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The combined C-reactive protein–triglyceride–glucose and frailty index in relation to incident cardiometabolic multimorbidity across cohorts in China and England

Hao Yan
Central South University
Lin Li
The Affiliated Changsha Hospital of Xiangya, Central South University
Min Wang
wangmin@pkuszh.com.cn

Central South University

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Abstract

Background

Cardiometabolic multimorbidity (CMM) is a growing burden among middle-aged and older adults. The C-reactive protein–triglyceride–glucose index (CTI) reflects inflammatory–metabolic dysfunction, whereas the frailty index (FI) captures physiological vulnerability. Whether CTI-FI is consistently associated with incident CMM and adds predictive value across populations remains uncertain. We evaluated associations of CTI-FI with incident CMM and its incremental predictive value.

Methods

Adults aged ≥ 45 years were analyzed in the China Health and Retirement Longitudinal Study (CHARLS; 2011–2020) and the English Longitudinal Study of Ageing (ELSA; 2004–2018). CTI-FI and cumulative CTI-FI (cumCTI-FI) were evaluated in separate cohorts. Adjusted cumulative incidence curves, Cox regression, and restricted cubic splines assessed associations; C-statistics and reclassification measures quantified added predictive value. Predictive performance was compared across eight machine-learning models developed in CHARLS: CatBoost, XGBoost, Extra Trees, random forest, recursive partitioning, support vector machine, k-nearest neighbors, and neural network; the selected models were externally validated in ELSA. Subgroup and sensitivity analyses assessed consistency across participant groups and analytic choices.

Results

Among 7,108 participants, adjusted cumulative incidence increased across CTI-FI quartiles in both cohorts (all $P < 0.001$). Per-unit adjusted HRs for CTI-FI were 1.48 (95% CI, 1.37–1.60) in CHARLS and 1.31 (1.17–1.47) in ELSA; Q4-versus-Q1 HRs were 3.40 and 2.62. Nonlinearity was observed for CTI-FI and cumCTI-FI in CHARLS and for cumCTI-FI in ELSA. In CHARLS, the CTI-FI association was stronger among participants aged < 60 years, married, or without hypertension. Adding CTI-FI increased C-statistics from 0.723 to 0.759 in CHARLS and 0.745 to 0.767 in ELSA; NRI improved significantly in both cohorts (0.40 and 0.35), and IDI improved significantly in CHARLS. cumCTI-FI yielded the highest C-statistics (0.763 and 0.768), and CTI-FI showed greater discrimination than CTI or FI. XGBoost had the highest mean cross-validated AUC (0.700); external AUCs were 0.689 and 0.695. SHAP ranked CTI-FI and cumCTI-FI as leading predictors.

Conclusions

CTI-FI was associated with incident CMM and improved prediction beyond conventional factors in both cohorts. By integrating inflammatory–metabolic dysfunction and frailty-related vulnerability, CTI-FI

supports multidimensional risk assessment. Repeated assessment may strengthen early identification and targeted CMM prevention.

Introduction

Cardiometabolic multimorbidity (CMM) denotes the presence of two or more of three conditions: heart disease, stroke, and diabetes[1]. Prospective studies consistently link CMM to excess mortality and reduced longevity[2, 3]. Chinese population-based studies further document a rapid rise in CMM prevalence as cardiometabolic diseases accumulate[4, 5]. In addition, multicohort studies link CMM to accelerated deterioration in cognitive and physical function, while population studies report poorer quality of life and greater healthcare use[6–8]. Identifying susceptible individuals before a second cardiometabolic condition emerges may therefore help prevent or delay CMM and limit its downstream consequences[9, 10].

Chronic inflammation and insulin resistance are implicated in biological aging, frailty, and cardiovascular disease, providing a rationale for their joint assessment[11, 12]. The C-reactive protein–triglyceride–glucose index (CTI) incorporates C-reactive protein (CRP) into the triglyceride–glucose index to represent concurrent inflammatory and metabolic dysregulation[13]; prospective cohort data show that CMM incidence increases with higher CTI levels[14]. The frailty index (FI), in turn, summarizes deficits accumulated across multiple health domains and the corresponding reduction in physiological reserve[15]; greater frailty has been linked to progression along the CMM trajectory[16]. CTI therefore characterizes inflammatory–metabolic status, whereas FI captures multisystem vulnerability accrued over time. Prospective evidence associating CTI-FI with incident stroke supports the clinical relevance of integrating these complementary domains within a single index[17].

However, it is not yet established whether CTI-FI is consistently associated with CMM or improves risk assessment across populations with different demographic, behavioral, and healthcare contexts. Therefore, we used two longitudinal aging cohorts: the China Health and Retirement Longitudinal Study (CHARLS) and the English Longitudinal Study of Ageing (ELSA). We evaluated CTI-FI and cumulative CTI-FI (cumCTI-FI) in relation to incident CMM, examined the form of these associations across the exposure range, and tested for differences across prespecified subgroups. We also determined whether either measure added predictive information to established risk factors. Prediction models were developed in CHARLS and externally validated in ELSA to assess performance in an independent national setting.

Methods

Data source and study population

This study drew on two national longitudinal studies of aging, CHARLS in China and ELSA in England. CHARLS began in 2011–2012 and conducted four subsequent waves in 2013–2014, 2015–2016, 2017–2018, and 2019–2020. ELSA began in 2002–2003 and conducted Waves 2–9 at two-year intervals from

2004–2005 through 2018–2019. Across both studies, trained fieldworkers collected sociodemographic, behavioral, clinical, functional, and biomarker data using standardized interviews and examinations. Sampling and fieldwork procedures are described in the original cohort reports[18, 19].

Ethical approval

for CHARLS was granted by the Peking University Biomedical Ethics Review Committee (IRB00001052-11015); ELSA was approved by the London Multicentre Research Ethics Committee (MREC/01/2/91). Both studies adhered to the Declaration of Helsinki, and all participants gave written informed consent. The analytical baseline was Wave 1 for CHARLS and Wave 2 for ELSA. CTI-FI was derived from data collected at these waves, whereas cumCTI-FI was calculated from the two assessments at CHARLS Waves 1 and 3 and ELSA Waves 2 and 4. Incident CMM was identified during subsequent waves, with time at risk for the cumulative analyses beginning at the second exposure assessment.

Definitions of the composite index (CTI-FI)

CTI was computed using the published equation: CTI = 0.412 × ln[CRP (mg/L)] + ln{[TG (mg/dL) × FPG (mg/dL)]/2} [20]. Frailty was quantified using a 28-deficit index developed according to the deficit-accumulation approach [21]. The selected deficits covered chronic conditions, physical functioning, depressive symptoms, and cognitive performance (Table S1). Each item contributed a score from 0 to 1, and FI was calculated by dividing the total deficit score by the number of available items. The index has a theoretical range of 0–1, with higher values representing greater frailty. Heart disease, stroke, and diabetes were excluded from the deficit set to prevent definitional overlap with CMM. Following previous CTI-FI formulations[17, 22], CTI-FI was calculated as the product of CTI and FI (CTI-FI = CTI × FI). Higher values therefore represent a greater joint burden of inflammatory–metabolic dysregulation and accumulated health deficits. Cumulative CTI-FI exposure was estimated using the trapezoidal rule: $\text{cumCTI-FI} = [\text{CTI-FI}(t_1) + \text{CTI-FI}(t_2)]/2 \times (t_2 - t_1)$, where t_1 and t_2 denote the first and second assessment times, respectively. The elapsed time was 3 years in CHARLS (2012–2015) and 4 years in ELSA (2004–2008).

Ascertainment of incident CMM

Incident CMM was the primary outcome and was identified when a participant had at least two of the following conditions: heart disease, stroke, and diabetes[23]. Heart disease and stroke were ascertained from participants' reports of a physician diagnosis. Diabetes was considered present if any of the following applied: a self-reported physician diagnosis of diabetes or hyperglycemia, use of glucose-lowering medication, fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L), or glycated hemoglobin (HbA1c) ≥ 6.5% (48 mmol/mol)[14]. The same operational criteria were applied in CHARLS and ELSA. Because CMM was assessed at discrete survey waves, the first follow-up assessment at which two qualifying conditions were recorded was treated as the event wave[24]. Follow-up began at cohort

baseline for the CTI-FI analyses and at the second exposure assessment for the cumCTI-FI analyses. Participants who remained free of CMM were censored at their last wave with sufficient information to determine outcome status.

Covariates

Covariates were prespecified on the basis of established CMM risk factors, clinical relevance, and comparability between CHARLS and ELSA. They covered five domains. Sociodemographic characteristics included age, sex, marital status (married vs other), and educational attainment (less than high school vs high school or above). Lifestyle and anthropometric factors comprised smoking status (never vs other), alcohol consumption (never vs other), and body mass index (BMI). Medical history included hypertension and dyslipidemia, whereas clinical measurements comprised systolic blood pressure (SBP) and diastolic blood pressure (DBP). Lipid biomarkers included total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). Age, BMI, SBP, DBP, TC, HDL-C, and LDL-C were treated as continuous variables. Hypertension was considered present if any of the following criteria were met: SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, a self-reported physician diagnosis of hypertension, or current antihypertensive medication use. Dyslipidemia was identified from a self-reported diagnosis or current use of lipid-lowering medication.

Statistical analyses

Distributional normality was judged from histograms together with the Shapiro–Wilk test. Approximately normal measures were summarized by the mean ± SD and compared using one-way analysis of variance. Skewed measures were summarized by the median (IQR), with comparisons based on the Kruskal–Wallis test. Categorical characteristics were tabulated as n (%) and compared using the χ^2 test. For exposure-category analyses, quartile cut points for CTI-FI and cumCTI-FI were derived separately within each cohort.

Associations with incident CMM were quantified by Cox proportional hazards regression. CTI-FI and cumCTI-FI were fitted in separate models, first on their continuous scales and then as cohort-specific four-level variables. The lowest quartile (Q1) served as the reference group, and estimates were expressed as HRs with 95% CIs. Covariate adjustment followed four successive models. Model 1 included age and sex. Model 2 added marital status, educational attainment, smoking status, alcohol consumption, and BMI. Hypertension and dyslipidemia were introduced in Model 3, followed by SBP, DBP, TC, HDL-C, and LDL-C in Model 4. Ordered scores from 1 to 4 were assigned to quartiles and fitted as a single term for trend testing. Proportionality over follow-up was checked using scaled Schoenfeld residuals. Using Model 4, covariate-standardized cumulative incidence was estimated for each exposure quartile by averaging individual model-based risks over the observed covariate distribution. A likelihood-ratio test compared this model with an otherwise identical model omitting the quartile term to assess overall differences. Pointwise 95% CIs were calculated from 500 bootstrap resamples. Dose–response

shape was examined using restricted cubic splines under the Model 4 adjustment scheme, with three knots at the cohort-specific 10th, 50th, and 90th percentiles. Likelihood-ratio tests yielded P values for the overall association and nonlinearity.

Potential effect modification was evaluated in strata defined by age, sex, BMI, marital status, smoking status, alcohol consumption, hypertension, and dyslipidemia. The variable defining each stratum was omitted from the corresponding adjustment set, and exposure-by-subgroup interaction terms were fitted. In the cumulative cohorts, incremental predictive value was assessed by sequentially adding FI, CTI, CTI-FI, or cumCTI-FI to the conventional risk-factor model. Model discrimination was summarized using C-statistics with 95% CIs, and differences were examined by DeLong tests. Continuous NRI and IDI were estimated from 1,000 bootstrap resamples. Adjusted generalized variance inflation factors (GVIFs) were calculated for Model 4 to assess multicollinearity. Primary analyses used the prespecified complete-case cohorts without imputing missing values.

Robustness to reverse causation, acute inflammation, extreme exposure values, exposure categorization, and FI item completeness was examined in sensitivity analyses. Analyses were repeated after excluding participants with CMM at the first post-index assessment, CRP > 10 mg/L, or CTI-FI or cumCTI-FI values outside their respective mean ± 3 SD. Additional analyses replaced quartiles with tertiles and permitted FI calculation when at least 23 of 28 items were available. Deaths preceding incident CMM were incorporated into Fine–Gray competing-risk models. E-values were used to gauge robustness to unmeasured confounding. A two-sided α level of 0.05 was used for statistical inference.

Machine learning

Two binary prediction analyses were performed for incident CMM in the CTI-FI and cumCTI-FI cohorts. CHARLS was stratified into development (70%) and internal test (30%) samples, and the corresponding ELSA samples provided external validation. Each model included the relevant composite measure and the prespecified covariates. CatBoost, Extra Trees, RANGER, XGBoost, RPART, KKNN, NNET and SVM were tuned by stratified 10-fold cross-validation in CHARLS. XGBoost was retained because it had the highest mean cross-validated AUC across the two tasks, and task-specific Youden thresholds were derived from out-of-fold predictions. After internal testing, each XGBoost model was refitted in the full corresponding CHARLS cohort and evaluated in ELSA. Performance was assessed by ROC-AUC, PR-AUC, Brier score, calibration, classification metrics and decision-curve analysis. Predictor relevance was assessed with Boruta in CHARLS, whereas kernel SHAP was calculated in ELSA from separate joint-exposure XGBoost models trained in CHARLS. These models included CTI, FI, the corresponding composite measure and the prespecified covariates and were distinct from those used to evaluate predictive performance. Global importance was summarized by mean absolute SHAP values. Analyses used R 4.4.1 with mlr3verse, catboost, Boruta, kernelshap and shapviz.

Results

Participant selection

Figure 1 summarizes the formation of the analytical samples. CHARLS screening began with 17,705 participants at Wave 1. Exclusions comprised age < 45 years (n = 775), insufficient data to calculate baseline CTI (n = 5,716), missing data for at least one of the 28 FI items (n = 5,301), prevalent CMM or unascertainable baseline CMM status (n = 236), incomplete baseline covariates (n = 773), and unavailable follow-up CMM information (n = 117). The baseline CHARLS analysis therefore included 4,787 participants. ELSA screening began with 20,312 participants at Wave 2. Corresponding exclusions were age < 45 years (n = 10,714), an incalculable baseline CTI (n = 6,130), missing data for at least one FI item (n = 17), prevalent CMM or unascertainable baseline CMM status (n = 60), incomplete baseline covariates (n = 634), and unavailable follow-up CMM information (n = 436), yielding 2,321 participants for the baseline ELSA analysis. To construct the cumulative analysis cohorts, participants were further excluded if CTI could not be calculated at the landmark wave (CHARLS Wave 3: n = 1,426; ELSA Wave 4: n = 1,085), any FI item was missing (n = 751 and n = 4, respectively), CMM was prevalent or unascertainable at the landmark wave (n = 109 and n = 13), or subsequent CMM information was unavailable (n = 127 and n = 108). The final cumulative analysis included 2,374 CHARLS and 1,111 ELSA participants. Table S2 presents the percentage missing for each candidate covariate before complete-case exclusion.

Baseline characteristics of participants

Baseline characteristics by incident CMM status are shown in Table 1. The baseline cohorts comprised 4,787 participants in CHARLS (mean age, 58.2 years; 41.9% women) and 2,321 in ELSA (mean age, 63.3 years; 53.9% women); 467 (9.8%) and 160 (6.9%), respectively, developed CMM during follow-up. Across both cohorts, participants who developed CMM were characterized by older age, a greater prevalence of both hypertension and dyslipidemia, and higher BMI, SBP, FPG, TG, CRP, HbA1c, CTI, FI, and CTI-FI; HDL-C levels were lower in this group than among participants who remained free of CMM (all $P < 0.05$). Participants with incident CMM were less often married in CHARLS, whereas in ELSA they were more often men, had lower educational attainment, and were more likely to report never drinking (all $P < 0.05$). cumCTI-FI was higher among participants who developed CMM in both cohorts ($P < 0.001$).

Table 1
Baseline characteristics of participants according to incident CMM status

Variables	CHARLS				ELSA			
	Total (N = 4787)	No incident CMM (N = 4320)	Incident CMM (N = 467)	P	Total (N = 2321)	No incident CMM (N = 2161)	Incident CMM (N = 160)	P
Age, Mean ± SD	58.2 ± 8.8	58.1 ± 8.8	59.5 ± 8.2	< 0.001	63.3 ± 7.2	63.2 ± 7.1	65.0 ± 7.5	0.002
Sex, n (%)				0.318				< 0.001
Male	2779 (58.1)	2518 (58.3)	261 (55.9)		1070 (46.1)	969 (44.8)	101 (63.1)	
Female	2008 (41.9)	1802 (41.7)	206 (44.1)		1251 (53.9)	1192 (55.2)	59 (36.9)	
Marital status, n (%)				0.020				0.407
Married	4309 (90.0)	3903 (90.3)	406 (86.9)		1720 (74.1)	1597 (73.9)	123 (76.9)	
Others	478 (10.0)	417 (9.7)	61 (13.1)		601 (25.9)	564 (26.1)	37 (23.1)	
Education level, n (%)				0.600				0.015
Less than high school	4178 (87.3)	3774 (87.4)	404 (86.5)		879 (37.9)	804 (37.2)	75 (46.9)	
High school or above	609 (12.7)	546 (12.6)	63 (13.5)		1442 (62.1)	1357 (62.8)	85 (53.1)	
Smoke, n (%)				0.254				0.052
Never	2494 (52.1)	2239 (51.8)	255 (54.6)		908 (39.1)	857 (39.7)	51 (31.9)	

* Cumulative CTI-FI was summarized in the cumulative-exposure cohorts (CHARLS, N = 2,374; ELSA, N = 1,111); all other characteristics were summarized in the corresponding baseline cohorts.

Values are mean ± SD, median (IQR), or n (%), as appropriate. BMI, body mass index; CMM, cardiometabolic multimorbidity; CRP, C-reactive protein; CTI, C-reactive protein–triglyceride–glucose index; cumCTI-FI, cumulative C-reactive protein–triglyceride–glucose–frailty index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FI, frailty index; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Variables	CHARLS				ELSA			
	Total (N = 4787)	No incident CMM (N = 4320)	Incident CMM (N = 467)	P	Total (N = 2321)	No incident CMM (N = 2161)	Incident CMM (N = 160)	P
Others	2293 (47.9)	2081 (48.2)	212 (45.4)		1413 (60.9)	1304 (60.3)	109 (68.1)	
Alcohol drinking, n (%)				0.743				0.045
Never	2057 (43.0)	1853 (42.9)	204 (43.7)		169 (7.3)	151 (7.0)	18 (11.2)	
Others	2730 (57.0)	2467 (57.1)	263 (56.3)		2152 (92.7)	2010 (93.0)	142 (88.8)	
Hypertension, n (%)				< 0.001				< 0.001
No	2895 (60.5)	2718 (62.9)	177 (37.9)		1111 (47.9)	1069 (49.5)	42 (26.2)	
Yes	1892 (39.5)	1602 (37.1)	290 (62.1)		1210 (52.1)	1092 (50.5)	118 (73.8)	
Dyslipidemia, n (%)				< 0.001				0.003
No	4340 (90.7)	3986 (92.3)	354 (75.8)		1936 (83.4)	1816 (84.0)	120 (75.0)	
Yes	447 (9.3)	334 (7.7)	113 (24.2)		385 (16.6)	345 (16.0)	40 (25.0)	
BMI, Median (IQR)	23.0 (20.8, 25.6)	22.9 (20.8, 25.4)	24.7 (22.0, 27.2)	< 0.001	26.9 (24.5, 30.0)	26.8 (24.4, 29.8)	28.7 (26.1, 31.8)	< 0.001
SBP, Mean ± SD	128.8 ± 21.0	128.2 ± 20.8	134.3 ± 21.4	< 0.001	133.7 ± 18.0	133.4 ± 17.9	138.4 ± 18.8	< 0.001
DBP, Mean ± SD	75.5 ± 12.3	75.2 ± 12.3	78.0 ± 12.3	< 0.001	76.6 ± 10.5	76.5 ± 10.4	77.8 ± 11.2	0.112

* Cumulative CTI-FI was summarized in the cumulative-exposure cohorts (CHARLS, N = 2,374; ELSA, N = 1,111); all other characteristics were summarized in the corresponding baseline cohorts.

Values are mean ± SD, median (IQR), or n (%), as appropriate. BMI, body mass index; CMM, cardiometabolic multimorbidity; CRP, C-reactive protein; CTI, C-reactive protein–triglyceride–glucose index; cumCTI-FI, cumulative C-reactive protein–triglyceride–glucose–frailty index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FI, frailty index; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Variables	CHARLS				ELSA			
	Total (N = 4787)	No incident CMM (N = 4320)	Incident CMM (N = 467)	P	Total (N = 2321)	No incident CMM (N = 2161)	Incident CMM (N = 160)	P
TC, Mean ± SD	193.0 ± 37.4	192.3 ± 37.1	199.1 ± 39.1	< 0.001	234.3 ± 44.5	235.1 ± 44.5	224.5 ± 43.1	0.004
HDL-C, Mean ± SD	51.6 ± 15.4	52.1 ± 15.5	46.8 ± 14.1	< 0.001	60.7 ± 14.6	61.2 ± 14.6	54.4 ± 13.2	< 0.001
LDL-C, Mean ± SD	115.8 ± 34.4	115.2 ± 34.0	121.6 ± 37.7	< 0.001	146.8 ± 37.5	147.4 ± 37.5	138.4 ± 37.5	0.003
FPG, Mean ± SD	108.3 ± 33.8	106.9 ± 31.0	121.1 ± 51.8	< 0.001	89.7 ± 14.8	89.2 ± 13.9	97.1 ± 23.2	< 0.001
TG, Median (IQR)	103.5 (73.5, 152.2)	101.8 (71.7, 149.6)	124.8 (90.3, 183.2)	< 0.001	124.0 (88.6, 168.3)	115.1 (88.6, 168.3)	150.6 (106.3, 194.9)	< 0.001
CRP, Median (IQR)	1.0 (0.5, 2.1)	0.9 (0.5, 2.0)	1.3 (0.7, 2.6)	< 0.001	1.8 (0.8, 3.6)	1.7 (0.8, 3.5)	2.1 (1.1, 4.8)	0.002
HbA1c, Mean ± SD	5.2 ± 0.7	5.2 ± 0.7	5.6 ± 1.1	< 0.001	5.5 ± 0.5	5.4 ± 0.4	5.8 ± 0.7	< 0.001
CTI, Mean ± SD	8.7 ± 0.8	8.7 ± 0.8	9.1 ± 0.9	< 0.001	8.8 ± 0.7	8.8 ± 0.7	9.2 ± 0.7	< 0.001
FI, Median (IQR)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	< 0.001	0.1 (0.0, 0.2)	0.1 (0.0, 0.1)	0.1 (0.1, 0.2)	< 0.001
CTI-FI, Median (IQR)	0.9 (0.5, 1.6)	0.9 (0.5, 1.5)	1.3 (0.7, 2.2)	< 0.001	0.7 (0.4, 1.4)	0.7 (0.3, 1.3)	1.2 (0.5, 2.3)	< 0.001
cumCTI-FI, Median (IQR)*	2.8 (1.7, 4.6)	2.7 (1.7, 4.4)	4.1 (2.8, 6.4)	< 0.001	2.8 (1.5, 4.9)	2.7 (1.5, 4.6)	4.9 (2.3, 9.7)	< 0.001

* Cumulative CTI-FI was summarized in the cumulative-exposure cohorts (CHARLS, N = 2,374; ELSA, N = 1,111); all other characteristics were summarized in the corresponding baseline cohorts.

Values are mean ± SD, median (IQR), or n (%), as appropriate. BMI, body mass index; CMM, cardiometabolic multimorbidity; CRP, C-reactive protein; CTI, C-reactive protein–triglyceride–glucose index; cumCTI-FI, cumulative C-reactive protein–triglyceride–glucose–frailty index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FI, frailty index; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Incident CMM in relation to CTI-FI and cumCTI-FI

Adjusted cumulative incidence curves differed significantly across quartiles of CTI-FI and cumCTI-FI in both cohorts, with Q4 consistently showing the highest incidence throughout follow-up (overall $P < 0.001$ for all analyses; Fig. 2). Numbers at risk declined across all analyses, from approximately 1,200 to 836–1,015 in CHARLS and from 580 to 351–440 in ELSA, with similar reductions in the cumulative cohorts. CTI-FI and cumCTI-FI showed positive associations with incident CMM in each of the four models fitted in CHARLS and ELSA (Table 2). All adjusted GVIFs were < 5. Exposure-specific Schoenfeld tests showed no evidence of nonproportionality for CTI-FI or cumCTI-FI (Tables S3 and S4). In the fully adjusted models, the HR per 1-unit increase in CTI-FI was 1.48 (95% CI 1.37–1.60) in CHARLS and 1.31 (95% CI 1.17–1.47) in ELSA. For cumCTI-FI, the corresponding HRs were 1.17 (95% CI 1.12–1.23) and 1.08 (95% CI 1.03–1.13), respectively. Q4-versus-Q1 HRs for CTI-FI were 3.40 (95% CI 2.48–4.66) in CHARLS and 2.62 (95% CI 1.61–4.25) in ELSA; the corresponding cumCTI-FI HRs were 3.99 (95% CI 2.33–6.84) and 4.91 (95% CI 1.83–13.15), respectively. All linear trend tests were significant (P for trend < 0.001). Restricted cubic spline analyses showed increasing CMM risk with higher CTI-FI and cumCTI-FI in both cohorts (Fig. 3). Nonlinearity was detected for CTI-FI and cumCTI-FI in CHARLS ($P = 0.005$ and $P < 0.001$, respectively) and for cumCTI-FI in ELSA ($P = 0.047$), whereas the CTI-FI association in ELSA did not depart from linearity ($P = 0.280$).

Table 2
Cox regression of CTI-FI and cumulative CTI-FI with incident CMM

Variable	Model 1 HR (95% CI)	P	Model 2 HR (95% CI)	P	Model 3 HR (95% CI)	P	Model 4 HR (95% CI)	P
CHARLS								
CTI-FI	1.53 (1.42–1.64)	< 0.001	1.55 (1.44–1.67)	< 0.001	1.49 (1.38–1.60)	< 0.001	1.48 (1.37–1.60)	< 0.001
CTI-FI Quartiles								
Q1	Reference		Reference		Reference		Reference	
Q2	1.88 (1.35–2.62)	< 0.001	1.97 (1.41–2.75)	< 0.001	1.95 (1.39–2.71)	< 0.001	1.92 (1.37–2.68)	< 0.001
Q3	2.38 (1.73–3.29)	< 0.001	2.46 (1.78–3.40)	< 0.001	2.33 (1.68–3.22)	< 0.001	2.35 (1.70–3.25)	< 0.001
Q4	3.73 (2.74–5.08)	< 0.001	3.94 (2.88–5.39)	< 0.001	3.40 (2.48–4.66)	< 0.001	3.40 (2.48–4.66)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001		< 0.001
cumCTI-FI	1.18 (1.13–1.24)	< 0.001	1.20 (1.14–1.25)	< 0.001	1.17 (1.12–1.23)	< 0.001	1.17 (1.12–1.23)	< 0.001
cumCTI-FI Quartiles								
Q1	Reference		Reference		Reference		Reference	
Q2	1.41 (0.77–2.57)	0.267	1.56 (0.85–2.86)	0.153	1.44 (0.79–2.65)	0.235	1.34 (0.73–2.47)	0.341
Q3	2.91 (1.70–	< 0.001	3.24 (1.87–	< 0.001	2.93 (1.69–	< 0.001	2.96 (1.71–	< 0.001

Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, marital status, educational level, smoking status, BMI, and drinking status; Model 3 additionally adjusted for history of hypertension and dyslipidemia. Model 4 additionally adjusted for SBP, DBP, TC, HDL-C, and LDL-C. CTI-FI analyses used the baseline cohort, whereas cumCTI-FI analyses used the cumulative-exposure cohort. cumCTI-FI, cumulative C-reactive protein–triglyceride–glucose–frailty index; HR, hazard ratio; CI, confidence interval; CMM, cardiometabolic multimorbidity; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Variable	Model 1 HR (95% CI)	P	Model 2 HR (95% CI)	P	Model 3 HR (95% CI)	P	Model 4 HR (95% CI)	P
	4.99)		5.60)		5.06)		5.12)	
Q4	4.20 (2.48–7.11)	< 0.001	4.65 (2.71–7.96)	< 0.001	3.91 (2.28–6.69)	< 0.001	3.99 (2.33–6.84)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001		< 0.001
ELSA								
CTI-FI	1.49 (1.35–1.64)	< 0.001	1.37 (1.23–1.54)	< 0.001	1.33 (1.19–1.49)	< 0.001	1.31 (1.17–1.47)	< 0.001
CTI-FI Quartiles								
Q1	Reference		Reference		Reference		Reference	
Q2	1.19 (0.70–2.03)	0.523	1.19 (0.70–2.03)	0.520	1.17 (0.68–1.99)	0.570	1.16 (0.68–1.97)	0.597
Q3	1.25 (0.73–2.12)	0.416	1.14 (0.67–1.95)	0.626	1.12 (0.65–1.90)	0.689	1.04 (0.61–1.78)	0.878
Q4	3.72 (2.33–5.94)	< 0.001	2.85 (1.76–4.63)	< 0.001	2.69 (1.66–4.36)	< 0.001	2.62 (1.61–4.25)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001		< 0.001
cumCTI-FI	1.12 (1.08–1.17)	< 0.001	1.09 (1.04–1.15)	< 0.001	1.09 (1.04–1.14)	< 0.001	1.08 (1.03–1.13)	0.003
cumCTI-FI Quartiles								
Q1	Reference		Reference		Reference		Reference	

Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, marital status, educational level, smoking status, BMI, and drinking status; Model 3 additionally adjusted for history of hypertension and dyslipidemia. Model 4 additionally adjusted for SBP, DBP, TC, HDL-C, and LDL-C. CTI-FI analyses used the baseline cohort, whereas cumCTI-FI analyses used the cumulative-exposure cohort. cumCTI-FI, cumulative C-reactive protein–triglyceride–glucose–frailty index; HR, hazard ratio; CI, confidence interval; CMM, cardiometabolic multimorbidity; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Variable	Model 1 HR (95% CI)	P	Model 2 HR (95% CI)	P	Model 3 HR (95% CI)	P	Model 4 HR (95% CI)	P
Q2	2.39 (0.84–6.80)	0.102	2.29 (0.80–6.53)	0.122	2.30 (0.81–6.56)	0.119	2.43 (0.85–6.93)	0.098
Q3	2.34 (0.81–6.77)	0.119	1.95 (0.67–5.72)	0.222	1.93 (0.66–5.65)	0.231	1.75 (0.59–5.18)	0.308
Q4	7.68 (2.94–20.10)	< 0.001	5.57 (2.08–14.92)	< 0.001	5.31 (1.98–14.21)	< 0.001	4.91 (1.83–13.15)	0.002
P for trend		< 0.001		< 0.001		< 0.001		< 0.001

Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, marital status, educational level, smoking status, BMI, and drinking status; Model 3 additionally adjusted for history of hypertension and dyslipidemia. Model 4 additionally adjusted for SBP, DBP, TC, HDL-C, and LDL-C. CTI-FI analyses used the baseline cohort, whereas cumCTI-FI analyses used the cumulative-exposure cohort. cumCTI-FI, cumulative C-reactive protein–triglyceride–glucose–frailty index; HR, hazard ratio; CI, confidence interval; CMM, cardiometabolic multimorbidity; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Subgroup analyses

Across most subgroups, CMM risk increased with higher CTI-FI and cumCTI-FI in both continuous and quartile analyses (Table 3; Fig. 4; Tables S8 and S9). In the continuous-exposure analyses in CHARLS, the association between CTI-FI and CMM was stronger among participants aged < 60 years, married participants, and those without hypertension (P for interaction = 0.002, 0.008, and 0.003, respectively), whereas no significant interaction was observed for cumCTI-FI. In the quartile-based analyses, age also modified the association between cumCTI-FI and CMM in CHARLS (P for interaction = 0.014; Table S9). No significant interactions were observed in ELSA for either CTI-FI or cumCTI-FI (all P for interaction > 0.05).

Table 3
Subgroup analysis of the association between CTI-FI, cumulative CTI-FI and incident CMM

Subgroup	Variable	CHARLS			ELSA		
		CTI-FI	cumCTI-FI	P for interaction	CTI-FI	cumCTI-FI	P for interaction
Age	< 60	1.71 (1.54–1.90) P < 0.001	1.22 (1.15–1.31) P < 0.001	CTI-FI: 0.002 cumCTI-FI: 0.403	1.19 (0.96–1.47) P = 0.108	1.07 (0.97–1.17) P = 0.155	CTI-FI: 0.637 cumCTI-FI: 0.317
	≥ 60	1.32 (1.19–1.47) P < 0.001	1.14 (1.07–1.21) P < 0.001		1.37 (1.19–1.57) P < 0.001	1.10 (1.03–1.17) P = 0.004	
Sex	Male	1.47 (1.32–1.64) P < 0.001	1.23 (1.15–1.32) P < 0.001	CTI-FI: 0.700 cumCTI-FI: 0.133	1.34 (1.16–1.54) P < 0.001	1.04 (0.97–1.12) P = 0.250	CTI-FI: 0.806 cumCTI-FI: 0.064
	Female	1.49 (1.35–1.66) P < 0.001	1.14 (1.07–1.21) P < 0.001		1.35 (1.10–1.64) P = 0.003	1.18 (1.08–1.28) P < 0.001	
BMI (kg/m²)	< 25	1.44 (1.30–1.60) P < 0.001	1.19 (1.11–1.27) P < 0.001	CTI-FI: 0.765 cumCTI-FI: 0.518	1.28 (0.86–1.92) P = 0.221	1.01 (0.81–1.26) P = 0.906	CTI-FI: 0.574 cumCTI-FI: 0.298
	≥ 25	1.53 (1.37–1.72) P < 0.001	1.16 (1.09–1.24) P < 0.001		1.35 (1.21–1.52) P < 0.001	1.10 (1.04–1.16) P < 0.001	

Adjusted hazard ratios and 95% confidence intervals are reported per 1-unit increase in CTI-FI or cumCTI-FI. Models included age, sex, marital status, educational level, smoking status, drinking status, BMI, hypertension, dyslipidemia, SBP, DBP, TC, HDL-C, and LDL-C; the corresponding stratifying variable was omitted from each model. cumCTI-FI, cumulative CTI-FI; HR, hazard ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Subgroup	Variable	CHARLS			ELSA		
		CTI-FI	cumCTI-FI	P for interaction	CTI-FI	cumCTI-FI	P for interaction
Marital status	Married	1.56 (1.44–1.70) P < 0.001	1.19 (1.13–1.25) P < 0.001	CTI-FI: 0.008 cumCTI-FI: 0.359	1.37 (1.20–1.57) P < 0.001	1.09 (1.02–1.16) P = 0.012	CTI-FI: 0.237 cumCTI-FI: 0.617
	Others	1.20 (0.96–1.50) P = 0.103	1.17 (1.01–1.37) P = 0.038		1.25 (1.00–1.56) P = 0.051	1.11 (1.01–1.22) P = 0.037	
Smoke status	Never	1.48 (1.34–1.63) P < 0.001	1.18 (1.11–1.25) P < 0.001	CTI-FI: 0.842 cumCTI-FI: 0.626	1.35 (1.07–1.70) P = 0.012	1.22 (1.09–1.36) P < 0.001	CTI-FI: 0.613 cumCTI-FI: 0.457
	Others	1.49 (1.32–1.69) P < 0.001	1.17 (1.09–1.27) P < 0.001		1.32 (1.16–1.52) P < 0.001	1.08 (1.01–1.16) P = 0.020	
Drink status	Never	1.43 (1.28–1.60) P < 0.001	1.19 (1.12–1.27) P < 0.001	CTI-FI: 0.176 cumCTI-FI: 0.817	1.38 (0.96–1.98) P = 0.079	1.22 (0.93–1.60) P = 0.142	CTI-FI: 0.131 cumCTI-FI: 0.194
	Others	1.57 (1.41–1.75) P < 0.001	1.18 (1.10–1.26) P < 0.001		1.35 (1.19–1.53) P < 0.001	1.10 (1.04–1.16) P < 0.001	
Hypertension	No	1.76 (1.56–2.00)	1.23 (1.13–1.33)	CTI-FI: 0.003	1.27 (0.95–1.70)	1.03 (0.90–1.17)	CTI-FI: 0.921

Adjusted hazard ratios and 95% confidence intervals are reported per 1-unit increase in CTI-FI or cumCTI-FI. Models included age, sex, marital status, educational level, smoking status, drinking status, BMI, hypertension, dyslipidemia, SBP, DBP, TC, HDL-C, and LDL-C; the corresponding stratifying variable was omitted from each model. cumCTI-FI, cumulative CTI-FI; HR, hazard ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Subgroup	Variable	CHARLS			ELSA		
		CTI-FI	cumCTI-FI	P for interaction	CTI-FI	cumCTI-FI	P for interaction
		P < 0.001	P < 0.001	cumCTI-FI: 0.586	P = 0.102	P = 0.695	cumCTI-FI: 0.411
	Yes	1.37 (1.24–1.51) P < 0.001	1.15 (1.09–1.22) P < 0.001		1.31 (1.16–1.48) P < 0.001	1.10 (1.04–1.16) P = 0.002	
Dyslipidemia	No	1.48 (1.36–1.61) P < 0.001	1.19 (1.14–1.26) P < 0.001	CTI-FI: 0.482 cumCTI-FI: 0.564	1.33 (1.17–1.52) P < 0.001	1.10 (1.04–1.17) P < 0.001	CTI-FI: 0.779 cumCTI-FI: 0.209
	Yes	1.55 (1.30–1.84) P < 0.001	1.15 (1.04–1.28) P = 0.007		1.29 (0.99–1.67) P = 0.056	0.99 (0.84–1.16) P = 0.864	

Adjusted hazard ratios and 95% confidence intervals are reported per 1-unit increase in CTI-FI or cumCTI-FI. Models included age, sex, marital status, educational level, smoking status, drinking status, BMI, hypertension, dyslipidemia, SBP, DBP, TC, HDL-C, and LDL-C; the corresponding stratifying variable was omitted from each model. cumCTI-FI, cumulative CTI-FI; HR, hazard ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Incremental predictive value analysis

The conventional risk-factor model yielded C-statistics of 0.723 in CHARLS and 0.745 in ELSA; adding CTI-FI increased these values to 0.759 and 0.767, respectively (Table 4; Fig. 5A–B). With cumCTI-FI, the corresponding C-statistics were 0.763 and 0.768. CTI-FI showed higher discrimination than CTI or FI alone in both cohorts. CTI-FI and cumCTI-FI significantly improved continuous NRI in CHARLS (0.40 and 0.42) and ELSA (0.35 and 0.32; all $P < 0.05$). IDI gains were significant in CHARLS (0.02 and 0.03; both $P < 0.001$) but not in ELSA (Table 4). Overall, cumCTI-FI provided the greatest improvement in discrimination over the conventional risk-factor model in both cohorts.

Table 4
Incremental predictive performance of CTI-FI measures beyond conventional risk factors

Model	C-Statistic (95% CI)	*P*	NRI (Continuous) (95% CI)	*P*	IDI (95% CI)	*P*
CHARLS (n = 2374; events = 172)						
Conventional risk-factor model	72.3% (68.2%–76.5%)	Ref	Ref	Ref	Ref	Ref
+ FI	75.7% (71.9%–79.5%)	0.001	0.37 (0.22–0.52)	< 0.001	0.02 (0.01–0.03)	< 0.001
+ CTI	72.8% (68.7%–76.8%)	0.130	0.12 (-0.03–0.27)	0.122	0.00 (-0.00–0.00)	0.623
+ CTI-FI	75.9% (72.1%–79.7%)	< 0.001	0.40 (0.24–0.55)	< 0.001	0.02 (0.01–0.03)	< 0.001
+ cumCTI-FI	76.3% (72.5%–80.1%)	< 0.001	0.42 (0.25–0.57)	< 0.001	0.03 (0.01–0.04)	< 0.001
ELSA (n = 1111; events = 59)						
Conventional risk-factor model	74.5% (68.5%–80.6%)	Ref	Ref	Ref	Ref	Ref
+ FI	76.6% (70.5%–82.7%)	0.052	0.38 (0.12–0.64)	0.004	0.01 (-0.00–0.02)	0.069
+ CTI	75.0% (69.1%–80.9%)	0.595	0.11 (-0.13–0.38)	0.419	0.00 (-0.01–0.01)	0.796
+ CTI-FI	76.7% (70.7%–82.8%)	0.043	0.35 (0.08–0.61)	0.010	0.01 (-0.00–0.02)	0.065

The conventional risk-factor model included age, sex, marital status, educational level, smoking status, drinking status, hypertension, dyslipidemia, BMI, SBP, DBP, HDL-C, LDL-C, and TC. FI, CTI, CTI-FI, and cumCTI-FI were added separately to the conventional risk-factor model, and each extended model was compared with that model. P values for differences in C-statistics were obtained using DeLong tests; 95% CIs for continuous NRI and IDI were estimated from 1,000 bootstrap resamples. BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; IDI, integrated discrimination improvement; LDL-C, low-density lipoprotein cholesterol; NRI, net reclassification improvement; Ref, reference; SBP, systolic blood pressure; TC, total cholesterol.

Model	C-Statistic (95% CI)	*P*	NRI (Continuous) (95% CI)	*P*	IDI (95% CI)	*P*
+ cumCTI-FI	76.8% (70.7%–82.9%)	0.033	0.32 (0.06–0.57)	0.017	0.01 (-0.00–0.03)	0.082

The conventional risk-factor model included age, sex, marital status, educational level, smoking status, drinking status, hypertension, dyslipidemia, BMI, SBP, DBP, HDL-C, LDL-C, and TC. FI, CTI, CTI-FI, and cumCTI-FI were added separately to the conventional risk-factor model, and each extended model was compared with that model. P values for differences in C-statistics were obtained using DeLong tests; 95% CIs for continuous NRI and IDI were estimated from 1,000 bootstrap resamples. BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; IDI, integrated discrimination improvement; LDL-C, low-density lipoprotein cholesterol; NRI, net reclassification improvement; Ref, reference; SBP, systolic blood pressure; TC, total cholesterol.

Development and validation of predictive models

Cross-validated AUCs among the eight candidate algorithms ranged from 0.615 to 0.706 for the CTI-FI task and from 0.525 to 0.700 for the cumCTI-FI task (Table S5). XGBoost achieved AUCs of 0.701 and 0.700, respectively, and the highest mean AUC across both tasks; it was therefore selected as the common algorithm. External ROC and decision curves for the eight algorithms in the cumulative task are shown in Figure S1. In the CHARLS internal test sets, AUCs were 0.725 (95% CI 0.680–0.769) for the CTI-FI model and 0.760 (95% CI 0.692–0.828) for the cumCTI-FI model. The corresponding accuracies were 0.711 and 0.773, and Brier scores were 0.081 and 0.063. After refitting in the full CHARLS cohorts, external evaluation in ELSA yielded AUCs of 0.689 (95% CI 0.649–0.729) and 0.695 (95% CI 0.629–0.761), accuracies of 0.547 and 0.576, and Brier scores of 0.069 and 0.058, respectively (Table S6). At the thresholds fixed in CHARLS, external sensitivities were 0.744 and 0.763, with negative predictive values of 0.966 and 0.977. Calibration was close to ideal internally but attenuated in ELSA (Figure S4), whereas both XGBoost models yielded positive net benefit across the displayed external-validation threshold ranges (Figure S2). Boruta analysis in the CHARLS development cohorts confirmed CTI-FI and cumCTI-FI as important predictors for their respective prediction tasks (Figure S3). SHAP analyses ranked CTI-FI and cumCTI-FI as the leading predictors in their respective joint-exposure models, ahead of CTI and FI (Fig. 5).

Sensitivity analyses

The primary associations remained consistent across all sensitivity analyses. When death before CMM was treated as a competing event in Fine–Gray models, CTI-FI and cumCTI-FI remained significantly associated with CMM in both cohorts. sHRs ranged from 1.07 to 1.42 when the indices were modeled continuously and from 2.14 to 4.69 for Q4 versus Q1 (Table S7). After excluding participants with CMM identified at the first post-index assessment, associations remained significant for CTI-FI (HR = 1.43 in CHARLS and 1.27 in ELSA) and cumCTI-FI (HR = 1.18 and 1.07, respectively). Separate analyses

excluding participants with CRP > 10 mg/L or exposure values outside their respective mean ± 3 SD yielded results consistent with the primary models. Replacing quartiles with cohort-specific tertiles preserved the exposure–response gradients, with HRs for T3 versus T1 of 2.71 and 2.01 for CTI-FI and 3.47 and 3.17 for cumCTI-FI in CHARLS and ELSA, respectively (all P for trend < 0.001). Recalculating FI when at least 23 of 28 items (≥ 80%) were available yielded comparable estimates, indicating that the findings were not dependent on complete FI item ascertainment (Tables S10–S13). Finally, E-values for Q4 versus Q1 ranged from 4.68 to 9.29, with lower-bound values of 2.60–4.40, supporting robustness to unmeasured confounding (Table S14).

Discussion

Our study comprehensively evaluated the association of the CTI-FI composite index with incident CMM and its incremental predictive value. Across two nationally representative prospective cohorts from China and England, higher CTI-FI and cumCTI-FI were associated with increasing incident CMM risk, with significant trends across quartiles in both cohorts, and these associations persisted after multivariable adjustment. Dose–response patterns differed between cohorts, with nonlinearity observed for CTI-FI and cumCTI-FI in CHARLS and for cumCTI-FI in ELSA. Subgroup variation was more evident in CHARLS, whereas sensitivity analyses supported the robustness of the primary associations. Adding CTI-FI measures to conventional risk factors improved discrimination and reclassification in both cohorts, with cumCTI-FI providing the greatest incremental value. XGBoost achieved the highest mean cross-validated AUC across the two prediction tasks, and the resulting models retained discrimination in ELSA without updating, while SHAP analyses ranked CTI-FI and cumCTI-FI among the leading predictors in their respective models. Together, these findings highlight the clinical relevance of CTI-FI and underscore the significant value for CMM risk prediction, providing important clinical evidence for the early identification and targeted prevention of CMM among middle-aged and older adults.

The observed associations of CTI-FI with incident CMM are biologically and epidemiologically plausible because CTI and FI capture distinct but complementary dimensions of cardiometabolic vulnerability. Previous studies have consistently linked CTI and related inflammatory–metabolic indices to CMM. Yue et al. examined CTI and its central-obesity-modified derivatives in two prospective cohorts and reported positive associations with incident CMM[24]. This evidence was subsequently extended by Li et al., who evaluated cumulative inflammatory exposure and similarly observed an increased risk of CMM[25]. Together, these studies highlight CTI as an integrated marker of inflammatory and metabolic risk. Additionally, FI captures accumulated health deficits and declining physiological reserve. Longitudinal and pooled evidence has linked frailty with incident cardiovascular disease and mortality[26–28]. A cross-nationally harmonized analysis further showed that frailty increased progressively with the accumulation of cardiometabolic conditions[29], suggesting that CMM may also aggravate frailty once established. A national cohort study also reported a graded association between FI and incident cardiovascular events, including heart disease and stroke[30]. Accumulating prospective evidence indicates that CTI and FI capture complementary dimensions of susceptibility to cardiovascular, cerebrovascular, and metabolic disease, encompassing inflammatory–metabolic dysfunction and frailty-

related loss of physiological reserve. Taken together, these findings support the joint consideration of inflammatory–metabolic dysfunction and frailty-related vulnerability in the assessment of incident CMM.

Mechanistically, CTI-FI may capture a bidirectional interplay between inflammatory–metabolic dysfunction and frailty-related multisystem dysregulation. CTI incorporates C-reactive protein and a triglyceride–glucose signal of insulin resistance[31], which are linked to endothelial dysfunction, oxidative stress, atherogenic lipid handling, and impaired glucose homeostasis[32, 33]. Persistent inflammatory and metabolic stress may also promote loss of physiological reserve: in the Cardiovascular Health Study, higher insulin resistance and C-reactive protein levels predicted incident frailty[34], while chronic inflammation can drive catabolism, mitochondrial dysfunction, and impaired homeostatic signaling[35]. Frailty reflects the cumulative and nonlinear burden of dysregulation across multiple physiological systems[36]. Conversely, the muscle loss and inflammatory burden that accompany frailty may sustain this adverse milieu: lower limb and appendicular muscle mass predicted subsequent insulin resistance in nondiabetic older adults, and frail older adults exhibit higher circulating CRP, IL-6, and TNF-α levels[37, 38]. This self-reinforcing state may provide a common pathological substrate for the co-occurrence of heart disease, stroke, and diabetes. The convergence of these processes provides a biological basis for the combined assessment of CTI and FI in relation to CMM.

In this study, CTI-FI was constructed using a multiplicative model that integrates CTI, reflecting inflammatory–metabolic dysfunction, with FI, reflecting accumulated health deficits and declining physiological reserve. By emphasizing their concurrent elevation, this formulation captures the compounded burden of inflammatory–metabolic injury and frailty-related vulnerability rather than either domain in isolation. Previous studies have likewise shown that incorporating atherogenic or inflammatory burden alongside frailty can better characterize cardiovascular vulnerability[39, 40]. Consistent with these findings, CTI-FI was positively associated with incident CMM in both cohorts and outperformed CTI or FI alone in discriminating CMM risk. By extending prior CTI-FI research from stroke to incident CMM across nationally representative Chinese and English cohorts[17], the present study establishes CTI-FI as a multidimensional marker for cross-population CMM risk assessment and risk-stratified prevention.

Cumulative CTI-FI served as a time-integrated measure of inflammation, metabolic dysregulation and biological aging across the exposure interval. Compared with CTI-FI, cumCTI-FI showed a stronger risk gradient and numerically higher incremental discrimination, suggesting that the accumulated burden of this combined risk state may provide more information than a single assessment. Longitudinal studies of CTI have likewise shown that cumulative exposure and changing CTI levels are associated with subsequent CMM, cardiovascular disease and stroke[14, 41, 42]. These findings emphasize the relevance of repeated assessment for identifying individuals with a sustained burden of inflammatory–metabolic dysfunction and frailty-related vulnerability.

The differences in effect magnitude and dose–response shape between the Chinese and English cohorts may reflect population-specific expression of the components captured by CTI-FI[43, 44]. Similar

findings have been reported for other CTI-derived composite indices: a recent China–England study observed weaker but directionally concordant associations with CMM in ELSA, with more evident predictive improvement in CHARLS[24]. The between-cohort variation may reflect differences in underlying cardiometabolic risk, lifestyle patterns, measurement procedures, and healthcare context. Differences in the distribution of inflammatory–metabolic burden and frailty may therefore influence the apparent risk gradient of CTI-FI across cohorts[45]. Nevertheless, CTI-FI and cumCTI-FI were positively associated with incident CMM in both Chinese and English middle-aged and older adults, supporting the relevance of this integrated measure across these settings.

The incremental prediction and machine-learning analyses further support CTI-FI as a multidimensional risk-stratification construct rather than an isolated biomarker[46]. By combining inflammatory–metabolic dysfunction with accumulated frailty, CTI-FI may capture a broader pattern of cardiometabolic vulnerability than conventional risk factors alone; the stronger performance of cumCTI-FI is compatible with the relevance of sustained risk burden[47]. This interpretation accords with multicohort cardiovascular prediction studies that have incorporated functional, inflammatory and obesity-related domains to characterize risk across heterogeneous populations[48, 49]. The prominence of CTI-FI in the SHAP profiles when CTI, FI and established covariates were considered jointly further supports its predictive contribution. The XGBoost models retained discrimination in ELSA without updating, although their calibration was less favorable than in CHARLS. This attenuation may reflect differences between the cohorts in baseline risk, measurement procedures and harmonization, and healthcare context[50–52]. Thus, CTI-FI-informed models support cross-population CMM risk stratification, with recalibration and prospective evaluation needed before clinical implementation[53, 54].

This study has several strengths. First, the use of two nationally representative prospective cohorts from China and England enabled the findings to be examined across different population and healthcare contexts, strengthening assessment of their consistency and generalizability beyond a single cohort. Second, by integrating inflammatory–metabolic dysfunction with accumulated physiological vulnerability, CTI-FI captures complementary dimensions of CMM risk that may be incompletely represented by CTI or FI alone. Third, evaluating both CTI-FI and cumCTI-FI provided information on current risk status and sustained exposure burden, while the complementary analytical approaches strengthened the robustness of the findings. Finally, evaluating the XGBoost models in ELSA without updating provided an independent assessment of model transportability, and the use of routinely collected biomarkers and health-deficit items supports the potential feasibility of CTI-FI-based risk stratification.

Notwithstanding these strengths, several limitations warrant consideration. The observational design precludes causal inference, and residual confounding cannot be excluded. Heart disease and stroke were largely based on self-reported physician diagnoses, which may have caused outcome misclassification. CMM was identified at discrete survey waves, and cumCTI-FI was derived from only two assessments, limiting temporal resolution. Complete-case analyses may have introduced selection bias. Differences between cohorts in participant characteristics, measurement procedures, follow-up

and healthcare context may have contributed to variation in effect estimates and calibration; parallel rather than pooled analyses also limited formal comparison. The ELSA cumulative analysis included only 59 events, and models were evaluated without refitting or recalibration. Larger studies with adjudicated outcomes, repeated measurements and prospective impact assessment are needed before clinical implementation.

Conclusions

Across Chinese and English middle-aged and older populations, higher CTI-FI levels were associated with an increased risk of incident CMM. CTI-FI assessment improved CMM risk prediction beyond conventional risk factors, with accumulated CTI-FI burden providing the greatest incremental value. These findings support CTI-FI as a multidimensional marker for cross-population risk stratification and targeted prevention of CMM.

Abbreviations

AUC
area under the curve
BMI
body mass index
CHARLS
China Health and Retirement Longitudinal Study
CI
confidence interval
CMM
cardiometabolic multimorbidity
CRP
C-reactive protein
CTI
C-reactive protein–triglyceride–glucose index
CTI-FI
C-reactive protein–triglyceride–glucose–frailty index
cumCTI-FI
cumulative C-reactive protein–triglyceride–glucose–frailty index
DBP
diastolic blood pressure
ELSA
English Longitudinal Study of Ageing
FI
frailty index
FPG

fasting plasma glucose
GVIF
generalized variance inflation factor
HbA1c
glycated hemoglobin A1c
HDL-C
high-density lipoprotein cholesterol
HR
hazard ratio
IDI
integrated discrimination improvement
IQR
interquartile range
KKNN
kernel k-nearest neighbors
LDL-C
low-density lipoprotein cholesterol
NNET
neural network
NRI
net reclassification improvement
PR-AUC
area under the precision–recall curve
RANGER
random forest algorithm
ROC-AUC
area under the receiver operating characteristic curve
RPART
recursive partitioning and regression trees
SBP
systolic blood pressure
SD
standard deviation
SHAP
Shapley additive explanations
sHR
subdistribution hazard ratio
SVM
support vector machine
TC

total cholesterol
TG
triglycerides
XGBoost
extreme gradient boosting

Declarations

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

CHARLS was approved by the Peking University Biomedical Ethics Review Committee (IRB00001052-11015), and ELSA by the London Multicentre Research Ethics Committee (MREC/01/2/91). All participants provided written informed consent. The present study was a secondary analysis of deidentified data from the two cohorts and was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Clinical trial number

Not applicable.

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Author Contribution

HY conceived the study, developed the methodology, curated and analyzed the data, performed the statistical and machine-learning analyses, prepared the figures and tables, and drafted the manuscript. LL contributed to the methodology, validation, interpretation of the results, and critical revision of the

manuscript. MW conceived and supervised the study, contributed to the interpretation of the results, and critically revised the manuscript. All authors read and approved the final manuscript.

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Data Availability

The datasets analyzed during the current study are available to registered researchers from the CHARLS repository (https://charls.pku.edu.cn/en/) and the ELSA repository through the UK Data Service (https://www.elsa-project.ac.uk/), subject to the respective registration and data-use requirements.

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Figures

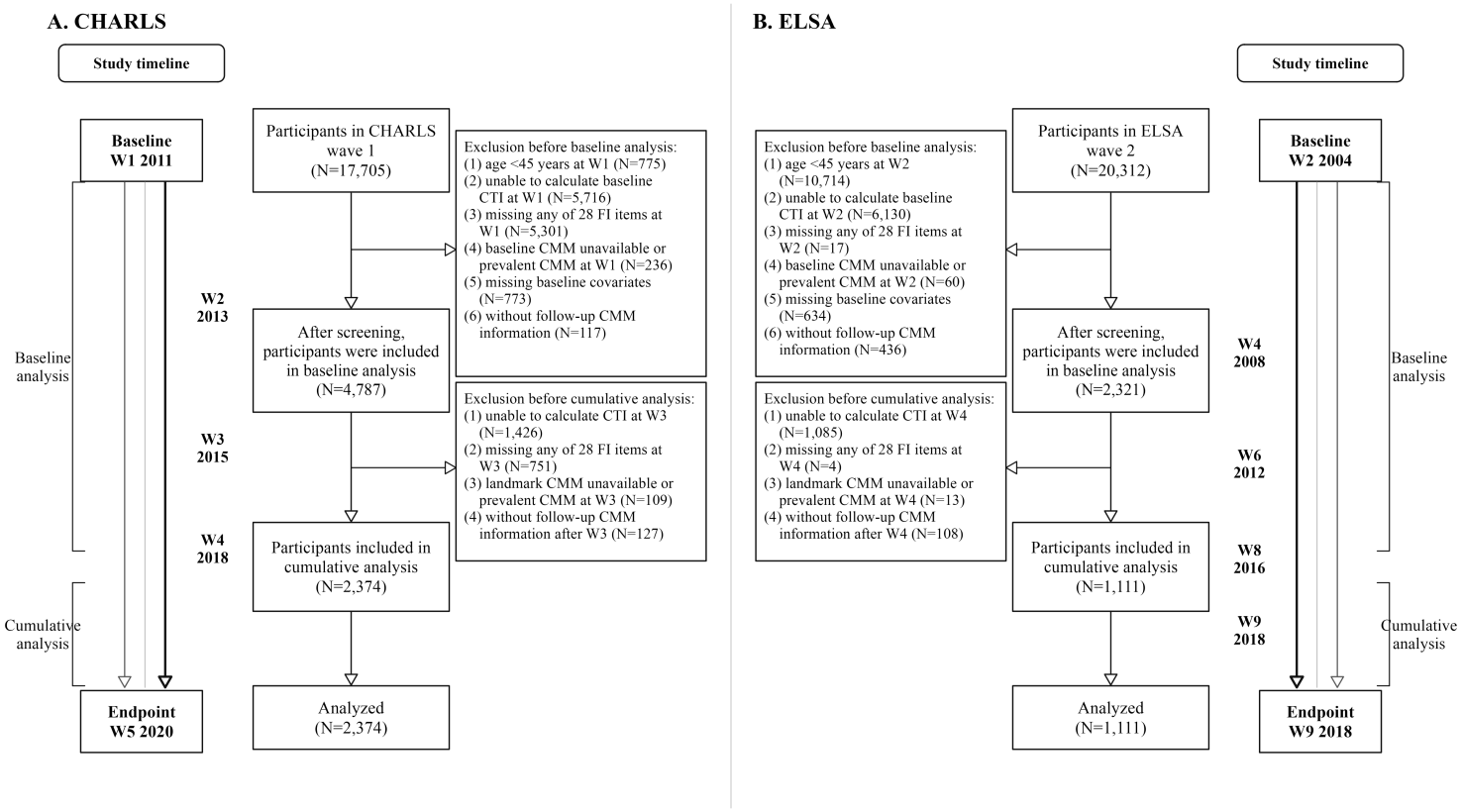


Figure 1

Participant screening flow in CHARLS and ELSA. Baseline and cumulative-exposure cohorts were constructed separately in each study. The cumulative analyses used the repeat-exposure wave as the landmark and included only participants with evaluable post-landmark CMM follow-up.

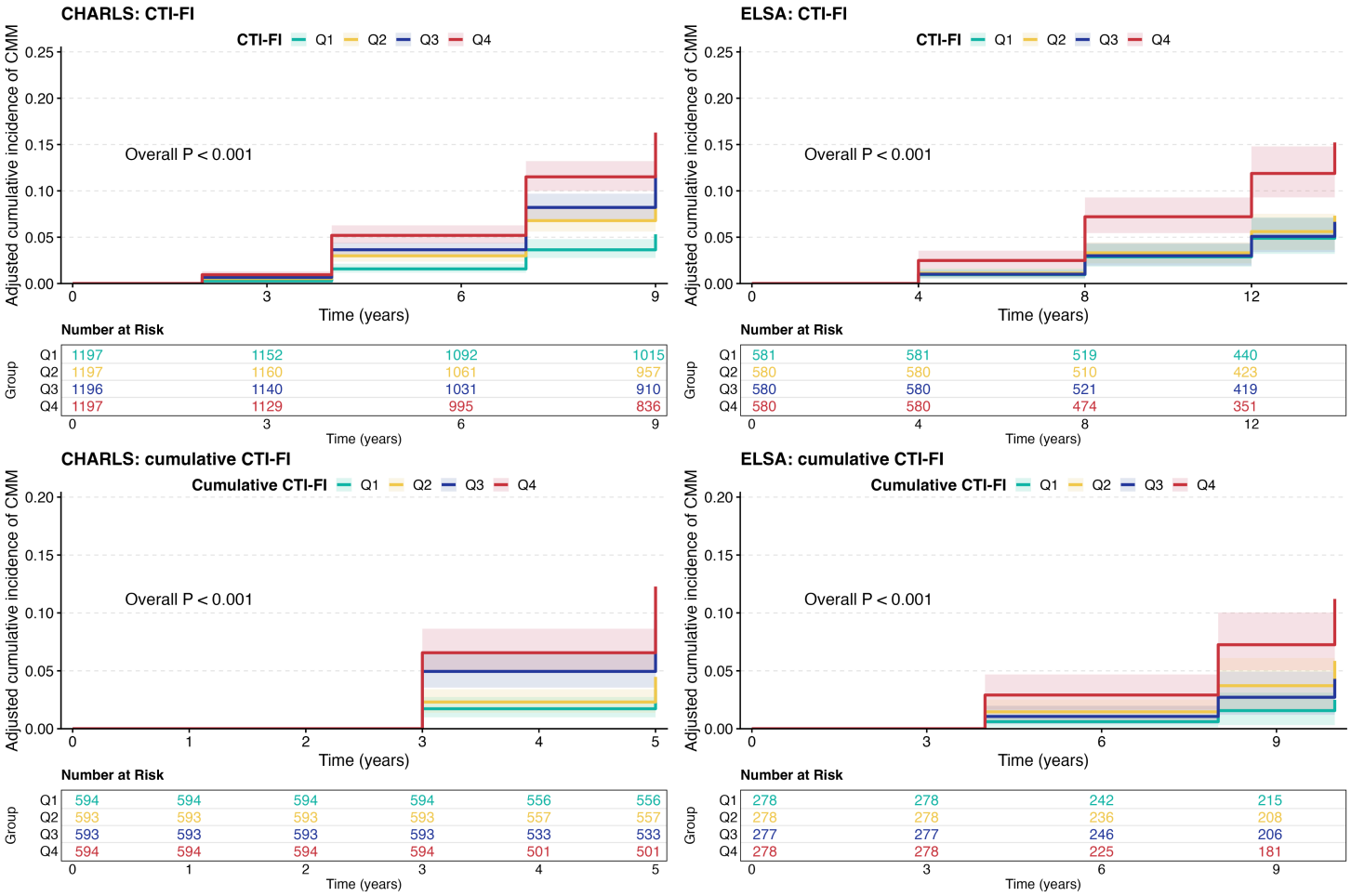


Figure 2

Adjusted cumulative CMM incidence curves across baseline and cumulative CTI-FI quartiles in CHARLS and ELSA. Curves were derived from multivariable Cox models adjusted for sociodemographic, lifestyle, clinical, and biochemical covariates; shaded areas indicate bootstrapped 95% confidence intervals, and observed numbers at risk are shown below each panel. Overall P values were obtained from likelihood-ratio tests.

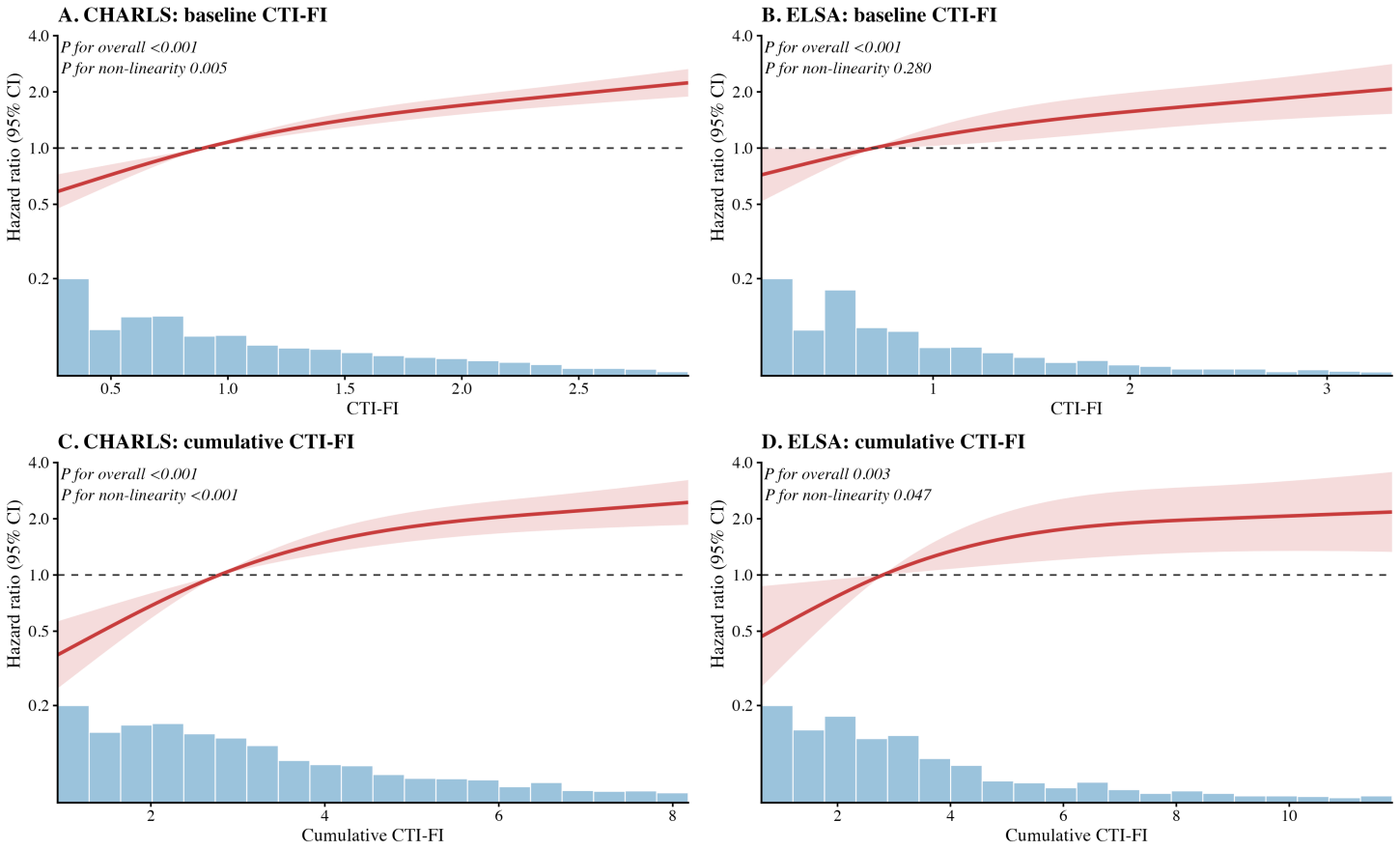


Figure 3

Dose-response associations of baseline and cumulative CTI-FI with incident cardiometabolic multimorbidity in CHARLS and ELSA. Restricted cubic spline curves show adjusted hazard ratios (solid lines) and 95% confidence intervals (shaded areas), with histograms showing the exposure distributions. Models were adjusted for sociodemographic, lifestyle, clinical, and biochemical covariates.

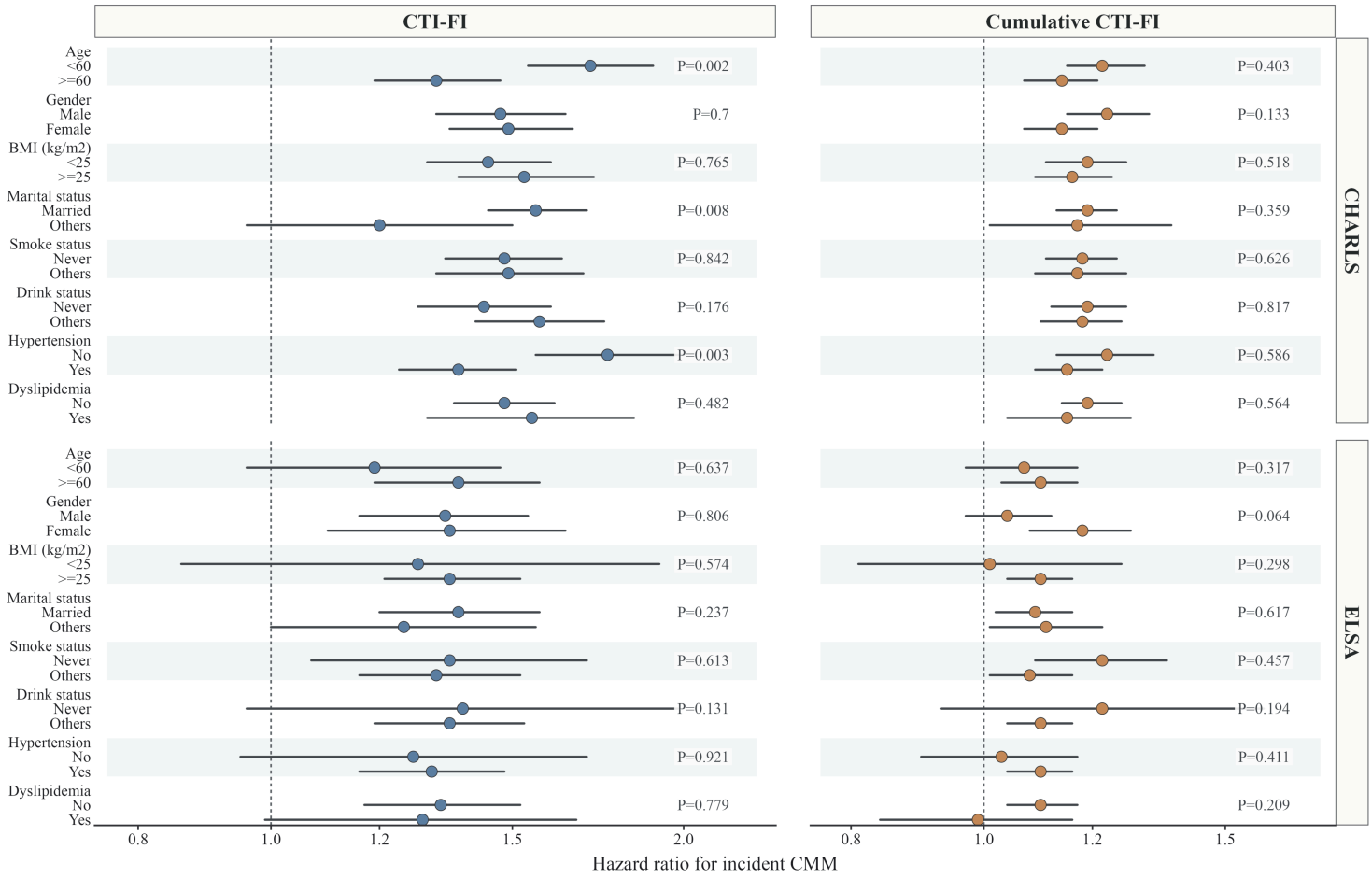


Figure 4

Subgroup-specific associations of baseline and cumulative CTI-FI with incident CMM in CHARLS and ELSA. Models were adjusted for sociodemographic, lifestyle, clinical, and biochemical covariates, excluding the corresponding stratifying variable. P values are for interaction.

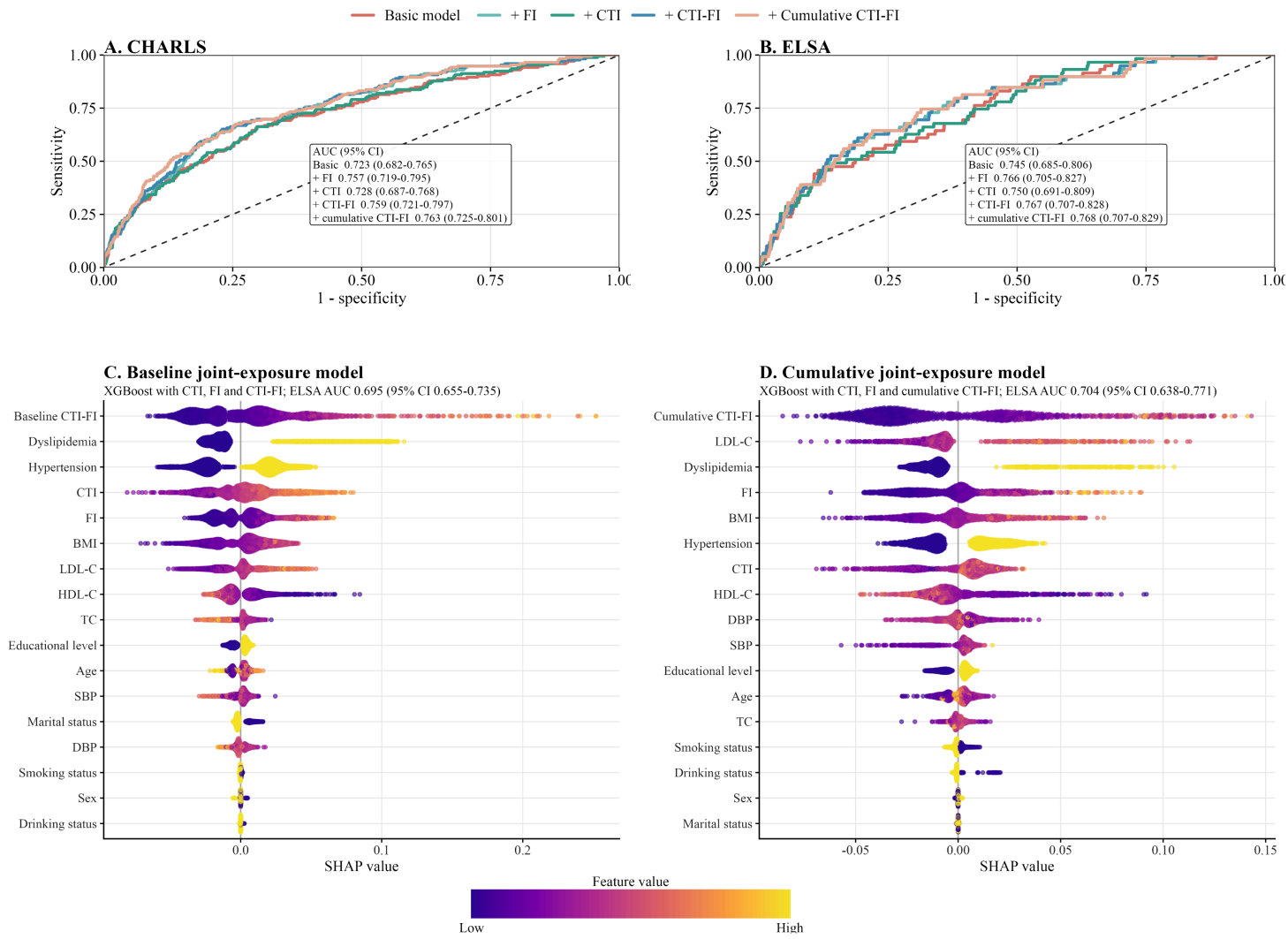


Figure 5

Incremental predictive performance and joint-exposure SHAP interpretation of CTI-FI models. (A, B) Receiver operating characteristic curves for conventional risk-factor models augmented separately with FI, CTI, CTI-FI, and cumulative CTI-FI in CHARLS and ELSA. (C, D) SHAP summary plots from separate joint-exposure XGBoost models in the complete-case ELSA baseline and cumulative cohorts. Color denotes relative feature values.

Supplementary Files

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- SupplementaryMaterials.docx