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Long-term cumulative and trajectory patterns of the C-reactive protein–triglyceride–glucose index and cardiometabolic multimorbidity: the mediating effects of adiposity indices

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Research Article

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Abstract

Background

Cardiometabolic multimorbidity (CMM) is increasingly prevalent in ageing populations and confers substantial clinical and societal burdens. The C-reactive protein–triglyceride–glucose index (CTI) integrates inflammatory and metabolic information, but evidence linking long-term CTI patterns to incident CMM and the role of adiposity as a potential mediator remains limited.

Methods

We included 5,778 participants aged ≥ 45 years who were free of CMM at baseline. Exposures were baseline CTI in 2012, cumulative CTI(cuCTI) from 2012 to 2015, and CTI change-pattern (trajectory) groups derived from repeated measurements. Incident CMM was assessed in 2018. Multivariable logistic regression models were pooled across multiple imputations; restricted cubic splines examined dose–response. Prediction performance was evaluated using C-statistics (DeLong test), net reclassification improvement, and integrated discrimination improvement. Mediation by adiposity indices was assessed.

Results

Incident CMM occurred in 333 participants (5.8%). In fully adjusted models, higher baseline CTI and greater cumulative CTI exposure were independently associated with higher odds of incident CMM (baseline CTI per IQR: OR 1.545 (95% CI 1.344–1.776); cuCTI per IQR: OR 1.651 (95% CI 1.429–1.907), both $P < 0.001$). Change-pattern (trajectory) analyses further indicated substantially higher risk among participants with persistently elevated CTI compared with those with persistently low CTI (OR 3.078 (95% CI 2.169–4.369), $P < 0.001$). Adding baseline CTI, cuCTI, or change-pattern grouping improved discrimination beyond the basic model and improved reclassification. Adiposity indices partially mediated the CTI–CMM associations.

Conclusions

Higher cumulative CTI and persistently elevated CTI change patterns were associated with incident cardiometabolic multimorbidity and improved risk prediction, with partial mediation by adiposity.

Contributions to the Literature

1. To extend previous evidence on CTI by showing its association with cardiometabolic multimorbidity, a clinically important outcome that better reflects the clustering of cardiometabolic diseases in ageing populations.

2. To identify people with persistently high CTI or greater cumulative CTI burden as a high risk group, providing evidence for population risk stratification and targeted prevention.

3. To provide public health evidence that repeated CTI assessment and adiposity related pathways may be relevant for early identification and prevention of cardiometabolic multimorbidity.

Background

Cardiometabolic multimorbidity (CMM), commonly defined as the coexistence of two or more cardiometabolic conditions in the same individual, has become a dominant public health and clinical challenge in ageing populations[1, 2]. It is clinically important because the clustering of diabetes, cardiovascular disease and stroke reflects shared upstream mechanisms, increases treatment complexity, and amplifies risks of disability and mortality[3]. In China, the rapid demographic transition and the high prevalence of metabolic risk factors have made early identification of individuals at risk of progressing from a single condition to multimorbidity a priority for prevention and integrated care[4]. Beyond the burden on individuals, CMM challenges healthcare systems by requiring long-term management across specialties and by increasing polypharmacy and competing risk-factor targets[5, 6].

Systemic inflammation and insulin resistance(IR) are closely intertwined and are considered core biological processes underlying cardiometabolic disease accumulation[7–9]. Chronic low-grade inflammation can impair insulin signaling, while IR can amplify inflammatory pathways, creating a self-reinforcing cycle that promotes vascular injury, metabolic deterioration, and end-organ damage[10–12]. C-reactive protein (CRP) is a widely used marker of systemic inflammation and has been incorporated into cardiovascular risk assessment frameworks[13, 14]. The triglyceride–glucose (TyG) index is a practical surrogate of IR derived from fasting triglycerides and glucose[15–17]. Building on these two dimensions, the C-reactive protein–triglyceride–glucose index (CTI) was proposed as a composite marker integrating inflammatory and insulin resistance components into a single metric[18–21].

Most epidemiologic studies rely on a single baseline biomarker measurement, which may incompletely represent long-term exposure due to within-person variability and temporal changes[18, 22]. Repeated measures enable complementary views of risk: a time-integrated cumulative burden that captures sustained exposure and a trajectory-based grouping that summarizes heterogeneous patterns over time. In prior work, CTI has been associated with incident stroke and cardiovascular outcomes, and trajectory-based CTI patterns have been used to stratify future risk[23, 24]. More recently, evidence from cohort analyses has linked CTI to cardiometabolic multimorbidity, supporting its relevance for multi-condition cardiometabolic risk[24].

However, several gaps remain in the current evidence. Whether CTI measures based on repeated assessments, including cumulative exposure and trajectory patterns, provide additional information beyond a single baseline measurement for incident CMM remains unclear. It is also uncertain whether these CTI-derived measures improve prediction beyond established demographic, behavioural, and clinical risk factors. In addition, the potential mediating role of adiposity in the association between CTI

and CMM has not been fully examined. Therefore, using CHARLS data with repeated biomarker assessment, we examined associations of baseline CTI (2012), cumulative CTI (cuCTI) exposure between 2012 and 2015, and data-driven CTI trajectories with incident CMM in 2018. We further evaluated dose–response relationships using restricted cubic splines, assessed incremental predictive performance beyond a conventional risk model using C-statistics, net reclassification improvement, and integrated discrimination improvement, and explored mediation by adiposity indices.

Methods

Study design and participants

We conducted a prospective cohort analysis within the China Health and Retirement Longitudinal Study (CHARLS), a nationally representative longitudinal study of Chinese adults aged ≥ 45 years that collects questionnaire data and standardized physical and laboratory measurements across survey waves[25]. The present analysis used CTI measurements in 2012 and 2015 and adjudicated incident CMM status in 2018, thereby aligning exposure assessment with subsequent outcome ascertainment.

CHARLS uses standardized interviews to collect sociodemographic characteristics, health behaviours, and physician-diagnosed conditions, and it incorporates physical examinations and laboratory measurements from fasting blood samples following study protocols. In the current analysis, we leveraged these harmonized data to define exposures, covariates, and outcomes consistently across waves.

A total of 11,847 participants were initially screened. We excluded 4,375 individuals with missing CTI measurements in 2012 or 2015, and a further 221 participants aged < 45 years or with missing age. We additionally excluded 1,473 participants with prevalent CMM prior to 2018 or missing CMM status. The final analytic sample included 5,778 participants(Fig. 1).

Exposure

CTI was calculated using the formula: 0.412 × ln(CRP [mg/L]) + ln(TG [mg/dL] × FPG [mg/dL]/2) [17]. CTI_{2012} and CTI_{2015} represent CTI measured in 2012 (Wave 1) and 2015 (Wave 3), respectively, with a 3-year interval between assessments.

To quantify long-term cumulative exposure, cumulative CTI was computed using the trapezoidal (area) approach: cuCTI = $(CTI_{2012} + CTI_{2015})/2 \times (2015 - 2012)$. The average of the two time points was used to reflect the mean exposure level and was multiplied by the duration to estimate cumulative exposure over time, consistent with cumulative metabolic index calculations in CHARLS and prior studies. Based on CTI levels, participants were further classified into three CTI change-pattern (trajectory) groups using k-means clustering applied to z-standardized CTI_{2012} and CTI_{2015} values (K = 3). Clusters were labeled according to mean CTI level as Persistent Low, Moderate, and Stable High (Fig. 2), consistent with prior

CHARLS-based CTI trajectory analyses. In line with prior literature that describes longitudinal CTI "changes" using repeated-measure patterning, we refer to these k-means clusters as CTI change-pattern (trajectory) groups rather than a simple two-point difference.

Outcome

CMM was defined as at least two of diabetes, heart disease, and stroke[26]. Diabetes was identified by self-report of physician diagnosis and objective evidence (use of anti-diabetic medication, fasting plasma glucose ≥ 126 mg/dL, or HbA1c ≥ 6.5%)[27]. Heart disease and stroke were ascertained by self-reported physician diagnosis.

Covariates

Covariates were selected a priori to reduce confounding and were organized into nested models to evaluate robustness of estimates to progressively broader adjustment. Model 1 included basic demographic characteristics (age and sex). Model 2 further adjusted for socio-demographic and lifestyle-related factors, including educational attainment, residential location, marital status, smoking status, and alcohol consumption. Model 3 additionally adjusted for clinical and physiological variables, including systolic blood pressure (SBP), diastolic blood pressure(DBP), hypertension, dyslipidaemia, sleep duration, estimated glomerular filtration rate(eGFR), and lipid-lowering medication use.

Missing data and multiple imputation

Missing covariate data were handled using multiple imputation by chained equations (MICE) to minimize potential bias and improve statistical efficiency (**Table S1**). During data preprocessing, extreme values were detected in BMI, BRI and WHtR indices.To limit the influence of extreme values while retaining observations, prespecified continuous variables were winsorized at the 1st and 99th percentiles prior to model fitting. This procedure was applied consistently within each imputed dataset where relevant to enhance the robustness of regression estimates in the presence of measurement error and outliers.

Statistical analysis

Baseline characteristics were summarized for the overall sample and across CTI trajectory groups. Normally distributed continuous variables are presented as mean ± standard deviation (SD), non-normally distributed variables as median (interquartile range, IQR), and categorical variables as number (percentage). Between-group comparisons were performed using one-way analysis of variance (ANOVA) for normally distributed continuous variables, the Kruskal–Wallis test for non-normally distributed variables, and the Pearson chi-square test for categorical variables.

Missing covariates were imputed under the missing-at-random assumption using multiple imputation by chained equations. Associations between CTI measures and incident CMM were estimated using logistic regression within each imputed dataset and pooled. Effect estimates are reported as odds ratios (ORs) with 95% confidence intervals (CIs) and two-sided P values. CTI_{2012} and cuCTI were analyzed per interquartile range (IQR) and by quartiles (Q1 as reference). Linear trends across quartiles and ordered trajectory groups were evaluated by entering category ranks as continuous terms (P for trend). Three models with increasing adjustment were fitted.

Dose–response relationships were examined using restricted cubic splines with four knots, with the median exposure as the reference. We report Poverall for the overall exposure–outcome association and Pnonlinear for departure from linearity and interpret spline curves alongside exposure distributions.

Incremental predictive value beyond conventional risk factors was assessed by comparing a basic model corresponding to Model 3 covariates with models additionally including CRP, TyG, baseline CTI, cuCTI, or CTI trajectories. Discrimination was quantified using the C-statistic and compared using DeLong's test for correlated ROC curves. Reclassification was evaluated using net reclassification improvement (NRI) and integrated discrimination improvement (IDI). ROC curves are provide, with summary prediction metrics in Table 3.

Table 3
Discrimination and reclassification improvement for incident cardiometabolic multimorbidity (CMM)

Model	C-statistics (95% CI)	*P* (DeLong vs Base)	NRI (95% CI)	*P* (NRI)	IDI (95% CI)	*P* (IDI)
Basic model	0.708(0.678–0.739)		Ref		Ref	
Basic model + CRP	0.710(0.679–0.740)	0.285	0.1414(0.0422–0.2406)	0.005	0.0003(-0.0006–0.0012)	0.474
Basic model + TyG	0.726(0.698–0.754)	0.002	0.1890(0.0781–0.3000)	< 0.001	0.0072(0.0031–0.0113)	< 0.001
Basic model + CTI	0.732(0.704–0.760)	< 0.001	0.2785(0.1676–0.3893)	< 0.001	0.0090(0.0044–0.0135)	< 0.001
Basic model + cuCTI	0.737(0.709–0.764)	< 0.001	0.3378(0.2273–0.4482)	< 0.001	0.0116(0.0063–0.0168)	< 0.001
Basic model + CTI trajectory	0.739(0.712–0.766)	< 0.001	0.3461(0.2488–0.4434)	< 0.001	0.0084(0.0051–0.0117)	< 0.001

Abbreviations: CTI, C-reactive protein–triglyceride–glucose index; cuCTI, cumulative CTI; CMM, cardiometabolic multimorbidity; OR, odds ratio; CI, confidence interval; IQR, interquartile range.

One-way mediation analyses assessed whether adiposity indices mediated CTI–CMM associations. Mediators included body mass index (BMI), body roundness index (BRI), and waist-to-height ratio (WHtR). Mediator models were specified using linear regression and outcome models using logistic regression including the exposure, mediator, and Model 3 covariates. Prespecified subgroup analyses were conducted by age group, sex, smoking, drinking, marital status, and hypertension status; effect modification was examined using multiplicative interaction terms. Sensitivity analyses included: (1) complete-case analyses without imputation and (2) analyses excluding participants with baseline diabetes, heart disease, or stroke. All analyses were conducted using R version 4.4.2, and statistical significance was defined as a two-sided $P < 0.05$.

Results

Baseline characteristics

Baseline characteristics by CTI trajectory are shown in Table 1. The mean age was 58.50 (8.31) years, and 50.7% were women. At baseline, 32.1% had at least one cardiometabolic condition. CTI trajectory

clustering identified three groups: Persistent Low (n = 2,206), Moderate (n = 2,474), and Stable High (n = 1,098). Participants in the Stable High trajectory group tended to have a more adverse cardiometabolic profile compared with the Persistent Low group, including higher blood pressure, more atherogenic lipid and glycaemic profiles, higher inflammatory burden, and higher adiposity-related indices. These differences are consistent with CTI integrating inflammatory and metabolic components and with a higher burden of established risk factors among individuals with persistently higher CTI.

Table 1
Baseline characteristics by CTI trajectory group

Variables	Overall	Persistent Low Group	Moderate Group	Stable High Group	p
n	5778	2206	2474	1098	
Age (mean (SD))	58.3 (8.5)	58.1 (8.6)	58.5 (8.5)	58.3 (8.2)	0.274
sex (%)					
Female	3158 (54.7)	1105 (50.1)	1401 (56.6)	652 (59.4)	< 0.001
Male	2620 (45.3)	1101 (49.9)	1073 (43.4)	446 (40.6)	
Education (%)					
Elementary school	1334 (23.1)	500 (22.7)	572 (23.1)	262 (23.9)	0.662
High school and above	543 (9.4)	219 (9.9)	217 (8.8)	107 (9.7)	
Junior high school	1180 (20.4)	434 (19.7)	516 (20.9)	230 (20.9)	
No formal education	2721 (47.1)	1053 (47.7)	1169 (47.3)	499 (45.4)	
Location (%)					
Rural	4919 (85.1)	1917 (86.9)	2105 (85.1)	897 (81.7)	< 0.001
Urban	859 (14.9)	289 (13.1)	369 (14.9)	201 (18.3)	
Marital (%)					
Married	5213 (90.2)	1998 (90.6)	2225 (89.9)	990 (90.2)	0.764
Other	565 (9.8)	208 (9.4)	249 (10.1)	108 (9.8)	
Smoking (%)					
No	4034 (69.8)	1473 (66.8)	1756 (71.0)	805 (73.3)	< 0.001
Yes	1744 (30.2)	733 (33.2)	718 (29.0)	293 (26.7)	
Drinking (%)					
No	4019 (69.6)	1470 (66.6)	1766 (71.4)	783 (71.3)	0.001
Yes	1759 (30.4)	736 (33.4)	708 (28.6)	315 (28.7)	

Baseline characteristics are shown overall and by CTI trajectory group (Persistent Low, Moderate, Stable High) derived from k-means clustering of CTI_{2012} and CTI_{2015}. Continuous variables are presented as mean (SD) or median [IQR]; categorical variables as n (%). P values compare characteristics across trajectory groups.

Variables	Overall	Persistent Low Group	Moderate Group	Stable High Group	p
Sleep-time (mean (SD))	6.4 (1.9)	6.4 (1.9)	6.3 (1.9)	6.4 (1.8)	0.276
SBP (mean (SD))	128.7 (20.7)	124.3 (19.4)	130.1 (20.9)	134.2 (21.2)	< 0.001
DBP (mean (SD))	75.1 (11.8)	72.7 (11.5)	76.0 (11.5)	78.2 (11.7)	< 0.001
TC (mean (SD))	193.0 (36.6)	184.2 (33.0)	194.8 (36.4)	206.4 (39.2)	< 0.001
TG (median [IQR])	104.4 [74.3, 152.2]	74.3 [59.3, 94.7]	115.1 [88.5, 152.2]	199.1 [143.4, 284.7]	< 0.001
HDL (mean (SD))	51.2 (14.9)	58.0 (14.6)	50.1 (13.0)	40.1 (11.7)	< 0.001
LDL (mean (SD))	116.2 (33.3)	111.9 (29.1)	120.2 (33.3)	116.1 (39.6)	< 0.001
Glu (median [IQR])	101.9 [94.3, 111.4]	97.8 [91.3, 105.1]	102.1 [95.2, 110.7]	112.4 [102.2, 133.3]	< 0.001
HbA1c (median [IQR])	5.1 [4.9, 5.4]	5.1 [4.8, 5.3]	5.1 [4.9, 5.4]	5.3 [5.0, 5.7]	< 0.001
CRP (median [IQR])	1.0 [0.5, 2.0]	0.6 [0.4, 1.0]	1.2 [0.7, 2.2]	2.1 [1.1, 4.6]	< 0.001
Tyg (mean (SD))	8.7 (0.7)	8.2 (0.4)	8.7 (0.4)	9.5 (0.7)	< 0.001
eGFR (mean (SD))	93.3 (13.5)	95.2 (12.3)	92.4 (13.7)	91.4 (14.5)	< 0.001
BMI (mean (SD))	23.6 (3.6)	22.2 (3.1)	23.8 (3.4)	25.6 (3.6)	< 0.001
BRI (mean (SD))	4.2 (1.4)	3.7 (1.2)	4.3 (1.4)	4.9 (1.5)	< 0.001
WHtR (mean (SD))	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)	0.6 (0.1)	< 0.001
CTI_{2012} (mean (SD))	8.7 (0.8)	8.0 (0.4)	8.8 (0.5)	9.8 (0.7)	< 0.001
CTI_{2015} (mean (SD))	8.9 (0.9)	8.1 (0.5)	9.0 (0.5)	10.0 (0.7)	< 0.001
cuCTI (median [IQR])	26.1 [24.8, 27.7]	24.4 [23.6, 25.0]	26.7 [26.1, 27.4]	29.4 [28.8, 30.4]	< 0.001
DM (%)	662 (11.5)	107 (4.9)	232 (9.4)	323 (29.4)	< 0.001
Heart (%)	529 (9.2)	167 (7.6)	264 (10.7)	98 (8.9)	0.001

Baseline characteristics are shown overall and by CTI trajectory group (Persistent Low, Moderate, Stable High) derived from k-means clustering of CTI_{2012} and CTI_{2015}. Continuous variables are presented as mean (SD) or median [IQR]; categorical variables as n (%). P values compare characteristics across trajectory groups.

Variables	Overall	Persistent Low Group	Moderate Group	Stable High Group	p
Stroke (%)	71 (1.2)	23 (1.0)	32 (1.3)	16 (1.5)	0.552
CMM2018 (%)	333 (5.8)	53 (2.4)	165 (6.7)	115 (10.5)	< 0.001

Baseline characteristics are shown overall and by CTI trajectory group (Persistent Low, Moderate, Stable High) derived from k-means clustering of CTI_{2012} and CTI_{2015}. Continuous variables are presented as mean (SD) or median [IQR]; categorical variables as n (%). P values compare characteristics across trajectory groups.

During follow-up, 333 participants developed CMM (5.8%). The proportion of incident CMM increased across the three trajectory groups and was highest in the Stable High group. Differences were also observed in biomarkers related to CTI components, including triglycerides, fasting glucose, and CRP, as well as in the related index TyG.

Associations of CTI measures with incident CMM

Main association results are summarized in Table 2. In the fully adjusted model (Model 3), baseline CTI per IQR was associated with higher odds of incident CMM (OR 1.545, 95% CI 1.344–1.776; P < 0.001). Similarly, cuCTI per IQR was associated with incident CMM (OR 1.651, 95% CI 1.429–1.907; P < 0.001).

Table 2
Logistic regression for incident cardiometabolic multimorbidity (CMM)

	Model 1		Model 2		Model 3	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Baseline CTI	1.824 (1.602, 2.076)	< 0.001	1.819 (1.597, 2.072)	< 0.001	1.545 (1.344, 1.776)	< 0.001
cuCTI	1.982 (1.733, 2.267)	< 0.001	1.974 (1.725, 2.258)	< 0.001	1.651 (1.429, 1.907)	< 0.001
Baseline CTI						
Q1	Ref		Ref		Ref	
Q2	1.464 (0.958, 2.237)	0.078	1.463 (0.957, 2.237)	0.079	1.315 (0.857, 2.020)	0.210
Q3	2.709 (1.842, 3.983)	< 0.001	2.692 (1.830, 3.959)	< 0.001	2.119 (1.429, 3.141)	< 0.001
Q4	3.931 (2.713, 5.696)	< 0.001	3.903 (2.693, 5.658)	< 0.001	2.637 (1.793, 3.878)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001
cuCTI						
Q1	Ref		Ref		Ref	
Q2	1.687 (1.076, 2.645)	0.023	1.683 (1.073, 2.640)	0.023	1.501 (0.953, 2.365)	0.080
Q3	3.319 (2.203, 4.998)	< 0.001	3.308 (2.196, 4.983)	< 0.001	2.576 (1.696, 3.912)	< 0.001
Q4	4.897 (3.296, 7.276)	< 0.001	4.856 (3.266, 7.220)	< 0.001	3.226 (2.139, 4.868)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001
CTI trajectory						
Low	Ref		Ref		Ref	
Middle	2.804 (2.045, 3.845)	< 0.001	2.793 (2.036, 3.830)	< 0.001	2.255 (1.633, 3.116)	< 0.001
High	4.550 (3.254, 6.361)	< 0.001	4.509 (3.223, 6.308)	< 0.001	3.078 (2.169, 4.369)	< 0.001

Odds ratios (OR) and 95% confidence intervals (CI) for incident cardiometabolic multimorbidity in 2018 associated with baseline CTI (2012), cumulative cuCTI (2012–2015), and CTI trajectory groups. Continuous exposure estimates are per IQR increase: IQR(CTI_{2012}) = 1.06938 and IQR(cuCTI) = 2.957853. Quartile cutpoints: CTI_{2012} min 5.98, Q1 8.12, median 8.63, Q3 9.19, max 13.15; cuCTI min 19.44, Q1 24.78, median 26.13, Q3 27.74, max 37.54.

	Model 1		Model 2		Model 3	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
P for trend		< 0.001		< 0.001		< 0.001

Odds ratios (OR) and 95% confidence intervals (CI) for incident cardiometabolic multimorbidity in 2018 associated with baseline CTI (2012), cumulative cuCTI (2012–2015), and CTI trajectory groups. Continuous exposure estimates are per IQR increase: IQR(CTI_{2012}) = 1.06938 and IQR(cuCTI) = 2.957853. Quartile cutpoints: CTI_{2012} min 5.98, Q1 8.12, median 8.63, Q3 9.19, max 13.15; cuCTI min 19.44, Q1 24.78, median 26.13, Q3 27.74, max 37.54.

Quartile analyses provided additional insight into risk gradients and potential thresholds. In general, associations were modest in the second quartile and became more pronounced in higher quartiles, with significant trends across quartiles for both baseline CTI and cuCTI (P for trend < 0.001). The strongest contrasts were observed comparing the highest quartile with the lowest quartile for both exposures (Table 2).

Trajectory analyses were consistent with continuous and quartile results. Compared with the Persistent Low group, both the Moderate and Stable High trajectory groups had higher odds of incident CMM in Model 3 (Moderate: OR 2.255, 95% CI 1.633–3.116; Stable High: OR 3.078, 95% CI 2.169–4.369; both P < 0.001), with evidence of a monotonic trend across trajectory levels.

Dose–response analyses

Restricted cubic spline models further characterized the shape of associations between CTI measures and incident CMM (Fig. 3). The overall association was statistically significant for both baseline CTI and cuCTI ($P_{overall} < 0.001$ for both). There was no strong evidence of departure from linearity for either exposure (baseline CTI: $P_{nonlinear} = 0.152$; cuCTI: $P_{nonlinear} = 0.161$), indicating approximately monotonic associations across the observed exposure ranges.

Prediction performance

Prediction performance is summarized in Fig. 4. The basic model had C-statistics 0.708 (0.678–0.739). Adding CRP yielded a small increase to 0.710 (0.679–0.740; DeLong P = 0.285), whereas adding TyG increased C-statistics to 0.726 (0.698–0.754; DeLong P = 0.002). Adding baseline CTI increased C-statistics to 0.732 (0.704–0.760; DeLong P < 0.001), adding cuCTI increased C-statistics to 0.737 (0.709–0.764; DeLong P < 0.001), and adding CTI trajectory increased C-statistics to 0.739 (0.712–0.766; DeLong P < 0.001).

These comparisons indicate that CTI-derived features improved discrimination more than CRP alone and at least comparably to TyG, consistent with CTI integrating inflammatory and metabolic information in a single index. Reclassification metrics supported these discrimination improvements: models incorporating CTI measures yielded positive NRI and IDI estimates with statistical significance (Table 3).

Mediation analyses

Mediation analyses suggested partial mediation by adiposity indices (Fig. 5). For baseline CTI, the proportion mediated by BMI was 18.5%; for cuCTI, the proportion mediated by BMI was 16.9%. BRI and WHtR also mediated smaller proportions of the association. Mediation results were broadly consistent across exposures, and direct effects remained after accounting for adiposity indices.

Sensitivity and subgroup analyses

Subgroup analyses (**Table S2-S4)** showed that associations were broadly consistent across strata defined by age group, sex, smoking, drinking, marital status, and hypertension status, with no strong evidence of effect modification across most subgroups.

Sensitivity analyses (**Table S5-S6**) supported the robustness of the associations for cuCTI and CTI trajectories under alternative analytic assumptions. Estimates remained directionally consistent in non-imputed datasets and in analyses excluding participants with baseline diabetes, heart disease, or stroke. Across sensitivity and subgroup analyses, the direction of associations was generally consistent.

Discussion

In this prospective CHARLS cohort analysis, baseline CTI, cumulative CTI, and CTI trajectories were consistently associated with higher odds of incident CMM by 2018. The pattern was coherent across different analytic representations, including per IQR, quartiles, and trajectories, and remained robust after adjustment for sociodemographic, behavioural, and clinical covariates. Dose response analyses supported significant overall associations and suggested largely monotonic relationships, with no strong evidence of nonlinearity. Beyond these etiologic associations, CTI related measures improved prediction beyond a conventional risk model. These findings support the translational relevance of CTI as a feasible composite index derived from routinely available biomarkers. Mediation analyses further suggested that adiposity indices partially mediated the association between CTI and CMM, highlighting potentially modifiable pathways while also indicating that additional mechanisms may contribute.

Our findings extend and complement prior CTI research. In studies of stroke, cumulative CTI exposure and dynamic CTI trajectories were associated with incident stroke, suggesting that CTI captures longitudinal inflammatory and metabolic burden relevant to vascular outcomes [16, 19–21]. In addition, another study found that different dimensions of CTI were associated with incident frailty, supporting its role as a marker of systemic vulnerability and ageing related phenotypes[23]. The present study extends these observations to cardiometabolic multimorbidity, a composite outcome that may better reflect the accumulation and clustering of cardiometabolic disease than a single event alone.

The emphasis on cumulative exposure and trajectories is particularly relevant to multimorbidity. CMM often develops progressively, so a measure that better reflects sustained exposure could plausibly show stronger or more consistent associations[7]. Cumulative exposure metrics also mitigate regression dilution bias that can occur when biomarkers have within-person variability[22]. In our analysis, both

cuCTI and CTI trajectory groups were strongly associated with incident CMM, supporting the relevance of longer-term inflammatory-metabolic burden in this context. The RCS analyses demonstrated statistically significant overall associations between CTI measures and incident CMM, with no strong evidence of nonlinearity. These findings suggest that the associations were broadly monotonic across the observed exposure ranges and that per-IQR estimates provide a reasonable summary of association strength.

CTI integrates inflammatory burden via CRP and metabolic dysregulation via the triglyceride–glucose component. Chronic low-grade inflammation may promote IR and dyslipidaemia through cytokine-mediated effects on adipose tissue, liver and muscle. In parallel, IR contributes to higher circulating triglycerides and glucose levels and may further stimulate inflammatory pathways via oxidative stress and endothelial activation[28, 29]. These interrelated processes may contribute to cardiometabolic disease development across multiple organ systems, which is consistent with the concept of CMM as a shared-pathway phenotype rather than simply the coexistence of independent diseases[28].

Among the adiposity related mediators, BMI accounted for the largest proportion of the association between CTI and CMM[30, 31]. This pattern is plausible because BMI captures overall adiposity, which is closely linked to the systemic inflammatory–metabolic milieu that CTI is designed to reflect: expansion of adipose tissue can promote chronic low-grade inflammation and worsen IR [28, 32–34]. In this context, BMI may be more closely linked than WHtR or BRI to both the inflammatory and metabolic components of CTI, and therefore may account for a larger proportion of the observed association[35]. By contrast, WHtR and BRI emphasize body shape and central adiposity[3, 36]; although clinically relevant, these indices can share substantial variance with BMI and may be more sensitive to waist-measurement variability, particularly in older adults, which could attenuate estimated indirect effects in fully adjusted models[37–40]. Similar patterns have been reported in CHARLS-based studies using other metabolic or lipid burden measures[41–43]. Overall, these findings suggest that adiposity-related pathways contribute to the association between CTI and CMM, although they do not fully explain it.

A key contribution of this study is the evaluation of incremental predictive performance. Adding baseline CTI, cumulative CTI, or CTI trajectory group to the basic model improved the C statistic, whereas the improvement observed with CRP alone was small and not statistically significant. CTI related measures also showed positive and statistically significant NRI and IDI values, indicating improved risk reclassification beyond conventional risk factors. Notably, the improvements were slightly greater for long term CTI related measures. Both cumulative CTI and CTI trajectory group showed higher C statistic and NRI values than baseline CTI, and cumulative CTI showed the largest IDI. These findings suggest that repeated assessment of CTI may provide additional predictive information for incident CMM.

Several limitations should be considered. CMM and component diseases were derived from questionnaire items indicating self-reported physician diagnosis; misclassification is possible and could attenuate associations. CTI was assessed at two time points (2012 and 2015), limiting trajectory granularity and potentially missing shorter-term variability. Although we adjusted for a broad set of

confounders, residual confounding may remain, including unmeasured diet, detailed physical activity, and medication classes beyond dyslipidaemia medication use.

Future work should validate CTI-based risk prediction in external cohorts and evaluate whether repeated CTI assessment over longer follow-up improves performance further. Mechanistic studies could assess whether interventions that reduce inflammatory–metabolic burden, improve adiposity, or address insulin resistance can modify CTI trajectories and reduce progression to multimorbidity. Finally, integrating CTI with additional multimorbidity-relevant markers and applying modern prediction approaches may help translate these findings into actionable risk stratification tools in both clinical and public health settings.

Conclusions

In this nationally representative CHARLS cohort, greater cumulative CTI exposure between 2012 and 2015, and persistently elevated CTI trajectories were associated with higher odds of incident CMM. Adding long-term CTI measures to a conventional risk model improved discrimination and reclassification, indicating potential utility for risk stratification. Mediation analyses suggested that adiposity contributes partially to these associations. CTI may help identify high-risk adults for integrated prevention of cardiometabolic disease clustering.

Abbreviations

BMI
body mass index
BRI
body roundness index
WHtR
waist-to-height ratio
CHARLS
China Health and Retirement Longitudinal Study
CI
confidence interval
CMM
cardiometabolic multimorbidity
CRP
C-reactive protein
CTI
C-reactive protein–triglyceride–glucose index
cuCTI
cumulative CTI
DBP
diastolic blood pressure

eGFR
estimated glomerular filtration rate
FPG
fasting plasma glucose
IDI
integrated discrimination improvement
IQR
interquartile range
MI
multiple imputation
NRI
net reclassification improvement
OR
odds ratio
RCS
restricted cubic spline
ROC
receiver operating characteristic
SBP
systolic blood pressure
TG
triglycerides
TyG
triglyceride–glucose index.

Declarations

Ethics approval and consent to participate

CHARLS was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015). All participants provided written informed consent at each survey wave. All study procedures were conducted in accordance with the Declaration of Helsinki.

Clinical trial number

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The data used in this study are from the China Health and Retirement Longitudinal Study (CHARLS). CHARLS datasets are available for download at the CHARLS home website (http://charls.pku.edu.cn/en).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YL and HA conceived and designed the study. YL performed the statistical analyses and drafted the manuscript. HA supervised the study and critically revised the manuscript for important intellectual content. Both authors read and approved the final manuscript.

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Figures

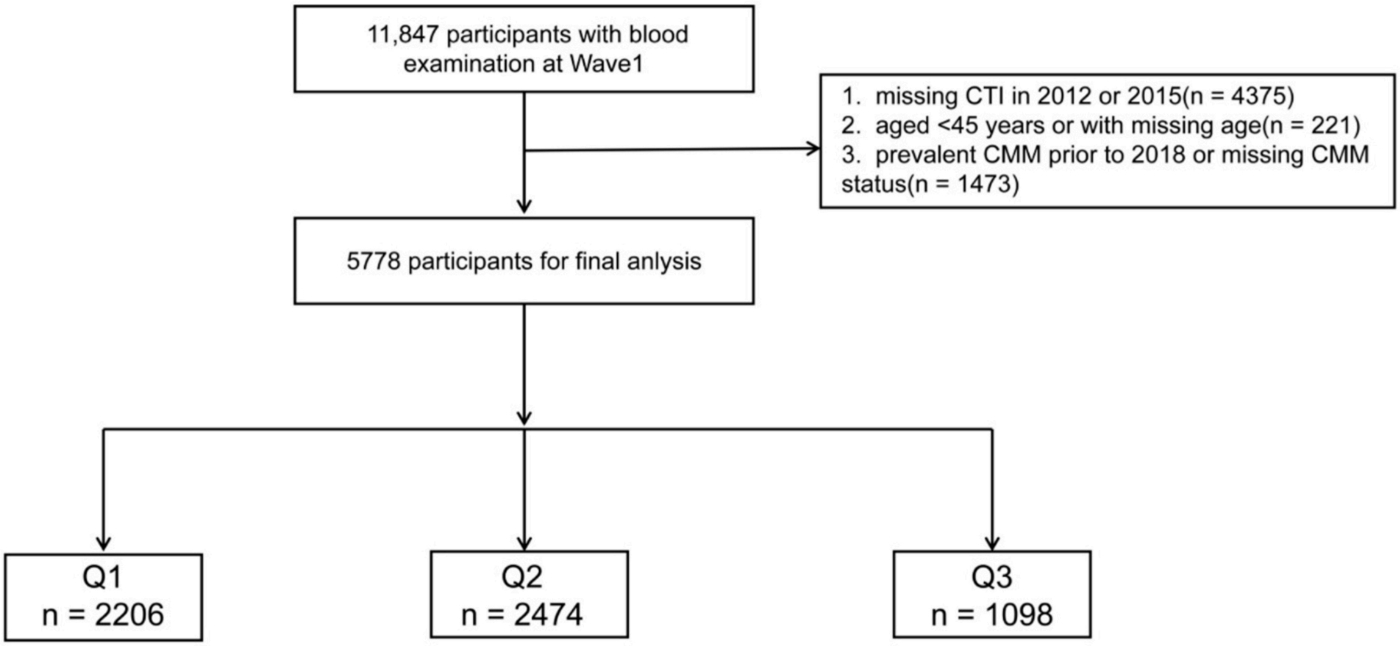

Figure 1

Flow chart of participant selection. Abbreviations: CTI, C-reactive protein–triglyceride–glucose index; CMM, cardiometabolic multimorbidity.

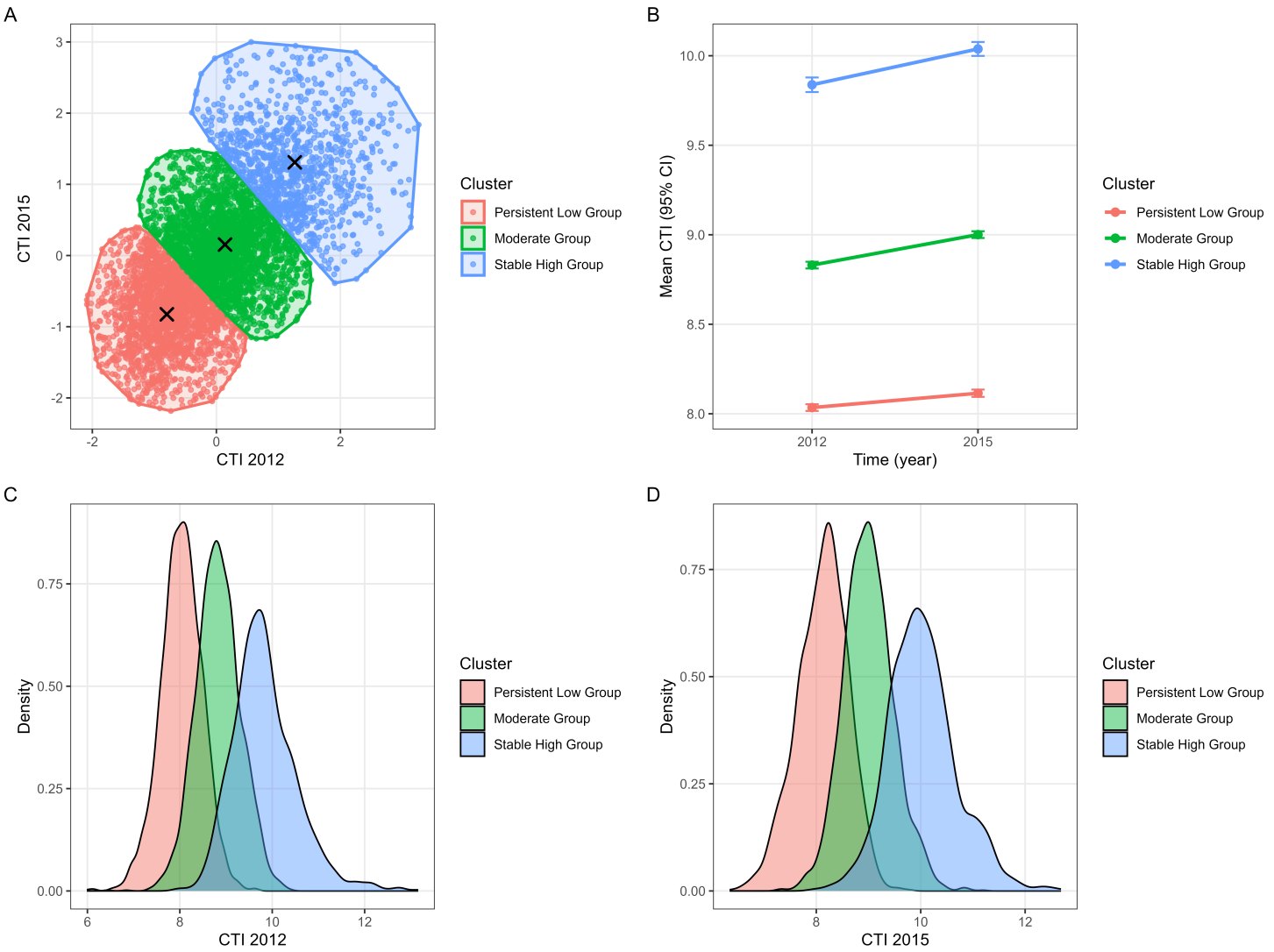

Figure 2

CTI change-pattern groups identified from repeated CTI measurements in 2012 and 2015. Abbreviations: CTI, C-reactive protein–triglyceride–glucose index; CI, confidence interval.

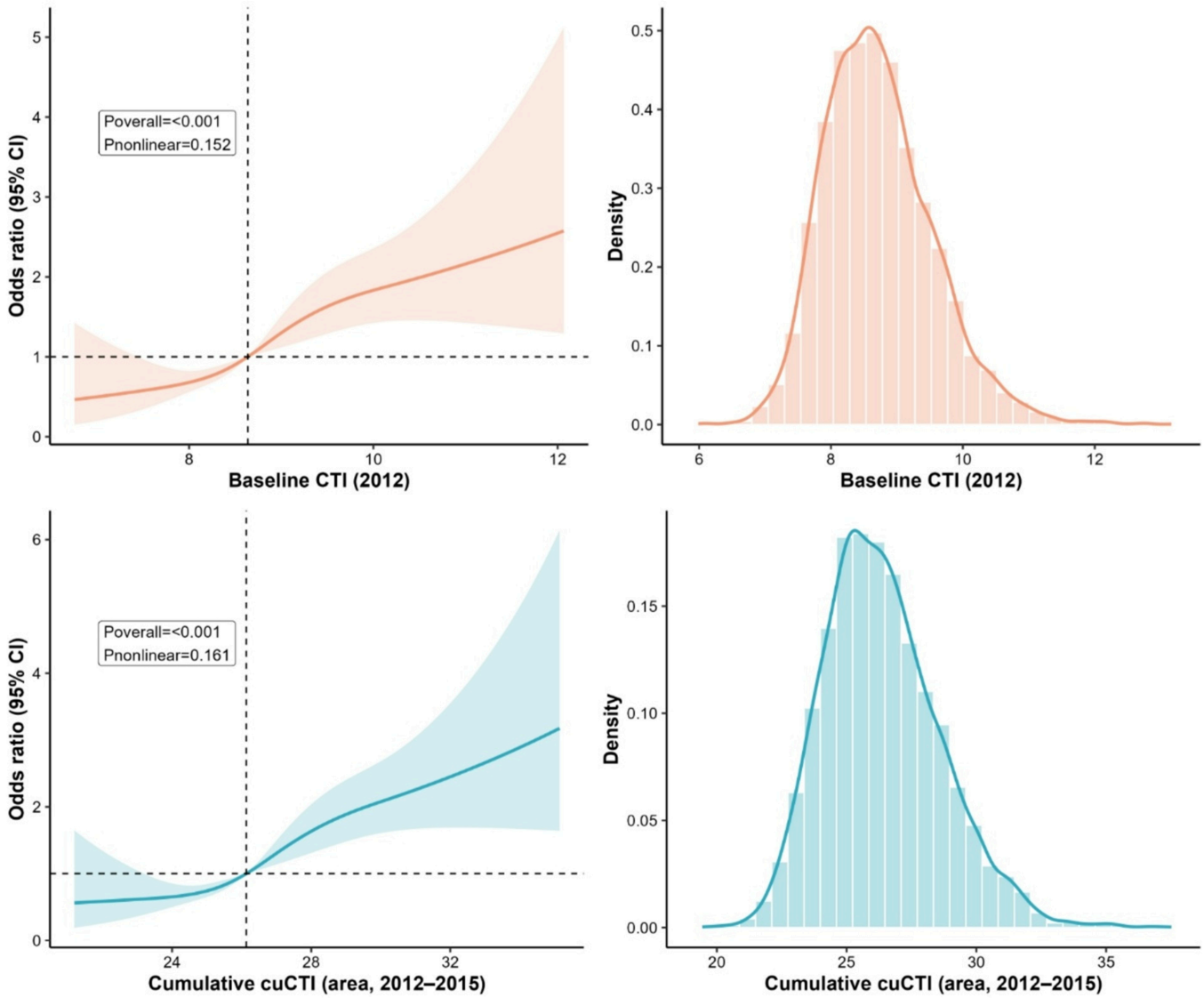

Figure 3

Restricted cubic spline analyses of the associations of baseline CTI and cumulative CTI with incident cardiometabolic multimorbidity. Abbreviations: CTI, C-reactive protein–triglyceride–glucose index; cuCTI, cumulative CTI; CI, confidence interval.

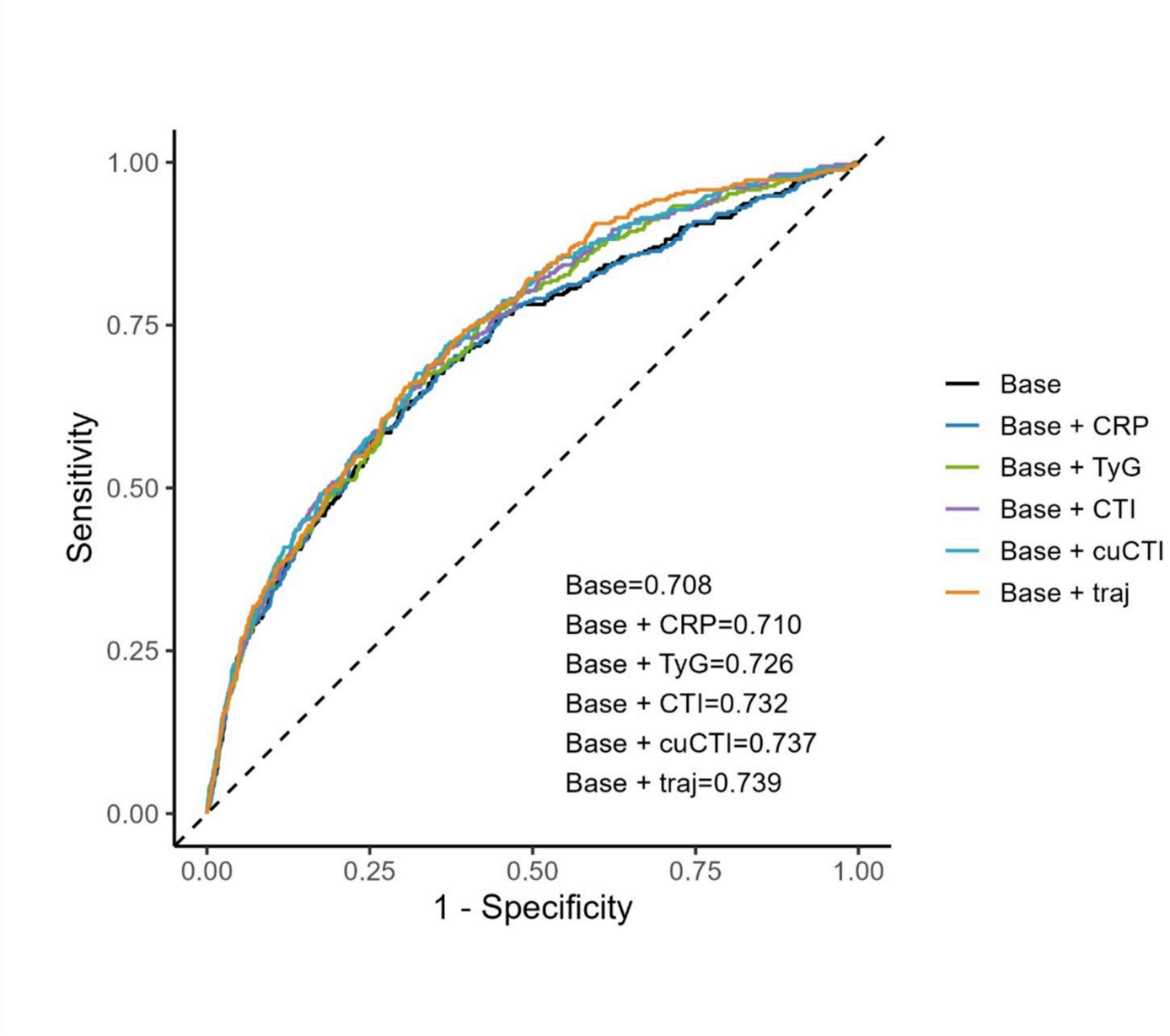

Figure 4

Receiver operating characteristic curves for the prediction of incident cardiometabolic multimorbidity by different models. Abbreviations: ROC, receiver operating characteristic; CRP, C-reactive protein; TyG, triglyceride–glucose index; CTI, C-reactive protein–triglyceride–glucose index; cuCTI, cumulative CTI.

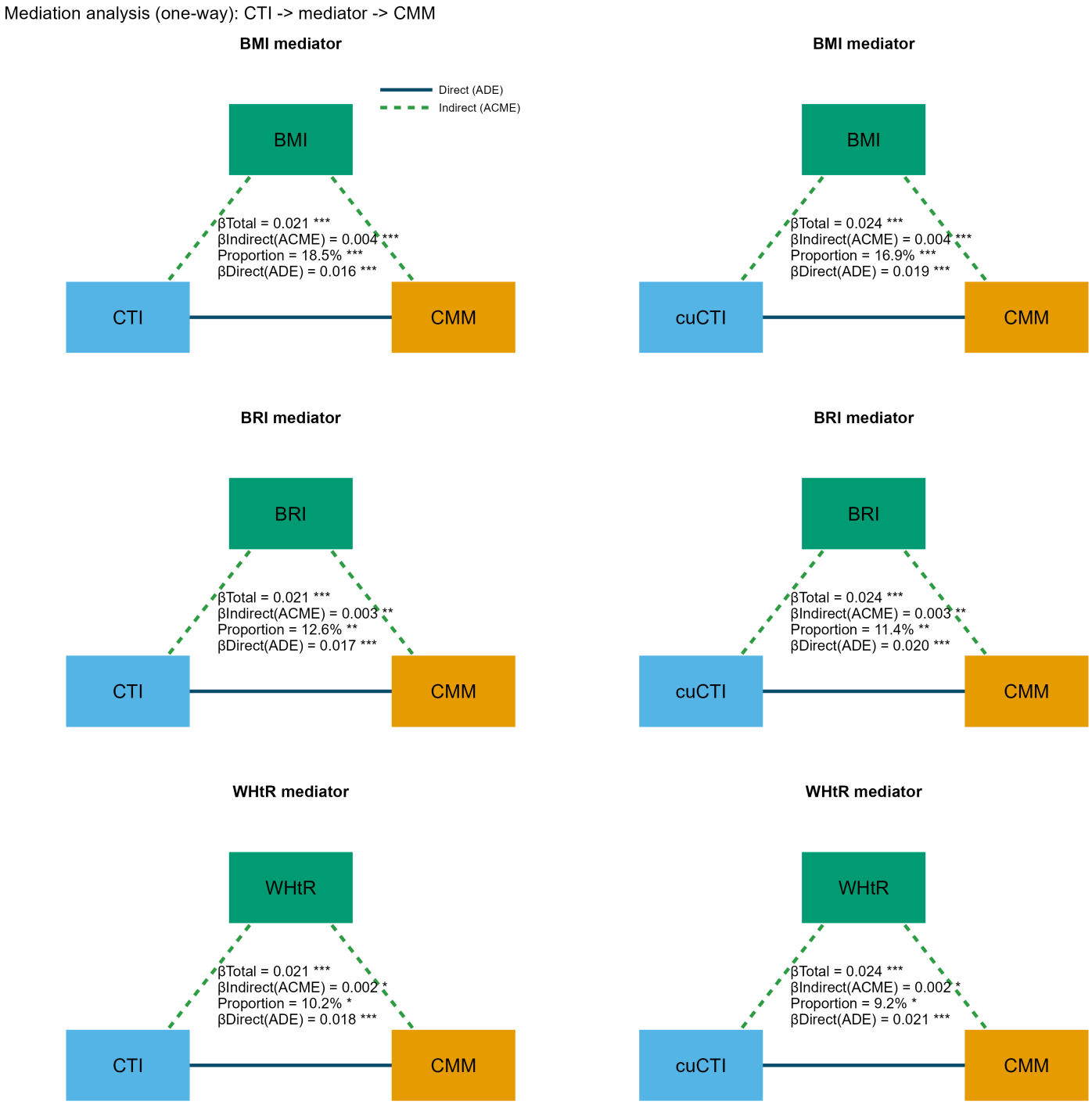

Figure 5

Mediation analyses of the associations of baseline CTI and cumulative CTI with incident cardiometabolic multimorbidity through adiposity indices. Abbreviations: CTI, C-reactive protein–triglyceride–glucose index; cuCTI, cumulative CTI; BMI, body mass index; BRI, body roundness index; WHtR, waist-to-height ratio.

Supplementary Files

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- SupplementaryTableS.docx