [19.90, 23.65] | 22.77 [20.56, 24.89] | 23.77 [21.67, 26.16] | 25.25 [22.99, 27.80] | < 0.001 |
| Waist, cm | 84.46 (12.13) | 79.68 (10.02) | 82.47 (11.75) | 85.83 (11.85) | 89.86 (12.34) | < 0.001 |
| DBP, mmHg | 74.76 ± 11.91 | 71.66 ± 10.98 | 73.82 ± 11.96 | 75.63 ± 11.78 | 77.91 ± 12.00 | < 0.001 |
| SBP, mmHg | 127.65 ± 20.47 | 122.32 ± 18.69 | 126.26 ± 20.25 | 129.34 ± 20.61 | 132.69 ± 20.87 | < 0.001 |
| TC, mg/dl | 194.30 (39.05) | 182.30 (33.89) | 189.69 (34.89) | 196.51 (37.54) | 208.72 (44.18) | < 0.001 |
| TG, mg/dl | 103.54 [73.46, 150.45] | 67.26 [54.87, 86.29] | 91.15 [71.68, 114.17] | 120.36 [92.93, 152.22] | 183.64 [134.52, 261.08] | < 0.001 |
| HbA1c(%) | 5.10 [4.90, 5.40] | 5.10 [4.80, 5.30] | 5.10 [4.90, 5.30] | 5.20 [4.90, 5.40] | 5.30 [5.00, 5.60] | < 0.001 |
| CRP, mg/l | 0.96 [0.54, 1.97] | 0.50 [0.34, 0.80] | 0.82 [0.52, 1.49] | 1.24 [0.72, 2.22] | 1.89 [1.06, 3.94] | < 0.001 |
| FBG, mg/dl, | 101.88 [94.50, 111.24] | 97.02 [91.08, 104.22] | 99.90 [93.24, 107.46] | 102.42 [95.76, 111.19] | 109.98 [100.98, 128.70] | < 0.001 |
| HDL, mg/dl | 51.23 (15.19) | 59.74 (15.34) | 54.07 (14.04) | 49.80 (12.95) | 41.30 (11.92) | < 0.001 |
| LDL, mg/dl | 117.40 (34.82) | 110.11 (29.17) | 118.12 (31.06) | 122.44 (34.84) | 118.93 (41.79) | < 0.001 |
| Serum creatinine, mg/dL | 0.75 [0.64, 0.86] | 0.72 [0.63, 0.85] | 0.74 [0.64, 0.86] | 0.75 [0.64, 0.86] | 0.76 [0.64, 0.87] | 0.048 |
| Cystatin C, mg/L | 0.97 [0.85, 1.10] | 0.97 [0.86, 1.09] | 0.98 [0.87, 1.11] | 0.97 [0.86, 1.11] | 0.94 [0.81, 1.10] | < 0.001 |
| UA, mg/dL | 4.33 (1.20) | 4.08 (1.10) | 4.23 (1.19) | 4.36 (1.17) | 4.65 (1.25) | < 0.001 |
| Antihypertension agents, n(%) | 763 (17.2) | 100 (9.0) | 144 (13.0) | 209 (18.9) | 310 (28.0) | < 0.001 |

Abbreviations: CTI, C-reactive protein-triglyceride glucose index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; TG, triglyceride; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; CMM, cardiometabolic multimoribidity

| Characteristics | Overall | cuCTI | | | | p |
|---|---|---|---|---|---|---|
| | | Q1 | Q2 | Q3 | Q4 | |
| Antidyslipidemia agents, n(%) | 231 (5.2) | 19 (1.7) | 43 (3.9) | 57 (5.2) | 112 (10.1) | < 0.001 |
| Antidiabetic agents, n(%) | 113 (2.6) | 9 (0.8) | 9 (0.8) | 22 (2.0) | 73 (6.6) | < 0.001 |
| Dyslipidemia, n(%) | 436 (9.9) | 47 (4.2) | 82 (7.4) | 101 (9.1) | 206 (18.6) | < 0.001 |
| Hypertension, n(%) | 1079 (24.4) | 150 (13.6) | 215 (19.4) | 311 (28.1) | 403 (36.4) | < 0.001 |
| Heart disease, n(%) | 427 (9.7) | 74 (6.7) | 116 (10.5) | 123 (11.2) | 114 (10.3) | 0.002 |
| Stroke, n(%) | 60 (1.4) | 10 (0.9) | 19 (1.7) | 17 (1.5) | 14 (1.3) | 0.371 |
| Diabetes, n(%) | 186 (4.2) | 16 (1.4) | 24 (2.2) | 40 (3.6) | 106 (9.6) | < 0.001 |
| CMM, n(%) | 423 (9.6) | 40 (3.6) | 80 (7.2) | 121 (10.9) | 182 (16.5) | < 0.001 |

Abbreviations: CTI, C-reactive protein-triglyceride glucose index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; TG, triglyceride; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; CMM, cardiometabolic multimoribidity

## Association between different dimensions of CTI and incident CMM

During follow-up, 423 participants (9.6%) developed CMM. The incidence rates of CMM across quartiles (Q1-Q4) of cuCTI were 3.6%, 7.2%, 10.9%, and 16.5%, respectively, indicating a clear dose-response relationship between cuCTI and CMM risk. The Cox proportional hazards models were constructed to evaluate the associations between different CTI dimensions and incident CMM. Across all three models, consistent and robust positive associations were observed for baseline CTI, cuCTI, and CTI trajectory patterns. For baseline CTI, the risk of incident CMM increased progressively across quartiles. In the fully adjusted Model 3, compared with the lowest quartile (Q1), the hazard ratios (HRs) for Q2, Q3, and Q4 were 1.58 (95% CI 1.21–2.06), 1.95 (95% CI 1.51–2.51), and 2.57 (95% CI 2.00–3.30), respectively (P for trend < 0.001). When analyzed as a continuous variable, each 1.0-SD increase in baseline CTI was associated with a 28% higher risk of CMM (HR = 1.28, 95% CI 1.19–1.37). Similarly, a significant dose-response relationship was observed between cuCTI and incident CMM. In the fully adjusted Model 3, compared with the lowest quartile (Q1), the hazard ratios (HRs) for Q2, Q3, and Q4 were 1.75 (95% CI 1.20–2.57), 2.37 (95% CI 1.64–3.41), and 2.88 (95% CI 2.00–4.16), respectively (P for trend < 0.001). When analyzed as a continuous variable, each 1.0-SD increase in cuCTI was associated with a 36% higher risk of new-onset CMM (HR = 1.36, 95% CI 1.24–1.50). In the CTI trajectory analysis, the risk of

incident CMM was significantly higher in individuals belonging to Class 2–4 compared to Class 1. In the fully adjusted model, the hazard ratios (HRs) for Class 2, Class 3, and Class 4 were 2.08 (95% CI 1.52–2.84), 2.04 (95% CI 1.48–2.82), and 2.71 (95% CI 1.94–3.80), demonstrating a significant increasing trend (P for trend < 0.001) (Table 2).

Table 2
Correlation between different dimensions of CTI and future risk of new-onset CMM

| Categories | Mode 1 | | Mode 2 | | Mode 3 | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value | HR (95% CI) | P value |
| Baseline CTI | | | | | | |
| Quartiles | | | | | | |
| Q1 | Ref. | | Ref. | | Ref. | |
| Q2 | 1.83 (1.41–2.38) | < 0.001 | 1.76 (1.35–2.29) | < 0.001 | 1.58 (1.21–2.06) | 0.001 |
| Q3 | 2.69 (2.10–3.45) | < 0.001 | 2.55 (1.99–3.27) | < 0.001 | 1.95 (1.51–2.51) | < 0.001 |
| Q4 | 4.69 (3.71–5.92) | < 0.001 | 4.40 (3.48–5.57) | < 0.001 | 2.57 (2.00-3.30) | < 0.001 |
| Per SD increase | 1.60 (1.51–1.70) | < 0.001 | 1.58 (1.49–1.68) | < 0.001 | 1.28 (1.19–1.37) | < 0.001 |
| P for trend | < 0.001 | | < 0.001 | | < 0.001 | |
| Cumulative CTI | | | | | | |
| Quartiles | | | | | | |
| Q1 | Ref. | | Ref. | | Ref. | |
| Q2 | 2.03 (1.39–2.97) | < 0.001 | 1.98 (1.36–2.90) | < 0.001 | 1.75 (1.20–2.57) | < 0.001 |
| Q3 | 3.14 (2.20–4.49) | < 0.001 | 3.02 (2.11–4.33) | < 0.001 | 2.37 (1.64–3.41) | < 0.001 |
| Q4 | 4.94 (3.51–6.96) | < 0.001 | 4.77 (3.38–6.73) | < 0.001 | 2.88 (2.00-4.16) | < 0.001 |
| Model 1: unadjusted for any covariates | | | | | | |
| Model 2: adjusted for sex, age, marital status, education level, and residence | | | | | | |
| Model 3: adjusted for sex, age, marital status, education level, residence, smoking status, drinking status, BMI, waist, SBP, DBP, hypertension medications, dyslipidemia medications, diabetes medications, dyslipidemia | | | | | | |

| Categories | Mode 1 | | Mode 2 | | Mode 3 | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value | HR (95% CI) | P value |
| Per SD increase | 1.64 (1.51–1.79) | < 0.001 | 1.63 (1.50–1.78) | < 0.001 | 1.36 (1.24–1.50) | < 0.001 |
| P for trend | < 0.001 | | < 0.001 | | < 0.001 | |
| Changes in CTI | | | | | | |
| Class1 | Ref. | | Ref. | | Ref. | |
| Class2 | 2.51 (1.85–3.41) | < 0.001 | 2.47 (1.82–3.36) | < 0.001 | 2.08 (1.52–2.84) | < 0.001 |
| Class3 | 2.79 (2.04–3.81) | < 0.001 | 2.70 (1.98–3.70) | < 0.001 | 2.04 (1.48–2.82) | < 0.001 |
| Class4 | 4.91 (3.62–6.68) | < 0.001 | 4.74 (3.47–6.45) | < 0.001 | 2.71 (1.94–3.80) | < 0.001 |
| P for trend | < 0.001 | | < 0.001 | | < 0.001 | |
| Model 1: unadjusted for any covariates | | | | | | |
| Model 2: adjusted for sex, age, marital status, education level, and residence | | | | | | |
| Model 3: adjusted for sex, age, marital status, education level, residence, smoking status, drinking status, BMI, waist, SBP, DBP, hypertension medications, dyslipidemia medications, diabetes medications, dyslipidemia | | | | | | |

Figure 3 illustrates the Kaplan-Meier cumulative incidence curves of CMM across different CTI dimensions. In Panel A, participants were stratified by baseline CTI quartiles. The cumulative incidence of CMM increased progressively from Q1 to Q4, with significant inter-group differences (P < 0.001). Panel B shows the curves according to cumulative CTI quartiles. Similarly, a graded rise in CMM incidence was observed across ascending quartiles, and the differences were statistically significant (P < 0.001). Panel C presents the analysis based on CTI trajectory classes. The cumulative incidence of CMM demonstrated a significant stepwise increase from Class 1 to Class 4 (P < 0.001).

As shown in Fig. 4, a four-knot RCS model adjusted for Model 3 covariates was applied to explore the dose-response relationships between baseline CTI, cuCTI, and new-onset CMM. For baseline CTI, a significant overall association with CMM risk was observed (P for overall < 0.001), with evidence of nonlinearity (P for nonlinear = 0.003). Similarly, cuCTI showed a significant overall association with CMM (P for overall < 0.001). However, the nonlinearity test was not significant (P for nonlinear = 0.246),

indicating a predominantly linear relationship. The risk of CMM increased steadily with rising cuCTI levels, without evidence of a threshold effect.

As illustrated in Fig. 5, ROC analysis was conducted to present the predictive performance of different indices for CMM. Baseline CTI demonstrated a significantly higher discriminative ability than baseline TyG index (AUC: 0.655 vs. 0.643; DeLong test $P < 0.05$). Although cuCTI did not show a statistically significant advantage over cumulative TyG index (DeLong test $P = 0.084$), its AUC was slightly higher (0.663 vs. 0.650). Moreover, cuCTI exhibited superior predictive performance compared with CTI 2015 (AUC: 0.663 vs. 0.641; $P < 0.05$) and TyG 2015 (AUC: 0.663 vs. 0.638; $P < 0.05$).

# Subgroup Analysis

Subgroup analyses were conducted to assess the reliability and stability of the associations between baseline CTI, cuCTI and CMM risk in the fully adjusted Model 3. Stratified analyses were performed by age ,sex, residence, marital status, smoking, alcohol consumption, BMI, hypertension, dyslipidemia, and diabetes, with interaction tests applied (Fig. 6). In most subgroups, both baseline CTI and cuCTI remained significantly associated with increased CMM risk, consistent with the primary findings. Significant interactions were observed for baseline CTI across BMI, hypertension, diabetes, and dyslipidemia strata. For cuCTI, a significant interaction was detected only in the hypertension subgroup (P for interaction = 0.011). Notably, among non-diabetic participants, baseline CTI (HR = 1.29, 95% CI 1.20–1.39) and cuCTI (HR = 1.36, 95% CI 1.22–1.51) were positively associated with CMM risk, whereas these associations were not statistically significant in participants with diabetes.

# Sensitivity analysis

To verify the robustness of the primary findings, a series of sensitivity analyses were performed. After excluding 1,348 participants with baseline CMD, 6,786 remained for baseline CTI analysis. Further excluding 1,324 individuals with CMD in wave1 or wave3 left 3,101 for cuCTI and trajectory assessments. The results (Table 3) demonstrated that baseline CTI, cuCTI, and CTI trajectory patterns remained significantly and independently associated with incident CMM risk. These findings were highly consistent with the primary analyses, further confirming the stability of the observed associations.

Table 3
Correlation between different dimensions of CTI and future risk of new-onset CMM in a population without CMD

| Categories | Mode 1 | | Mode 2 | | Mode 3 | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value | HR (95% CI) | P value |
| Baseline CTI | | | | | | |
| Quartiles | | | | | | |
| Q1 | Ref. | | Ref. | | Ref. | |
| Q2 | 2.09 (1.44–3.03) | < 0.001 | 2.01 (1.38–2.93) | < 0.001 | 1.86 (1.28–2.70) | 0.0012 |
| Q3 | 3.34 (2.35–4.75)) | < 0.001 | 3.16 (2.22–4.50) | < 0.001 | 2.51 (1.76–3.60) | < 0.001 |
| Q4 | 4.75 (3.38–6.67) | < 0.001 | 4.50 (3.20–6.33) | < 0.001 | 3.05 (2.14–4.34) | < 0.001 |
| Per SD increase | 1.54 (1.42–1.67) | < 0.001 | 1.53 (1.41–1.66) | < 0.001 | 1.32 (1.20–1.44) | < 0.001 |
| P for trend | < 0.001 | | < 0.001 | | < 0.001 | |
| Cumulative CTI | | | | | | |
| Quartiles | | | | | | |
| Q1 | Ref. | | Ref. | | Ref. | |
| Q2 | 2.01 (1.01–4.02) | 0.0479 | 2.00 (1.00–4.00)) | < 0.001 | 1.93 (0.96–3.87) | 0.0654 |
| Q3 | 2.98 (1.55–5.74) | 0.00110 | 2.98 (1.54–5.75) | 0.00115 | 2.68 (1.37–5.23) | 0.00397 |
| Q4 | 5.06 (2.72– | < 0.001 | 5.10 (2.73– | < 0.001 | 4.18 (2.17– | < 0.001 |
| Model 1: unadjusted for any covariates | | | | | | |
| Model 2: adjusted for sex, age, marital status, education level, and residence | | | | | | |
| Model 3: adjusted for sex, age, marital status, education level, residence, smoking status, drinking status, BMI, waist, SBP, DBP, hypertension medications, dyslipidemia medications, diabetes medications, dyslipidemia | | | | | | |

| Categories | Mode 1 | | Mode 2 | | Mode 3 | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value | HR (95% CI) | P value |
| | 9.42) | | 9.53) | | 8.06) | |
| Per SD increase | 1.60 (1.38–1.86) | < 0.001 | 1.61 (1.38–1.87) | < 0.001 | 1.47 (1.25–1.74) | < 0.001 |
| P for trend | < 0.001 | | < 0.001 | | < 0.001 | |
| Changes in CTI | | | | | | |
| Class1 | Ref. | | Ref. | | Ref. | |
| Class2 | 2.84 (1.56–5.15)) | < 0.001 | 2.89 (1.59–5.25) | < 0.001 | 2.74 (1.50–5.01) | 0.00102 |
| Class3 | 3.78 (2.08–6.87) | < 0.001 | 3.80 (2.08–6.91 | < 0.001 | 3.35 (1.81–6.18) | < 0.001 |
| Class4 | 5.47 (3.00–9.96) | < 0.001 | 5.57 (3.05–10.20) | < 0.001 | 4.43 (2.33–8.40) | < 0.001 |
| P for trend | < 0.001 | | < 0.001 | | < 0.001 | |
| Model 1: unadjusted for any covariates | | | | | | |
| Model 2: adjusted for sex, age, marital status, education level, and residence | | | | | | |
| Model 3: adjusted for sex, age, marital status, education level, residence, smoking status, drinking status, BMI, waist, SBP, DBP, hypertension medications, dyslipidemia medications, diabetes medications, dyslipidemia | | | | | | |

# Discussion

Based on the nationally representative longitudinal CHARLS cohort, this study was the first to comprehensively evaluate the associations of multidimensional CTI characteristics, including baseline level, cumulative exposure, and dynamic trajectories, with incident CMM. Several key findings emerged. First, both elevated baseline CTI and higher cuCTI were independently and positively associated with the risk of CMM, even after full adjustment for potential confounders. Second, trajectory analysis identified four distinct CTI patterns, among which the persistently high–level group exhibited the greatest CMM risk. Third, RCS analysis demonstrated different dose–response patterns: baseline CTI showed a nonlinear association with CMM risk, whereas cuCTI displayed a clear linear relationship. In ROC analyses, baseline CTI outperformed baseline CRP or baseline TyG index, while cuCTI demonstrated the

best predictive ability. Finally, subgroup and sensitivity analyses consistently confirmed the robustness and stability of these findings.

CMM, commonly defined as the coexistence of at least two cardiometabolic diseases, represents one of the most prevalent comorbidity patterns. The composite index CTI is biologically plausible for predicting CMM, as it integrates CRP and TyG index, two markers closely linked to major cardiometabolic disorders. From a pathophysiological perspective, CRP reflects the systemic inflammatory response, contributing to vascular impairment by inducing endothelial dysfunction, promoting oxidized lipoprotein accumulation and foam cell formation, and enhancing leukocyte infiltration with amplification of plaque–related inflammatory–thrombotic responses [20]. The TyG index, a surrogate marker of IR, promotes cardiometabolic diseases progression through mechanisms including systemic low–grade inflammation, oxidative stress, mitochondrial dysfunction, and endothelial impairment [21, 22]. A prospective study conducted by Rolver et al. [23] has shown that elevated CRP levels are associated with higher risks of ischemic stroke and all–cause mortality, with a graded increase across CRP concentrations. In addition, a study by Yu Liu et al. [24] based on the National Health and Nutrition Examination Survey(NHANES) database investigated the association between high-sensitivity C–reactive protein (hs–CRP) and the prevalence of cardiovascular disease (CVD) and found that hs–CRP was associated with CVD prevalence. Similarly, another study reported a significant association between hs–CRP and incident diabetes [25]. Consistently, the American College of Cardiology(ACC) has emphasized the central role of chronic low–grade inflammation in cardiovascular pathophysiology and recommended hs–CRP screening in both primary and secondary prevention settings [9]. Numerous studies have confirmed that higher TyG levels are associated with increased risks of CMDs. For example, a study by Zhang et al. [26] showed that a higher TyG index was associated with an increased risk of incident CMM. Importantly, inflammation and IR have both been established as independent risk factors for CMDs and act synergistically in the pathogenesis of CMD [27, 28]. In recent years, accumulating evidence has indicated that the combination of the TyG index and inflammatory markers provides better predictive performance for CMDs than either indicator alone; accordingly, integrating the TyG index with inflammatory biomarkers has been recommended to further optimize cardiometabolic risk stratification [29, 30].

The CTI was first proposed by Ruan et al. [12] as a prognostic indicator in oncology. By integrating CRP and TyG into a single metric, CTI simultaneously captures two key pathophysiological processes underlying cardiometabolic disorders. This multidimensional feature provides a theoretical basis for its potential utility in predicting new-onset CMM. Growing evidence supports a close association between CTI and cardiometabolic outcomes. A study based on CHARLS demonstrated that elevated CTI was independently associated with an increased risk of incident CVD, with a linear dose–response relationship [31]. Another study confirmed that CTI was significantly associated with new–onset coronary heart disease diagnosis among metabolically heterogeneous individual [32]. Huo et al. [33] further reported that higher CTI levels were associated with greater stroke risk across populations with normal glucose regulation and prediabetes. In addition, a prospective cohort showed that among individuals in Cardiovascular-Kidney-Metabolic Syndrome (CKM) stages 0–3, the risk of CMM

progressively increased across higher CTI percentiles [13]; these observations are supported by the findings reported by Niu et al [34]. Some studies have also confirmed that CTI is associated with the risks of all-cause mortality and cardiovascular mortality [35–37]. These findings were consistent with our primary results. Nevertheless, most prior studies relied on single–time–point measurements of CTI, thereby overlooking its temporal variability and cumulative exposure. The lack of longitudinal assessment of cumulative CTI may introduce regression dilution bias and underestimate long-term risk associations.

Compared with previous studies, our study incorporated cumulative CTI exposure and trajectory analysis, thereby providing a more dynamic framework for risk stratification. These findings suggest that sustained exposure to an elevated inflammatory–metabolic state may accelerate vascular injury and disease clustering, consistent with the established mechanism whereby chronic low–grade inflammation and metabolic dysregulation act synergistically to promote atherosclerotic progression and cardiometabolic deterioration.

Furthermore, compared with single–time–point CTI, the TyG index, or CRP alone, cuCTI demonstrated superior predictive performance. By integrating repeated measurements, cuCTI more comprehensively captures the cumulative burden of inflammation and insulin resistance. This observation was consistent with evidence from other cumulative metabolic indicators. For example, a prospective cohort study by Yan et al. [38] reported that cumulative estimated glucose disposal rate (eGDR) showed stronger predictive value for incident CVD than single–time–point eGDR or the TyG index.

Trajectory analysis further identified four distinct CTI patterns, among which the persistently high CTI group exhibited the greatest risk of CMM. These findings suggested that longitudinal changes in CTI better reflect disease progression than isolated measurements. A persistently high trajectory may indicate the initiation of a vicious cycle between inflammation and metabolic dysregulation, whereas the impact of short–term fluctuations or mild elevations may be relatively modest. This result was consistent with a previous study showing that dynamic changes in the TyG index predict stroke risk in individuals at early CKM stages [39], underscoring the value of trajectory analysis in capturing progressive cardiometabolic deterioration.

Furthermore, RCS analysis revealed a nonlinear association between baseline CTI levels and the risk of CMM. In contrast, cuCTI exhibited a clear linear dose–response relationship with CMM risk. These findings were consistent with those reported by Ma et al. [40], who also documented a linear association between cuCTI and CVD risk. Mechanistically, CTI reflects the combined burden of insulin resistance and inflammation, which may interact through adipose tissue dysfunction, endothelial injury, and oxidative stress to form a self–reinforcing cycle. This synergistic interplay may explain the observed nonlinear risk pattern, with accelerated risk beyond a certain threshold. In contrast, cuCTI represents cumulative long–term exposure, more closely mirroring the natural course of CMM—a gradual process driven by sustained metabolic and inflammatory injury that ultimately leads to multisystem comorbidities. Accordingly, cuCTI demonstrates a progressive linear increase in risk with greater exposure. Collectively,

baseline CTI may signal a critical transition point for risk escalation, whereas cuCTI delineates the gradient of long–term cumulative risk. Concurrent evaluation of baseline and cumulative CTI may therefore enhance early risk identification and longitudinal management of CMM in clinical practice.

Subgroup analyses of baseline CTI and cuCTI consistently demonstrated positive associations with outcome risk across most populations, supporting the robustness and generalizability of CTI as an integrated marker of insulin resistance and inflammation. Significant interactions were observed for baseline CTI across BMI, hypertension, diabetes, and dyslipidemia strata, whereas cuCTI showed a significant interaction only in the hypertension subgroup. This discrepancy suggested that single–time–point CTI may be more susceptible to short–term metabolic fluctuations, resulting in greater heterogeneity across metabolic phenotypes. In contrast, cuCTI, which integrated multi–time–point exposure, provided a more stable estimate and exhibited effect modification primarily in the presence of established vascular pathology such as hypertension. Notably, both baseline CTI and cuCTI demonstrated stronger associations with CMM risk among individuals without hypertension or diabetes. The findings were consistent with several previous studies [41, 42]. One plausible explanation is that some participants may have had undiagnosed metabolic abnormalities, with elevated CTI reflecting early inflammatory–metabolic burden preceding clinical diagnosis. Conversely, individuals with diagnosed conditions are more likely to receive pharmacological treatment and lifestyle interventions, which may attenuate CMM progression and modify CTI–related biomarkers, thereby weakening the observed associations. Improved health behaviors after diagnosis may further delay disease progression, rendering CTI more predictive in populations without chronic conditions. These findings emphasize the importance of monitoring elevated CTI, particularly cumulative exposure, even among individuals without diagnosed hypertension or diabetes, as it may indicate subclinical metabolic–inflammatory dysregulation and heightened the risk of CMM. Owing to the intrinsic association between the TyG index and diabetes, we conducted additional sensitivity analyses excluding participants with baseline heart disease, stroke, or diabetes to minimize potential bias. The results remained consistent with the primary analyses, confirming the stability and robustness of our findings across model specifications and population restrictions.

This study has several limitations. First, despite adjustment for multiple confounders and additional sensitivity analyses, the observational design precludes causal inference, and residual confounding cannot be entirely excluded. Second, CMM and its component diseases were primarily identified through self-reported data, which may introduce recall bias and underreporting, potentially affecting risk estimates. Third, CTI, particularly cuCTI, was derived from a limited number of biochemical measurements and might not fully reflect long–term variability; moreover, CRP levels could be influenced by acute inflammatory conditions, leading to potential misclassification based on single–time–point assessments. Finally, the study population consisted of middle–aged and older Chinese adults, limiting generalizability to younger individuals or other ethnic groups. Future prospective studies with larger sample sizes, repeated biomarker assessments, and more diverse populations are warranted to validate these findings and to further elucidate the underlying mechanisms and clinical utility.

# Conclusion

In this study, baseline CTI, cuCTI, and its dynamic trajectories were all significantly associated with the risk of new–onset CMM. Among these indicators, cuCTI demonstrated superior predictive performance. The associations remained robust after adjustment for potential confounders. These findings suggest that longitudinal monitoring of CTI, in conjunction with conventional risk factors, may enhance early identification and risk stratification of individuals at high risk for CMM. Considering its accessibility and low cost, CTI may represent a practical tool for primary prevention, particularly in resource–limited settings.

# Abbreviations

**ACC** American College of Cardiology

**ADA** American Diabetes Association

**BMI** Body mass index

**CHARLS** China Health and Retirement Longitudinal Study

**CKM** Cardiovascular-Kidney-Metabolic Syndrome

**CMD** Cardiometabolic disease

**CMM** Cardiometaboic multimorbidity

**CRP** C-reactive protein

**CTI** C-reactive protein–triglyceride glucose index

**CVD** Cardiovascular disease

**DBP** Diastolic blood pressure

**FBG** Fasting blood glucose

**HbA1c** Hemoglobin A1c

**HDL-C** High-density lipoprotein cholesterol

**Hs-CRP** High-sensitivity C-reactive protein

**IR** Insulin resistance

**LDL-C** Low-density lipoprotein cholesterol

**RCS** Restricted cubic splines

**ROC** Receiver operating characteristic

**SBP** Systolic blood pressure

**TC** Total cholesterol

**TG** Triglycerides

**TyG** Triglyceride-glucose index

**UA** Uric acid

# Declarations

### Ethics approval and consent to participate

In accordance with the Declaration of Helsinki, the CHARLS survey received ethical clearance from the Institutional Review Board of Peking University (IRB 00001052-11015). Signed informed consent was obtained from all individuals involved. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies.

### Consent for publication

Not applicable.

### Availability of data and materials

All data used in this study are available from the CHARLS database (http://charls.pku.edu.cn/en).

### Competing interests

The authors declare that they have no competing interests.


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### Authors' contributions

SY conceived the study and developed the methodology. SY and XL performed data curation. SY and FL conducted the investigation and drafted the original manuscript. TG and ML were responsible for validation and manuscript editing. XL oversaw project administration, and supervised the study. All authors read and approved the final manuscript.

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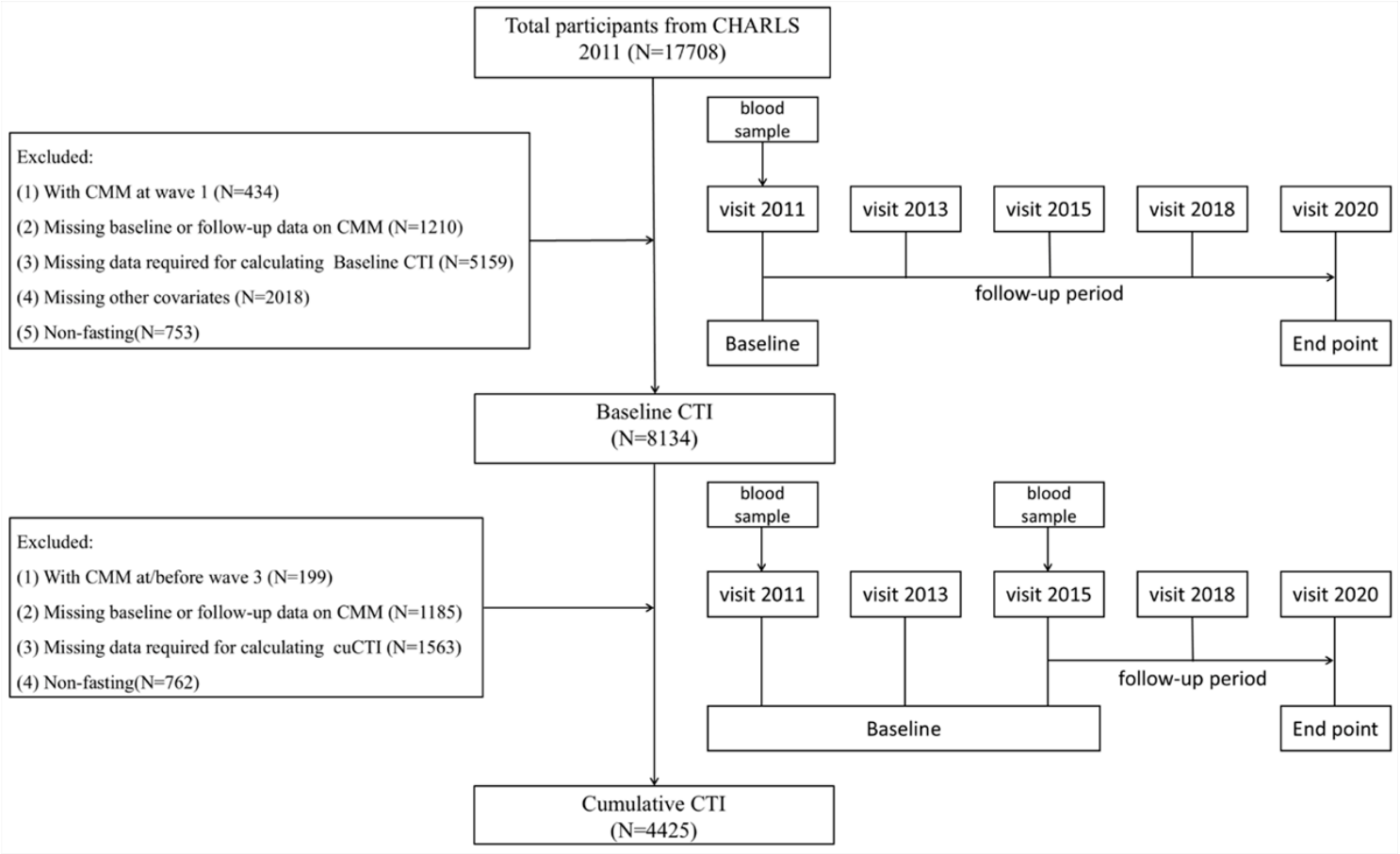
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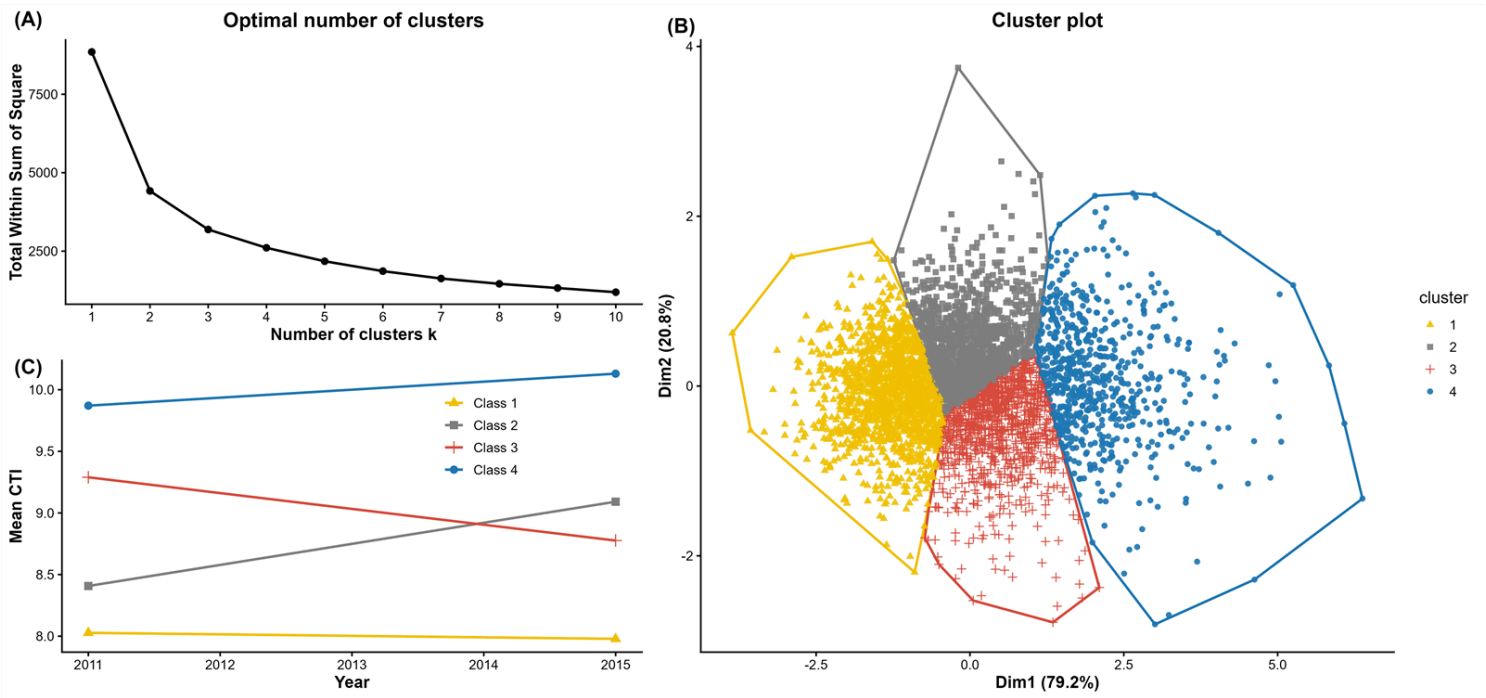
# Figures




## Figure 1

Flowchart of the study population.

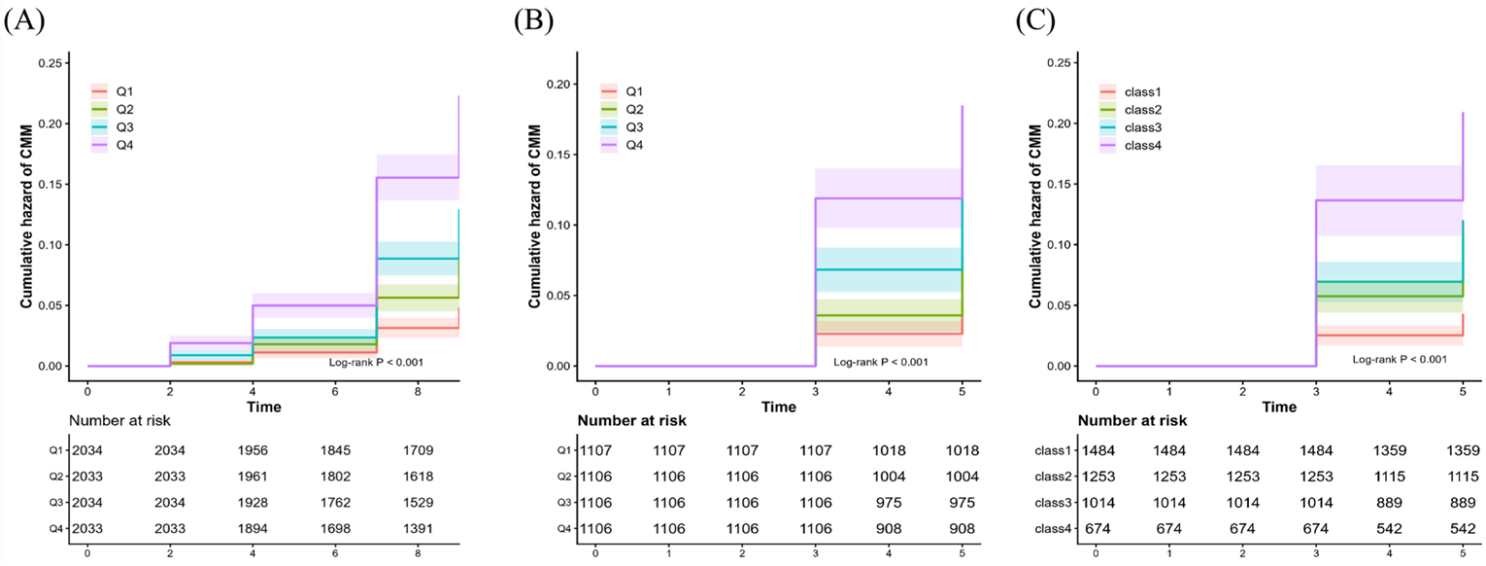
CMM, cardiometabolic multimorbidity; CTI, C-reactive protein-triglyceride glucose index.



## Figure 2

Clustering of the changes in CTI from 2012 to 2015.

(A) The elbow method plot for optimal cluster determination (K = 4); (B) Cluster plot showing participant distribution across four classes; (C) Mean CTI trajectories from 2011 to 2015; CTI, C-reactive protein-triglyceride glucose index.




## Figure 3

Kaplan-Meier cumulative hazard curves for incident CMM across different CTI dimensions.

(A) Cumulative hazard of CMM stratified by baseline CTI quartiles (Q1–Q4); (B) Cumulative hazard of CMM stratified by cuCTI quartiles (Q1–Q4); (C) Cumulative hazard of CMM stratified by four dynamic CTI trajectory classes (Class 1–4); Log-rank tests demonstrate significant differences in the risk of incident CMM across all groups (P < 0.001). Shaded areas represent 95% confidence intervals. The "Number at risk" tables below each plot indicate the number of participants remaining at each follow-up time point. CMM, cardiometabolic multimorbidity; CTI, C-reactive protein-triglyceride glucose index. cuCTI, cumulative CTI.

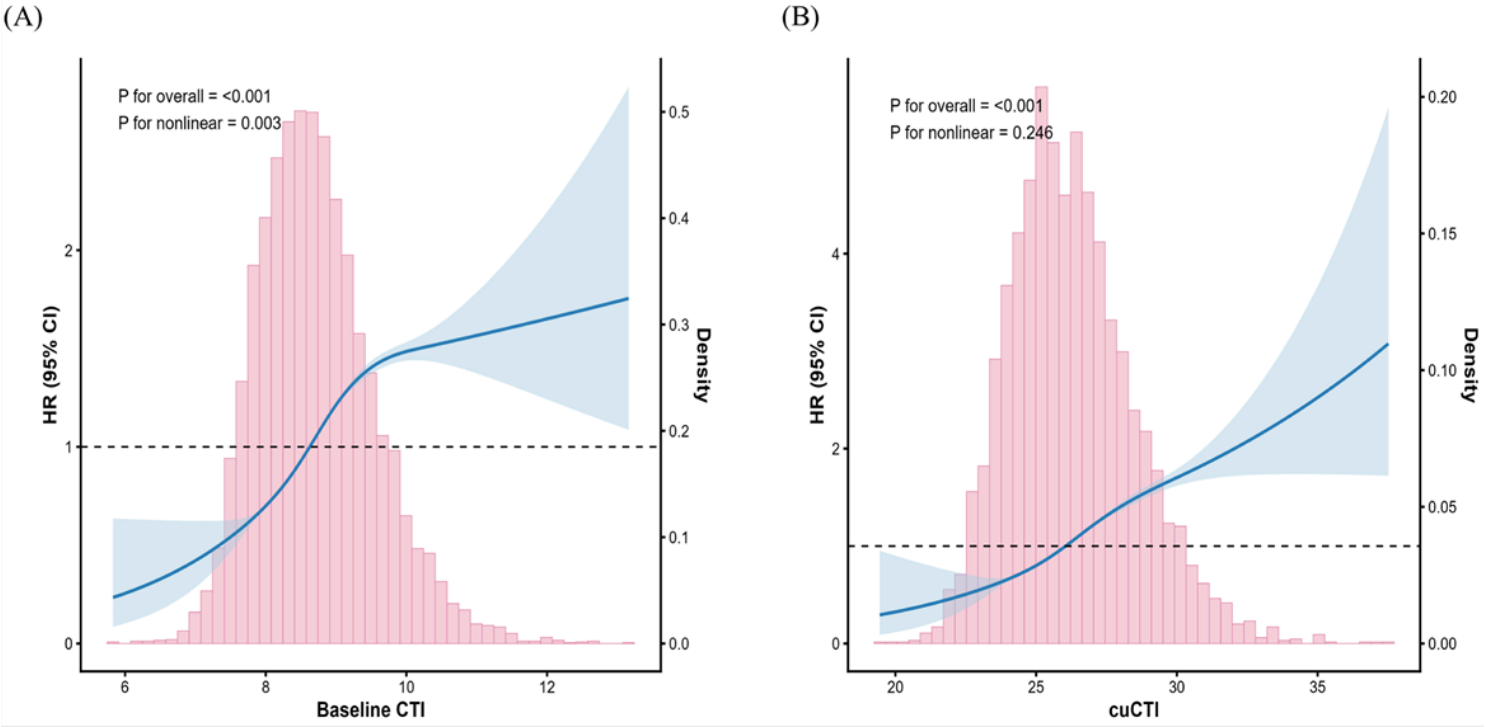



**Figure 4**

Dose-response relationships between CTI dimensions and incident CMM risk analyzed by restricted cubic spline models.

(A) Baseline CTI; (B) cuCTI. Model 3 was adjusted for sex, age, marital status, education level, residence, smoking status, drinking status, BMI, waist, SBP, DBP, hypertension medications, dyslipidemia medications, diabetes medications, dyslipidemia. CMM, cardiometabolic multimorbidity; CTI, C-reactive protein-triglyceride glucose index. cuCTI, cumulative CTI; BMI, body mass inde, SBP, systolic blood pressure, DBP, diastolic blood pressure.

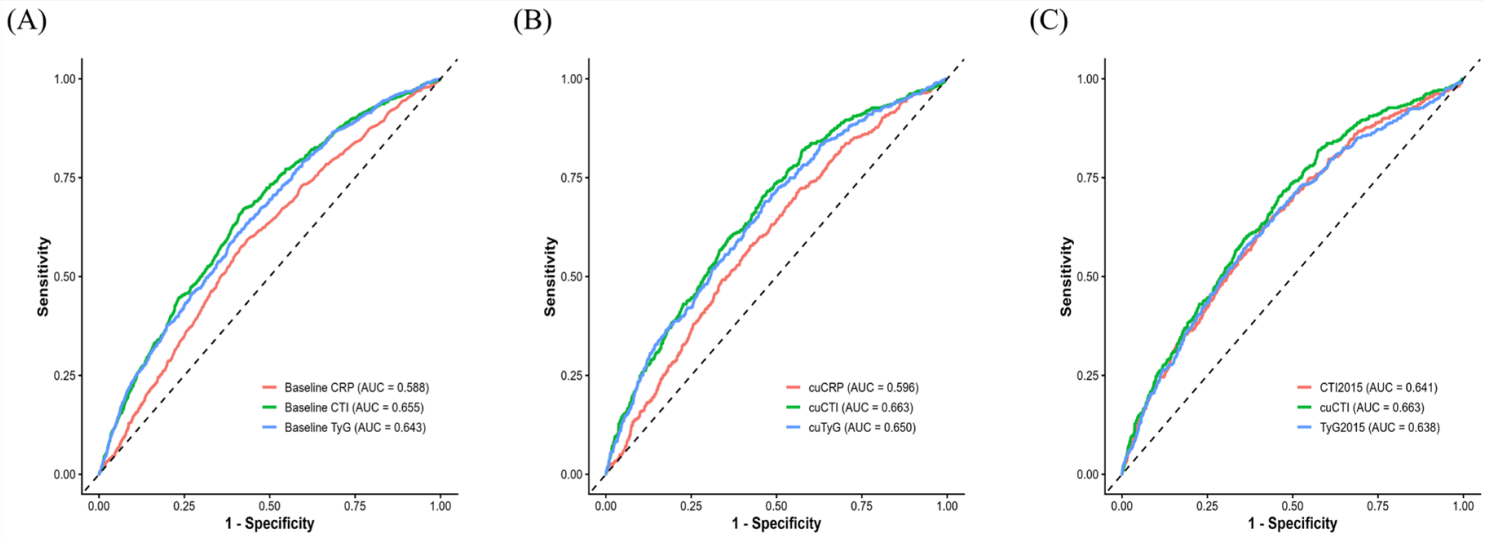
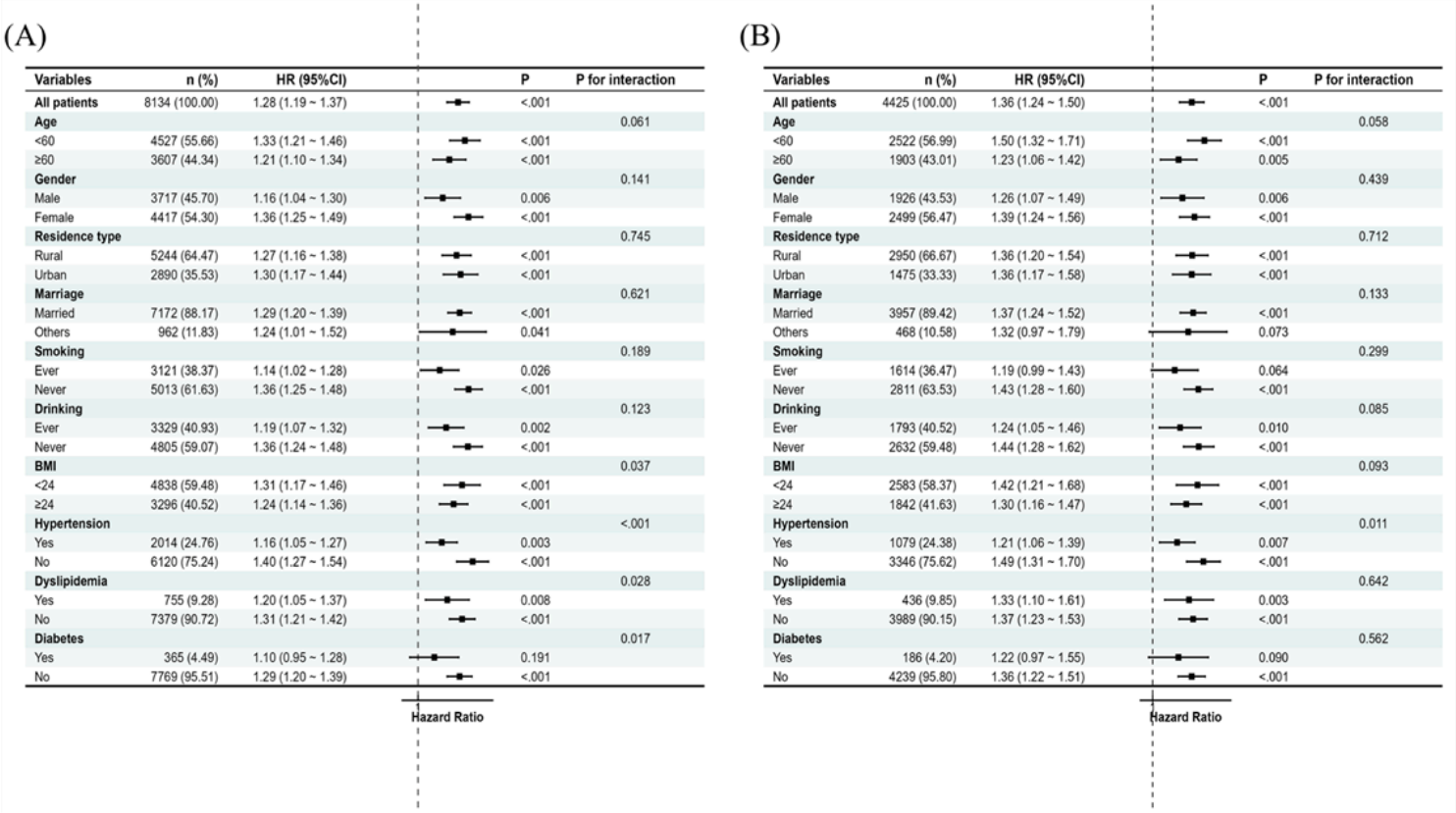



**Figure 5**

Comparison of predictive performance for incident CMM using receiver operating characteristic curves analysis.

(A) Predictive performance of baseline CTI, baseline TyG, and baseline CRP. (B) Predictive performance of cumulative exposure indicators, including cuCTI, cuTyG, and cuCRP. (C) Predictive performance of CTI 2015, TyG 2015, and cuCTI. CMM, cardiometabolic multimorbidity; CTI, C-reactive protein-triglyceride glucose index; TyG index, triglyceride-glucose index; CRP, C–reactive protein; cuCTI, cumulative CTI; cuTyG, cumulative TyG; cuCRP, cumulative CRP.




| Variables | n (%) | HR (95%CI) | P | P for interaction |
|---|---|---|---|---|
| **All patients** | 8134 (100.00) | 1.28 (1.19 ~ 1.37) | <.001 | |
| **Age** | | | | 0.061 |
| <60 | 4527 (55.66) | 1.33 (1.21 ~ 1.46) | <.001 | |
| ≥60 | 3607 (44.34) | 1.21 (1.10 ~ 1.34) | <.001 | |
| **Gender** | | | | 0.141 |
| Male | 3717 (45.70) | 1.16 (1.04 ~ 1.30) | 0.006 | |
| Female | 4417 (54.30) | 1.36 (1.25 ~ 1.49) | <.001 | |
| **Residence type** | | | | 0.745 |
| Rural | 5244 (64.47) | 1.27 (1.16 ~ 1.38) | <.001 | |
| Urban | 2890 (35.53) | 1.30 (1.17 ~ 1.44) | <.001 | |
| **Marriage** | | | | 0.621 |
| Married | 7172 (88.17) | 1.29 (1.20 ~ 1.39) | <.001 | |
| Others | 962 (11.83) | 1.24 (1.01 ~ 1.52) | 0.041 | |
| **Smoking** | | | | 0.189 |
| Ever | 3121 (38.37) | 1.14 (1.02 ~ 1.28) | 0.026 | |
| Never | 5013 (61.63) | 1.36 (1.25 ~ 1.48) | <.001 | |
| **Drinking** | | | | 0.123 |
| Ever | 3329 (40.93) | 1.19 (1.07 ~ 1.32) | 0.002 | |
| Never | 4805 (59.07) | 1.36 (1.24 ~ 1.48) | <.001 | |
| **BMI** | | | | 0.037 |
| <24 | 4838 (59.48) | 1.31 (1.17 ~ 1.46) | <.001 | |
| ≥24 | 3296 (40.52) | 1.24 (1.14 ~ 1.36) | <.001 | |
| **Hypertension** | | | | <.001 |
| Yes | 2014 (24.76) | 1.16 (1.05 ~ 1.27) | 0.003 | |
| No | 6120 (75.24) | 1.40 (1.27 ~ 1.54) | <.001 | |
| **Dyslipidemia** | | | | 0.028 |
| Yes | 755 (9.28) | 1.20 (1.05 ~ 1.37) | 0.008 | |
| No | 7379 (90.72) | 1.31 (1.21 ~ 1.42) | <.001 | |
| **Diabetes** | | | | 0.017 |
| Yes | 365 (4.49) | 1.10 (0.95 ~ 1.28) | 0.191 | |
| No | 7769 (95.51) | 1.29 (1.20 ~ 1.39) | <.001 | |

| Variables | n (%) | HR (95%CI) | P | P for interaction |
|---|---|---|---|---|
| **All patients** | 4425 (100.00) | 1.36 (1.24 ~ 1.50) | <.001 | |
| **Age** | | | | 0.058 |
| <60 | 2522 (56.99) | 1.50 (1.32 ~ 1.71) | <.001 | |
| ≥60 | 1903 (43.01) | 1.23 (1.06 ~ 1.42) | 0.005 | |
| **Gender** | | | | 0.439 |
| Male | 1926 (43.53) | 1.26 (1.07 ~ 1.49) | 0.006 | |
| Female | 2499 (56.47) | 1.39 (1.24 ~ 1.56) | <.001 | |
| **Residence type** | | | | 0.712 |
| Rural | 2950 (66.67) | 1.36 (1.20 ~ 1.54) | <.001 | |
| Urban | 1475 (33.33) | 1.36 (1.17 ~ 1.58) | <.001 | |
| **Marriage** | | | | 0.133 |
| Married | 3957 (89.42) | 1.37 (1.24 ~ 1.52) | <.001 | |
| Others | 468 (10.58) | 1.32 (0.97 ~ 1.79) | 0.073 | |
| **Smoking** | | | | 0.299 |
| Ever | 1614 (36.47) | 1.19 (0.99 ~ 1.43) | 0.064 | |
| Never | 2811 (63.53) | 1.43 (1.28 ~ 1.60) | <.001 | |
| **Drinking** | | | | 0.085 |
| Ever | 1793 (40.52) | 1.24 (1.05 ~ 1.46) | 0.010 | |
| Never | 2632 (59.48) | 1.44 (1.28 ~ 1.62) | <.001 | |
| **BMI** | | | | 0.093 |
| <24 | 2583 (58.37) | 1.42 (1.21 ~ 1.68) | <.001 | |
| ≥24 | 1842 (41.63) | 1.30 (1.16 ~ 1.47) | <.001 | |
| **Hypertension** | | | | 0.011 |
| Yes | 1079 (24.38) | 1.21 (1.06 ~ 1.39) | 0.007 | |
| No | 3346 (75.62) | 1.49 (1.31 ~ 1.70) | <.001 | |
| **Dyslipidemia** | | | | 0.642 |
| Yes | 436 (9.85) | 1.33 (1.10 ~ 1.61) | 0.003 | |
| No | 3989 (90.15) | 1.37 (1.23 ~ 1.53) | <.001 | |
| **Diabetes** | | | | 0.562 |
| Yes | 186 (4.20) | 1.22 (0.97 ~ 1.55) | 0.090 | |
| No | 4239 (95.80) | 1.36 (1.22 ~ 1.51) | <.001 | |

**Figure 6**

Subgroup analysis of the association between (A) baseline CTI and (B) cumulative CTI and CMM risk in model 3.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementaryfiles.docx
- GraphicalAbstract.tif