

Associations of baseline, cumulative, and dynamic trajectories of the cardiometabolic-frailty index with incident cardiovascular disease: a longitudinal analysis based on the China Health and Retirement Longitudinal Study (CHARLS)

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Abstract

Background

Cardiovascular disease (CVD) remains the leading cause of death worldwide [1]. Both cardiometabolic dysregulation and frailty are independently associated with increased CVD risk [2,3], yet an integrated marker capturing both dimensions has not been fully evaluated. We constructed the cardiometabolic-frailty index (CMIFI) as the product of the cardiometabolic index (CMI) and the frailty index (FI), and examined its baseline levels, cumulative exposure, and longitudinal trajectories in relation to incident CVD.

Methods

We used data from CHARLS (2011/2012–2020) [4]. Adults aged ≥ 45 years without baseline CVD and with complete CMIFI and covariate data were included ($n = 7,748$). CMIFI was calculated as $CMI \times FI$. Cumulative CMIFI was defined as $\text{mean}(CMIFI_{2011}, CMIFI_{2015}) \times 3$ years. Group-based trajectory modeling (GBTM) was the primary approach for identifying longitudinal CMIFI trajectories, with K-means clustering as an exploratory sensitivity check. Cox proportional hazards models, restricted cubic splines (RCS) [5], subgroup analyses, and CMI $\times$ FI interaction were performed. An illustrative prediction analysis examined discrimination, calibration, decision curve analysis (DCA), and SHAP values. Sensitivity analyses included standardized CMIFI, separate heart disease and stroke outcomes, stratified Cox regression, inverse probability weighting (IPW) Cox [7], exclusion of baseline diseases and early events, reclassification of smoking/drinking, competing-risk scenarios under assumed death hazards, and over-adjustment models excluding lipid variables. Cardiometabolic multimorbidity (CMM) was evaluated as a secondary outcome.

Results

Among 7,748 participants, 1,750 incident CVD events occurred during a median follow-up of 9 years. Compared with the lowest quartile (Q1), the highest baseline CMIFI quartile (Q4) was associated with a 1.72-fold increased risk of CVD (95% CI 1.47–2.01; P for trend < 0.001) after full adjustment. Each 1-SD higher baseline CMIFI was associated with a 1.11-fold higher CVD risk (95% CI 1.07–1.15). GBTM identified two trajectories in the longitudinal subsample ($n = 3,495$): low-stable ($n = 3,420$) and high-declining ($n = 75$). Compared with the low-stable group, the high-declining group had a 1.84-fold (95% CI 1.28–2.65) higher CVD risk after full adjustment; the bootstrap 95% CI was 1.29–2.61. Cumulative CMIFI showed a stronger dose-response: Q4 versus Q1 HR 2.99 (95% CI 2.42–3.69). CMI and FI showed a sub-multiplicative joint effect (multiplicative interaction HR 0.79, 95% CI 0.64–0.97; RERI -0.29 , 95% CI -0.56 to -0.01), consistent with the product form of CMIFI as a pragmatic simplification. An illustrative prediction model achieved an AUC of 0.671 in the validation set; NRI and IDI were null to small and are reported in Supplementary Table S7. DCA is shown in Fig. 6 and SHAP in Supplementary Figure S5. As a secondary outcome, incident CMM occurred in 464 of 7,326 participants over 4 years; Q4 versus Q1 HR was 5.86 (95% CI 4.23–8.11). Results were robust across sensitivity analyses.

Conclusions

Higher baseline, cumulative, and high-declining CMIFI trajectories were independently associated with increased CVD risk in Chinese middle-aged and older adults. CMIFI was also associated with incident cardiometabolic multimorbidity. CMIFI may serve as a simple, integrative indicator for CVD risk stratification and long-term monitoring.

Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality and morbidity worldwide, accounting for nearly one-third of all deaths globally [1]. With rapid population ageing and epidemiological transition, the burden of CVD in China has risen substantially, driven by metabolic risk factors, lifestyle changes, and demographic shifts [7, 8]. Traditional risk prediction models rely on single biomarkers or established risk factors, but they often fail to capture the cumulative, multisystem deterioration that characterizes high-risk individuals [9].

The cardiometabolic index (CMI), calculated as $(TG/HDL-C) \times (\text{waist}/\text{height})$, integrates atherogenic dyslipidemia, insulin resistance, and central obesity into a single continuous measure [1, 10]. Elevated CMI has been associated with diabetes, hypertension, atherosclerosis, and CVD events in multiple populations [11–13]. Separately, the frailty index (FI) quantifies cumulative health deficits across physical, cognitive, psychological, and chronic-disease domains and is a well-established predictor of CVD, disability, and mortality [3, 14, 15].

The link between metabolism and frailty is bidirectional and partly mediated by chronic low-grade inflammation. Adipose-tissue insulin resistance and central obesity drive release of interleukin-6, tumour necrosis factor- α , and C-reactive protein (CRP), while frailty

reflects the accumulated systemic consequences of these inflammatory, hormonal, and metabolic perturbations [2, 3, 14, 15, 53]. CMIFI therefore situates an individual within a metabolism-frailty-inflammation triangle: high CMI flags the metabolic driver, high FI flags downstream multisystem vulnerability, and their product amplifies joint risk beyond a simple sum. We tested whether the CMI x FI product form is supported by additive and multiplicative interaction analyses and whether the CMIFI-CVD association is independent of baseline CRP.

Although CMI and FI each predict CVD, their combination—termed the cardiometabolic-frailty index (CMIFI)—may capture both metabolic dysregulation and multisystem decline simultaneously, potentially providing superior prognostic information [16, 17]. Two recent CHARLS studies are directly relevant. Huo et al. multiplied the atherogenic index of plasma (AIP) by FI and found an association with incident CVD [9]; however, AIP is limited to the TG/HDL-C ratio, whereas CMI additionally incorporates waist/height, thereby capturing central obesity and insulin resistance [1]. Separately, Li and Wei showed that both baseline and cumulative CMI were associated with incident CVD in CHARLS, but they did not integrate CMI with frailty [12]. We therefore build on these reports by combining CMI with FI, and by evaluating baseline CMIFI, cumulative CMIFI exposure, and longitudinal CMIFI change patterns as predictors of incident CVD. Cumulative exposure and trajectory analyses better characterize the dynamic, sustained nature of cardiometabolic and frailty burdens [18–20].

Using data from the China Health and Retirement Longitudinal Study (CHARLS), a nationally representative longitudinal cohort, we evaluated the associations of baseline CMIFI, cumulative CMIFI, and longitudinal CMIFI trajectories with incident CVD. The central novelty of this study is the simultaneous assessment of baseline, cumulative, and dynamic CMIFI exposures, which distinguishes it from prior single-time-point indices. We further assessed the incremental predictive value of CMIFI beyond traditional risk factors and conducted extensive sensitivity analyses to ensure robustness.

Methods

Study design and population

We used publicly available data from CHARLS, an ongoing nationally representative cohort of Chinese adults aged ≥ 45 years and their spouses [4]. Baseline surveys were conducted in 2011/2012, with follow-up waves in 2013, 2015, 2018, and 2020.

Participants were eligible if they were aged ≥ 45 years, had no baseline CVD (self-reported physician diagnosis of heart disease or stroke), and had complete CMIFI and key covariate data. After applying these criteria, 7,748 participants were retained for baseline analyses. A longitudinal subsample of 3,495 participants had complete CMIFI data at both baseline (2011/2012) and the 2015 follow-up wave and were included in cumulative and trajectory analyses.

Data collection and covariates

Trained interviewers collected data using standardized questionnaires and physical examinations. Baseline information included age, sex, smoking, drinking, BMI, waist circumference, height, SBP, DBP, hypertension, diabetes, dyslipidemia, heart disease, stroke, FBG, HbA1c, TC, TG, HDL-C, and LDL-C. Hypertension was defined as self-reported physician diagnosis, use of antihypertensive medication, SBP ≥ 140 mmHg, or DBP ≥ 90 mmHg. Diabetes was defined as FBG ≥ 126 mg/dL, HbA1c $\geq 6.5\%$, self-reported diagnosis, or use of antidiabetic medication. Dyslipidemia was defined as abnormal lipid levels (TG ≥ 150 mg/dL, TC ≥ 240 mg/dL, HDL-C < 40 mg/dL, LDL-C ≥ 160 mg/dL), self-reported diagnosis, or use of lipid-lowering drugs.

Calculation of CMIFI, cumulative CMIFI, and trajectories

CMI was calculated as $(\text{TG}/\text{HDL-C}) \times (\text{waist circumference}/\text{height})$, with TG and HDL-C converted to mmol/L (TG/88.57, HDL-C/38.67) and waist and height in centimeters [1]. Biologically implausible values (TG < 20 or > 2000 mg/dL, HDL-C < 5 or > 300 mg/dL, height < 100 or > 250 cm, waist < 30 or > 200 cm) were set to missing. FI was constructed as a cumulative deficit index using 32 items: 6 activities of daily living, 5 instrumental activities of daily living, 3 cognitive function items, 10 psychological items (CESD-10), and 8 self-reported chronic conditions [14, 15]. A deficit was scored when the criterion for each item was met (details in Supplementary Table S2). FI was calculated as the number of deficits divided by the number of valid items, multiplied by 100. CMIFI was then computed as CMI x FI.

Cumulative CMIFI was calculated for participants with repeated CMIFI measurements at baseline and 2015 using the trapezoidal approximation: $\text{cumulative CMIFI} = \text{mean}(\text{CMIFI}_{\text{baseline}}, \text{CMIFI}_{2015}) \times 3 \text{ years}$. This metric represents the area under the CMIFI trajectory and integrates both the magnitude and duration of exposure, distinguishing it from a simple average of two measurements.

Group-based trajectory modeling (GBTM) was applied to standardized baseline and 2015 CMIFI values as the primary trajectory analysis [54]. Models with 2–4 latent classes were fitted using the *lcmm* package with linear time and no random effects; the optimal number of classes was selected by the Bayesian information criterion, and participants were assigned to classes by posterior probabilities. As an exploratory sensitivity check, we also applied K-means clustering with the elbow method [21].

Outcome definition

The primary outcome was incident CVD during follow-up, defined as a self-reported physician diagnosis of heart disease (including coronary heart disease, angina, or heart failure) or stroke at any follow-up wave. Follow-up time was calculated from baseline (2011) to the first report of CVD or the last known follow-up wave for censored participants.

Statistical analysis

Baseline characteristics were described by CMIFI quartiles. Continuous variables were presented as median (interquartile range) and categorical variables as frequency (percentage); group comparisons used Kruskal-Wallis or chi-square tests. The Kolmogorov-Smirnov test was used to assess normality. None of the candidate baseline variables had missing rates > 20% (highest: dyslipidemia 1.68%); therefore, no variable was excluded solely because of missingness. Remaining missing continuous variables were imputed by predictive mean matching and categorical variables by logistic regression using multiple imputation ($m = 5$). Continuous variables were winsorized at the 0.1st and 99.9th percentiles.

Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of baseline CMIFI, cumulative CMIFI, and trajectory groups with incident CVD. Four models were fitted: Model 1, unadjusted; Model 2, adjusted for age and sex; Model 3, additionally adjusted for hypertension, diabetes, dyslipidemia, smoking, and drinking; and Model 4, adjusted for age, sex, dyslipidemia, smoking, drinking, SBP, DBP, FBG, HbA1c, TC, and LDL-C. Categorical hypertension and diabetes were excluded from Model 4 because their diagnostic thresholds are captured by the continuous SBP/DBP and FBG/HbA1c terms, respectively; including both forms induces over-adjustment. TG and HDL-C were also excluded because they are direct components of the TG/HDL-C term in CMI; adjusting for them would over-adjust the CMIFI-CVD association. BMI was not included in Model 4 because it is mathematically collinear with the waist/height component of CMI. The proportional hazards assumption was assessed using Schoenfeld residuals.

RCS with 4 knots was used to model dose-response relationships of baseline and cumulative CMIFI with CVD risk [5]; non-linearity was assessed by likelihood-ratio tests. In the longitudinal subsample, standardized 2011 and 2015 CMIFI values were used as inputs for group-based trajectory modeling (GBTM) as the primary trajectory analysis; K-means clustering was performed as an exploratory sensitivity check. Subgroup analyses were performed by age, sex, diabetes, hypertension, and dyslipidemia status, with interaction tests. We additionally examined whether baseline C-reactive protein (CRP) modified the association between CMIFI and CVD by including a CMIFI $\times$ $\log(\text{CRP})$ interaction term in the fully adjusted Cox model and by reporting stratum-specific HRs for participants with CRP below and above the median.

To examine whether the multiplicative product $\text{CMIFI} = \text{CMI} \times \text{FI}$ is a statistically exact interaction model or a pragmatic simplification, we dichotomized CMI and FI at their medians and fitted a fully adjusted Cox model with a CMI $\times$ FI multiplicative interaction term. We also calculated additive interaction indices—relative excess risk due to interaction (RERI), attributable proportion (AP), and synergy index (S)—using bootstrap resampling [55]. A multiplicative interaction HR below 1 together with a negative RERI indicates a sub-multiplicative joint effect; in that case, treating CMIFI as a simple product is a pragmatic simplification rather than a statistically exact interaction model.

For illustrative prediction only, the baseline cohort was randomly split 7:3 into training and validation sets. Cox models including traditional risk factors with or without CMIFI (z score) were constructed. Discrimination was assessed by the area under the receiver operating characteristic curve (AUC), calibration by calibration curves, and clinical utility by decision curve analysis (DCA). Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated [8] and are reported in Supplementary Table S7. Shapley additive explanations (SHAP) values were used to illustrate variable contributions. ROC, calibration,

and SHAP results are presented in Supplementary Figure S5; DCA is presented as the main-text illustration. These analyses are intended as supplementary illustration rather than formal development of a new risk score.

Sensitivity analyses included standardizing CMIFI; examining heart disease and stroke as separate outcomes; stratified Cox regression by age, sex, and hypertension; excluding events occurring in the first 1, 2, or 3 years; using 2015 as a new baseline; calculating E-values for unmeasured confounding [23]; examining variance inflation factors (VIF); an over-adjustment model excluding all lipid variables (TC, TG, HDL-C, LDL-C); IPW Cox regression [7]; excluding participants with baseline diabetes, heart disease, or stroke; and reclassifying smoking and drinking as current/former/never. A medication-exclusion sensitivity analysis was not feasible because CHARLS did not collect medication-use variables in this extract. Because death data were unavailable, we performed scenario-based competing-risk sensitivity analyses by simulating death under plausible annual mortality rates (1%, 2%, 3%) and death hazard ratios per 1-SD CMIFI (1.2, 1.5, 2.0), then fitting Fine-Gray models [6] across 200 imputations to bound the subdistribution HR. Schoenfeld residual tests in the final Model 4 showed no evidence of proportional-hazards violation (global $P = 0.29$). Cardiometabolic multimorbidity (CMM), defined as having two or more of hypertension, diabetes, and dyslipidemia, was evaluated as a secondary outcome. All analyses were performed using R software (version 4.6.0), and a two-sided P value < 0.05 was considered statistically significant.

Results

Baseline characteristics

The final baseline cohort included 7,748 participants. Median age was 58 years (IQR 52–65), and 52.5% (4,070/7,748) were women. Participants with higher CMIFI quartiles were older, more likely to be women, had higher BMI and waist circumference, and had higher levels of SBP, DBP, FBG, HbA1c, TG, and LDL-C, but lower HDL-C (all $P < 0.05$). The prevalence of hypertension, diabetes, and dyslipidemia also increased across CMIFI quartiles (Table 1).

Table 1
Baseline characteristics of the study population by baseline cardiometabolic-frailty index quartiles.

Characteristic	Overall N = 7,748	Q1 N = 1,937	Q2 N = 1,937	Q3 N = 1,937	Q4 N = 1,937	p-value ²
Age, years	58.00 (52.00, 65.00)	56.00 (49.00, 62.00)	58.00 (51.00, 65.00)	59.00 (53.00, 66.00)	59.00 (54.00, 66.00)	< 0.001
Sex						< 0.001
Male	3,678 (47%)	1,145 (59%)	1,015 (52%)	832 (43%)	686 (35%)	
Female	4,070 (53%)	792 (41%)	922 (48%)	1,105 (57%)	1,251 (65%)	
Body mass index, kg/m ²	23.00 (20.74, 25.56)	22.32 (20.34, 24.48)	22.30 (20.27, 24.69)	23.11 (20.82, 25.71)	24.39 (21.95, 27.06)	< 0.001
Waist circumference, cm	84.20 (77.80, 91.40)	81.20 (76.00, 88.00)	82.00 (76.20, 89.00)	85.00 (78.20, 92.00)	89.00 (82.00, 96.00)	< 0.001
Triglycerides, mg/dL	103.54 (74.34, 150.45)	75.22 (58.41, 101.78)	85.85 (65.49, 113.28)	109.74 (83.19, 144.26)	169.04 (126.56, 245.15)	< 0.001
HDL-C, mg/dL	49.87 (40.98, 60.31)	56.44 (47.55, 67.65)	54.12 (46.01, 64.18)	49.10 (41.37, 57.99)	40.21 (34.02, 47.94)	< 0.001
Cardiometabolic index	0.48 (0.29, 0.84)	0.30 (0.19, 0.46)	0.35 (0.24, 0.53)	0.52 (0.36, 0.78)	1.04 (0.68, 1.68)	< 0.001
Frailty index	12.50 (6.25, 21.88)	3.13 (0.00, 6.25)	12.50 (6.25, 15.63)	15.63 (10.34, 24.14)	23.33 (15.63, 34.38)	< 0.001
Cardiometabolic frailty index	5.81 (2.51, 12.63)	1.21 (0.00, 1.84)	3.98 (3.22, 4.84)	8.40 (7.03, 10.18)	21.76 (16.01, 32.82)	< 0.001
Systolic blood pressure, mmHg	126.00 (113.50, 141.00)	123.00 (112.00, 135.50)	124.50 (112.00, 139.50)	127.50 (114.00, 142.50)	130.50 (117.00, 146.50)	< 0.001
Diastolic blood pressure, mmHg	74.50 (66.50, 82.50)	73.00 (65.50, 81.00)	73.50 (66.00, 82.00)	74.50 (67.00, 83.00)	76.00 (68.50, 84.50)	< 0.001
Fasting glucose, mg/dL	102.24 (94.32, 112.86)	99.90 (92.52, 108.18)	100.98 (93.42, 109.80)	102.24 (94.32, 112.86)	106.92 (97.74, 121.86)	< 0.001
Glycated hemoglobin, %	5.10 (4.90, 5.40)	5.10 (4.80, 5.30)	5.10 (4.80, 5.40)	5.10 (4.90, 5.40)	5.20 (4.90, 5.60)	< 0.001
Total cholesterol, mg/dL	190.59 (167.01, 215.34)	185.95 (164.30, 209.54)	187.11 (165.08, 211.08)	191.37 (168.94, 215.34)	197.55 (170.88, 225.77)	< 0.001
LDL-C, mg/dL	114.05 (93.36, 137.24)	111.73 (91.24, 132.22)	114.43 (94.33, 135.70)	117.14 (97.81, 139.56)	114.05 (87.76, 142.27)	< 0.001
Smoking	3,067 (40%)	902 (47%)	827 (43%)	709 (37%)	629 (32%)	< 0.001
Alcohol drinking	2,633 (34%)	832 (43%)	737 (38%)	583 (30%)	481 (25%)	< 0.001
Hypertension	1,763 (23%)	140 (7.2%)	377 (19%)	529 (27%)	717 (37%)	< 0.001
Diabetes	392 (5.1%)	24 (1.2%)	67 (3.5%)	106 (5.5%)	195 (10%)	< 0.001
Dyslipidemia	562 (7.3%)	40 (2.1%)	90 (4.6%)	155 (8.0%)	277 (14%)	< 0.001
Note: LDL-C is not a component of CMIFI. Because CMIFI is driven by HDL-C, triglycerides, waist-to-height ratio and frailty deficits, its correlation with LDL-C is weak and the LDL-C distribution across CMIFI quartiles is not expected to be monotonic. Consequently, the Q4 median LDL-C (114.05 mg/dL) coincides with the overall median.						

Association between baseline CMIFI and incident CVD

Among 7,748 participants, 1,750 incident CVD events occurred during a median follow-up of 9 years. Kaplan-Meier curves showed a graded increase in CVD incidence across baseline CMIFI quartiles (log-rank $P < 0.001$) (Fig. 2).

In Cox regression, CVD risk increased across CMIFI quartiles. In the fully adjusted Model 4, the HRs for Q2, Q3, and Q4 versus Q1 were 1.32 (95% CI 1.12–1.55), 1.74 (95% CI 1.48–2.05), and 1.72 (95% CI 1.47–2.01), respectively (P for trend < 0.001). Each 1-SD increase in baseline CMIFI was associated with a 1.11-fold higher CVD risk (95% CI 1.07–1.15) (Table 2).

Table 2
Association between baseline cardiometabolic-frailty index and incident cardiovascular disease.

Model	Comparison	HR	Lower	Upper	P	HR_95_CI
Model 1 (Crude)	Q2 vs Q1	1.44	1.23	1.69	< 0.001	1.44 (1.23–1.69)
Model 1 (Crude)	Q3 vs Q1	2.05	1.76	2.40	< 0.001	2.05 (1.76–2.40)
Model 1 (Crude)	Q4 vs Q1	2.25	1.94	2.60	< 0.001	2.25 (1.94–2.60)
Model 2 (Age- and sex-adjusted)	Q2 vs Q1	1.37	1.17	1.61	< 0.001	1.37 (1.17–1.61)
Model 2 (Age- and sex-adjusted)	Q3 vs Q1	1.89	1.61	2.22	< 0.001	1.89 (1.61–2.22)
Model 2 (Age- and sex-adjusted)	Q4 vs Q1	2.03	1.74	2.36	< 0.001	2.03 (1.74–2.36)
Model 3 (Multivariable-adjusted I)	Q2 vs Q1	1.27	1.08	1.49	0.003	1.27 (1.08–1.49)
Model 3 (Multivariable-adjusted I)	Q3 vs Q1	1.66	1.42	1.95	< 0.001	1.66 (1.42–1.95)
Model 3 (Multivariable-adjusted I)	Q4 vs Q1	1.61	1.37	1.88	< 0.001	1.61 (1.37–1.88)
Model 4 (Multivariable-adjusted II)	Q2 vs Q1	1.32	1.12	1.55	< 0.001	1.32 (1.12–1.55)
Model 4 (Multivariable-adjusted II)	Q3 vs Q1	1.74	1.48	2.05	< 0.001	1.74 (1.48–2.05)
Model 4 (Multivariable-adjusted II)	Q4 vs Q1	1.72	1.47	2.01	< 0.001	1.72 (1.47–2.01)
Per 1-SD increase in CMIFI		1.11	1.07	1.15	< 0.001	1.11 (1.07–1.15)
P for trend across CMIFI quartiles					< 0.001	
Model 1: Crude. Model 2: Adjusted for age and sex. Model 3: Adjusted for age, sex, hypertension, diabetes, dyslipidemia, smoking, and drinking. Model 4: Adjusted for age, sex, dyslipidemia, smoking, drinking, systolic BP, diastolic BP, fasting glucose, HbA1c, total cholesterol, and LDL-C. Categorical hypertension and diabetes were excluded from Model 4 because their diagnostic thresholds are captured by continuous SBP/DBP and FBG/HbA1c terms; triglycerides and HDL-C were excluded because they are direct components of the cardiometabolic index.						

Longitudinal trajectories and cumulative CMIFI

In the 3,495-participant longitudinal subsample, GBTM selected a two-class trajectory solution by the Bayesian information criterion. The larger low-stable class comprised 3,420 participants (97.9%) with mean CMIFI values of 9.4 at baseline and 11.7 in 2015; the smaller high-declining class comprised 75 participants (2.1%) with mean CMIFI values of 98.7 and 82.8, respectively. In the fully adjusted model, the high-declining group had a 1.84-fold (95% CI 1.28–2.65) higher CVD risk than the low-stable group; the bootstrap 95% CI was 1.29–2.61 (Fig. 3, Table 3).

Figure 3A. Bayesian information criterion for GBTM model selection.

Cumulative CMIFI was also strongly associated with CVD risk. In the fully adjusted model, Q2, Q3, and Q4 versus Q1 had HRs of 1.65 (95% CI 1.31–2.08), 2.31 (95% CI 1.86–2.87), and 2.99 (95% CI 2.42–3.69), respectively (Table 3). RCS analyses indicated significant nonlinear associations for both baseline CMIFI (P for non-linearity < 0.001) and cumulative CMIFI (P for non-linearity < 0.001) (Fig. 4).

Table 3
Association between longitudinal CMIFI trajectory / cumulative CMIFI and incident cardiovascular disease.

Model	Comparison	HR	Lower	Upper	P	HR_95_CI
Trajectory: Model 1 (Crude)	high-declining vs low-stable	2.06	1.45	2.92	< 0.001	2.06 (1.45–2.92)
Trajectory: Model 2 (Age- and sex-adjusted)	high-declining vs low-stable	1.83	1.28	2.61	< 0.001	1.83 (1.28–2.61)
Trajectory: Model 3 (Further adjusted for SES)	high-declining vs low-stable	1.85	1.29	2.66	< 0.001	1.85 (1.29–2.66)
Trajectory: Model 4 (Fully adjusted)	high-declining vs low-stable	1.84	1.28	2.65	< 0.001	1.84 (1.28–2.65)
Cumulative CMIFI: Model 1 (Crude)	Q2 vs Q1	1.84	1.46	2.33	< 0.001	1.84 (1.46–2.33)
Cumulative CMIFI: Model 1 (Crude)	Q3 vs Q1	2.65	2.14	3.27	< 0.001	2.65 (2.14–3.27)
Cumulative CMIFI: Model 1 (Crude)	Q4 vs Q1	3.84	3.13	4.71	< 0.001	3.84 (3.13–4.71)
Cumulative CMIFI: Model 4 (Fully adjusted)	Q2 vs Q1	1.65	1.31	2.08	< 0.001	1.65 (1.31–2.08)
Cumulative CMIFI: Model 4 (Fully adjusted)	Q3 vs Q1	2.31	1.86	2.87	< 0.001	2.31 (1.86–2.87)
Cumulative CMIFI: Model 4 (Fully adjusted)	Q4 vs Q1	2.99	2.42	3.69	< 0.001	2.99 (2.42–3.69)
Trajectory models: Model 1: Crude. Model 2: Adjusted for age and sex. Model 3: Adjusted for age, sex, education, marital status, and hukou. Model 4: Adjusted for Model 3 covariates plus smoking and drinking. Cumulative CMIFI models: Model 1: Crude. Model 4: Adjusted for age, sex, dyslipidemia, smoking, drinking, systolic BP, diastolic BP, fasting glucose, HbA1c, total cholesterol, and LDL-C. Triglycerides and HDL-C were excluded because they are direct components of the cardiometabolic index.						

The multiplicative interaction between CMI and FI was statistically significant but below unity (HR 0.79, 95% CI 0.64–0.97; $P = 0.023$), and additive interaction indices indicated a negative interaction (RERI – 0.29, 95% CI –0.56 to –0.01; AP –0.19, 95% CI –0.35 to –0.01; synergy index 0.65, 95% CI 0.46–0.98). These findings indicate a sub-multiplicative joint effect; treating CMIFI as the simple product CMI x FI is therefore a pragmatic simplification rather than a statistically exact multiplicative interaction model (Supplementary Table S10).

As an exploratory sensitivity check, K-means clustering suggested three trajectories in the longitudinal subsample: low-stable ($n = 2,855$), moderate ($n = 580$), and high-declining ($n = 60$). The moderate and high-declining groups had adjusted HRs of 2.01 (95% CI 1.68–2.41) and 2.21 (95% CI 1.51–3.24), respectively, versus the low-stable group. Because GBTM is likelihood-based and explicitly models heterogeneity in change over time, the two-class GBTM solution was retained as the primary trajectory analysis, with the three-cluster K-means solution reported as exploratory (Supplementary Table S11).

Subgroup and prediction analyses

Subgroup analyses showed that each 1-SD increase in baseline CMIFI was significantly associated with CVD in men, participants aged < 65 years, those without diabetes, those without hypertension, and those without dyslipidemia. Significant interactions were observed for sex (P for interaction = 0.033) and dyslipidemia (P for interaction = 0.050); interactions for age, diabetes, and hypertension were not significant (Fig. 5).

In the illustrative prediction analysis, univariable and multivariable Cox regression results in the training cohort are shown in Table 4. The model integrating CMIFI with traditional risk factors achieved an AUC of 0.671 in the validation set (Supplementary Table S7). NRI and IDI were null to small and are reported in Supplementary Table S7. DCA is shown in Fig. 6 and SHAP feature importance in Supplementary Figure S5.

We further examined whether inflammation modified the CMIFI-CVD association. The interaction between baseline CMIFI and log-transformed CRP was not statistically significant (P for interaction = 0.28). The HR per 1-SD increase in CMIFI was 1.14 (95% CI 1.08–

1.20) among participants with low CRP ($\leq$ median) and 1.07 (95% CI 1.02–1.12) among those with high CRP ($>$ median), suggesting that the association of CMIFI with CVD is largely independent of baseline systemic inflammation (Supplementary Table S8).

Table 4
Univariable and multivariable Cox regression for incident cardiovascular disease in the training cohort.

Variable	Univariable_HR	Univariable_95CI	Univariable_P	Multivariable_HR	Multivariable_95CI	Multivariable_P
Age, years	1.03	1.02–1.03	< 0.001	1.03	1.02–1.03	< 0.001
Sex (Male vs Female)	1.17	1.05–1.30	0.005	1.25	1.06–1.48	0.010
Dyslipidemia	1.93	1.59–2.34	< 0.001	1.75	1.45–2.12	< 0.001
Smoking	0.97	0.85–1.10	0.603	1.12	0.94–1.33	0.204
Alcohol drinking	0.91	0.80–1.03	0.138	1.02	0.87–1.19	0.849
Systolic BP, mmHg	1.01	1.01–1.01	< 0.001	1.00	1.00–1.01	0.156
Diastolic BP, mmHg	1.01	1.01–1.02	< 0.001	1.01	1.00–1.02	0.023
Fasting glucose, mg/dL	1.00	1.00–1.00	0.027	1.00	1.00–1.00	0.145
Glycated hemoglobin, %	1.14	1.07–1.21	< 0.001	1.13	1.01–1.26	0.033
Total cholesterol, mg/dL	1.00	1.00–1.00	0.099	1.00	1.00–1.00	0.463
LDL-C, mg/dL	1.00	1.00–1.00	0.243	1.00	1.00–1.01	0.309
CMIFI (per 1-SD)	1.13	1.09–1.18	< 0.001	1.12	1.08–1.16	< 0.001
Triglycerides, mg/dL	1.00	1.00–1.00	0.035	—	—	—
HDL-C, mg/dL	1.00	0.99–1.00	0.166	—	—	—
Hypertension	1.93	1.72–2.16	< 0.001	—	—	—
Diabetes	1.33	1.05–1.69	0.019	—	—	—
Univariable and multivariable Cox proportional hazards models in the training cohort (70% of the sample). CMIFI was standardized (z-score) before inclusion. Triglycerides, HDL-C, hypertension, and diabetes were not included in the multivariable model because triglycerides and HDL-C are direct components of CMI, and categorical hypertension/diabetes are captured by continuous BP and glucose/HbA1c terms. HR: hazard ratio; CI: confidence interval.						

Sensitivity analyses

Results were robust across multiple sensitivity analyses. Excluding events in the first 1, 2, or 3 years yielded per 1-SD HRs of 1.11 (95% CI 1.07–1.15), 1.10 (95% CI 1.06–1.15), and 1.10 (95% CI 1.06–1.15), respectively. Because follow-up waves occurred at approximately 2, 4, 7, and 9 years, the 2- and 3-year exclusions were operationally identical. When 2015 was used as the new baseline, the per-quartile HR was 1.46 (95% CI 1.36–1.57). The two-class GBTM trajectory was the primary longitudinal analysis (Table 3). IPW Cox regression [7] yielded an HR of 1.35 (95% CI 1.21–1.50) for high versus low CMIFI. Exclusion of participants with baseline diabetes, heart disease, or stroke (HR 1.21, 95% CI 1.15–1.26), reclassification of smoking/drinking (HR 1.20, 95% CI 1.14–1.25), the over-adjustment model excluding all lipid variables (HR 1.20, 95% CI 1.14–1.25), and stratified Cox regression by age, sex, or hypertension (HRs 1.17–1.20) produced consistent results. Separate outcome analyses showed per 1-SD HRs of 1.07 (95% CI 1.03–1.12) for heart disease and 1.18 (95% CI 1.13–1.23) for stroke. E-values for the main associations ranged from 2.27 to 3.65 (Supplementary Tables S5–S6). In scenario-

based competing-risk analyses, the subdistribution HR for baseline CMIFI Q4 versus Q1 remained above 1.64 even under the extreme assumption of 3% annual mortality and a two-fold higher death risk per 1-SD CMIFI (Supplementary Table S12).

Discussion

In this nationally representative Chinese cohort, we found that higher baseline CMIFI, higher cumulative CMIFI, and a high-declining CMIFI trajectory were independently associated with increased risk of incident CVD. These associations remained robust after extensive multivariable adjustment and multiple sensitivity analyses, including IPW, exclusion of baseline diseases and early events, reclassification of lifestyle factors, stratified Cox regression, and GBTM validation. As a secondary outcome, CMIFI was also strongly associated with incident cardiometabolic multimorbidity.

CMI integrates atherogenic dyslipidemia (TG/HDL-C) and central obesity (waist/height), reflecting insulin resistance and metabolic dysregulation [1, 10, 11]. FI captures cumulative deficits across multiple physiological systems and is a well-established marker of biological ageing and vulnerability to stressors [3, 14, 15]. By multiplying CMI and FI, CMIFI simultaneously captures both metabolic burden and multisystem decline, potentially providing a more comprehensive risk profile than either component alone [16, 17]. Because BMI is mathematically collinear with the waist/height term in CMI, we did not include BMI in the fully adjusted Model 4, underscoring that CMIFI captures adiposity-related risk through CMI rather than through a separate BMI term. The sub-multiplicative CMI x FI interaction and the null CRP modification together support a metabolism-frailty-inflammation interpretation: CMI and FI capture overlapping but not identical biology, and the CMIFI-CVD association is not explained away by baseline systemic inflammation. High CMI reflects adipose-tissue dysfunction and insulin resistance that drive low-grade inflammation, while FI registers the accumulated multisystem consequences. The CMIFI product is best understood as a pragmatic simplification that amplifies risk when both metabolic burden and multisystem decline are elevated, not as a statistically exact multiplicative interaction model.

Our study also differs from the recent CHARLS analysis by Huo et al. that combined the atherogenic index of plasma (AIP) with FI [9]. AIP is based only on lipid ratios, whereas CMI additionally incorporates waist-to-height ratio as a marker of central obesity and insulin resistance. More importantly, Huo et al. examined a single baseline exposure and a single CVD outcome, whereas we evaluated baseline CMIFI, cumulative CMIFI exposure over three years, longitudinal CMIFI trajectories, and incident cardiometabolic multimorbidity as a secondary endpoint (Supplementary Table S13). These extensions strengthen the evidence that integrating cardiometabolic burden with frailty identifies high-risk individuals across multiple time frames and outcomes.

Our longitudinal trajectory analysis extends previous cross-sectional or single-time-point studies by demonstrating that a high-declining CMIFI pattern confers substantially higher CVD risk than a stable low pattern [18–20]. GBTM selected a parsimonious two-class solution, and bootstrap validation supported the stability of the high-declining association. These findings suggest that repeated assessment of CMIFI may improve risk stratification and that interventions targeting both metabolic control and frailty reduction could be beneficial for CVD prevention.

The stronger association observed for cumulative CMIFI than for baseline CMIFI highlights the importance of exposure duration. Unlike a simple average of two measurements, cumulative exposure integrates both the level and persistence of CMIFI over time, aligning with the biological concept that chronic, sustained metabolic and frailty burdens are more harmful than transient elevations [18, 24].

Although CMIFI was independently associated with CVD, its incremental contribution to traditional risk prediction was modest (validation AUC 0.671). This pattern is expected for risk factor indices added to models that already contain the major Framingham/PCE covariates: once traditional risk factors are included, new composite indices rarely yield large gains in discriminative metrics such as AUC [9, 51, 52]. We therefore present the prediction analysis as an illustrative supplementary exercise; NRI and IDI are reported in Supplementary Table S7, while DCA (Fig. 6) illustrates potential net benefit at selected threshold probabilities. Rather than replacing established risk scores, CMIFI's primary value lies in risk stratification and communication: it integrates two clinically important yet distinct dimensions—metabolic dysregulation and frailty—into a single, cost-free measure that can be calculated from routine anthropometric and questionnaire data. Its simplicity makes it particularly suitable for primary care and resource-limited settings where laboratory panels or specialized frailty assessments are unavailable, and for longitudinal monitoring of cardiometabolic-frailty burden over time.

The absence of death data precluded formal Fine-Gray competing-risks analysis [6]. Nevertheless, competing mortality is unlikely to reverse our findings. CMIFI captures dimensions (metabolic dysregulation and frailty) that are strongly linked to both CVD incidence and non-CVD mortality; under a subdistribution hazard framework, the association with CVD would have to be strongly biased by selective

survival to nullify the observed hazard ratios [41, 44]. Scenario-based sensitivity analyses that imposed annual mortality rates of 1–3% and death hazard ratios per 1-SD CMIFI of 1.2-2.0 produced subdistribution HRs for Q4 versus Q1 ranging from 1.64 to 1.99, remaining materially above the null (Supplementary Table S12). These bounds support the robustness of the main findings.

Strengths of this study include the large, nationally representative longitudinal design; simultaneous evaluation of baseline, cumulative, and trajectory exposures; evaluation of the CMI x FI interaction through additive and multiplicative analyses; and the use of multiple advanced methods including GBTM primary trajectory analysis with K-means and competing-risk scenario sensitivity checks, prediction illustration, and extensive sensitivity analyses. Limitations include the reliance on self-reported CVD outcomes, the absence of death data preventing formal competing-risks analysis, and the lack of medication information for some sensitivity analyses. Additionally, the observational design limits causal inference, and residual confounding cannot be fully excluded.

Conclusions

In Chinese middle-aged and older adults, higher baseline CMIFI, higher cumulative CMIFI, and a high-declining CMIFI trajectory were independently associated with increased risk of incident CVD. CMIFI was also associated with incident cardiometabolic multimorbidity. Rather than replacing established risk scores, CMIFI offers a simple, cost-free integration of metabolic and frailty information that may be especially useful for risk communication and longitudinal monitoring in resource-limited settings.

Abbreviations

- AUC
- area under the curve
- BMI
- body mass index
- CHARLS
- China Health and Retirement Longitudinal Study
- CI
- confidence interval
- CMI
- cardiometabolic index
- CMIFI
- cardiometabolic-frailty index
- CVD
- cardiovascular disease
- AP
- attributable proportion due to interaction
- DBP
- diastolic blood pressure
- DCA
- decision curve analysis
- FI
- frailty index
- FBG
- fasting blood glucose
- GBTM
- group-based trajectory modeling
- HbA1c
- glycated hemoglobin
- HDL-C
- high-density lipoprotein cholesterol
- HR
- hazard ratio
- IDI

integrated discrimination improvement
IPW
inverse probability weighting
LDL-C
low-density lipoprotein cholesterol
NRI
net reclassification improvement
RCS
restricted cubic splines
RERI
relative excess risk due to interaction
SBP
systolic blood pressure
SD
standard deviation
SHAP
Shapley additive explanations
TC
total cholesterol
TG
triglycerides.

Declarations

Author Contribution

Chengdi Chen, Zibei Feng, Xinyue Chen, Shian Huang and Lingpin Pang were involved in the design of this study. Chengdi Chen and Zibei Feng contributed to manuscript writing. Xinyue Chen was responsible for data collection and data management. Chengdi Chen, Zibei Feng and Xinyue Chen contributed to the statistical analysis. Lingpin Pang and Shian Huang participated in data review and manuscript revision. All authors have reviewed and approved the final manuscript.

Data Availability

CHARLS data are publicly available at <https://charls.pku.edu.cn/>. The R code used for data preprocessing, statistical analysis, and figure generation is available from the corresponding author upon reasonable request.

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Figures

A. CVD incidence by baseline CMIFI quartiles

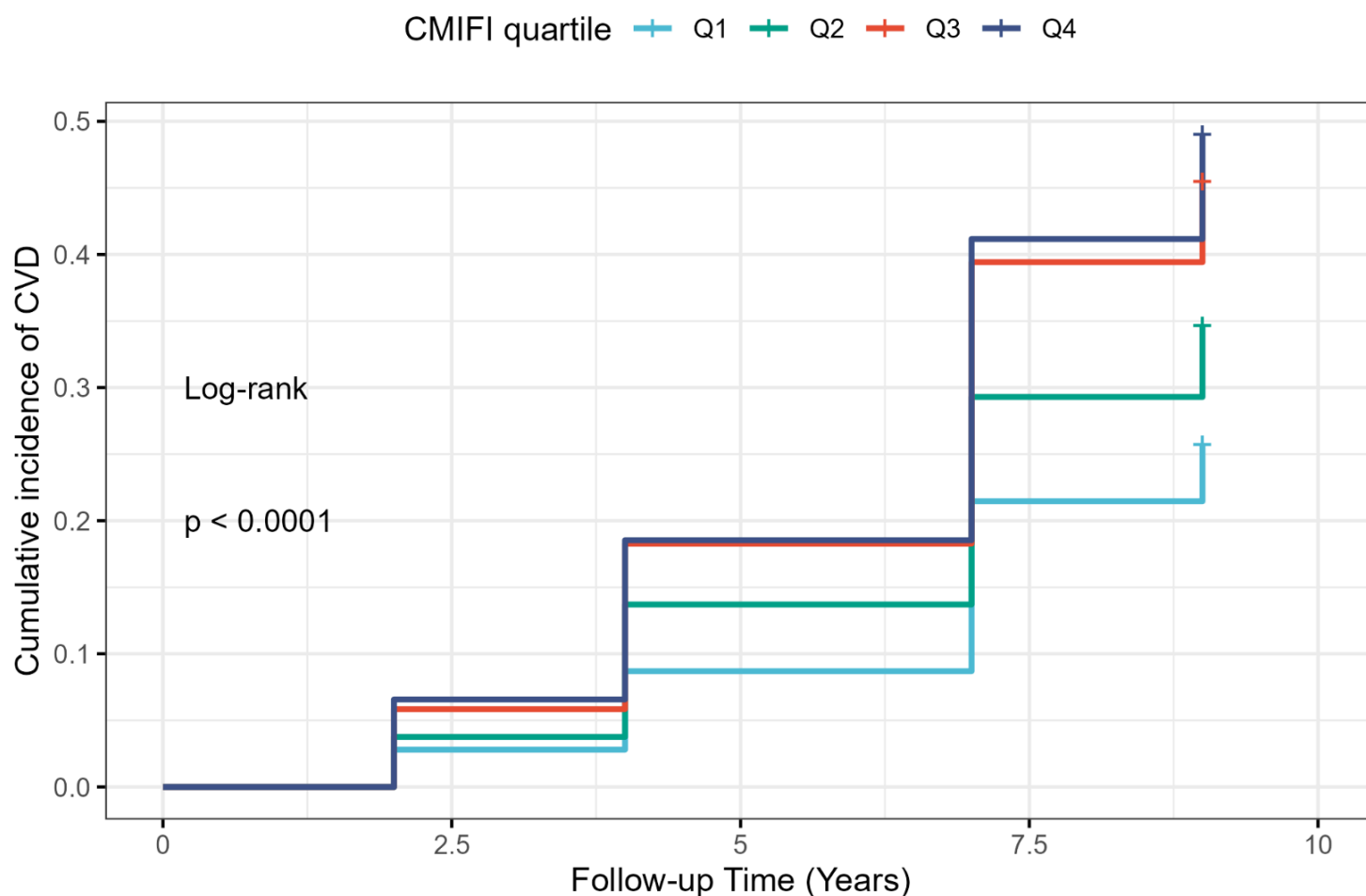


Figure 1

Figure 2A. Kaplan-Meier cumulative incidence of CVD by baseline CMIFI quartiles.

A. GBTM model selection

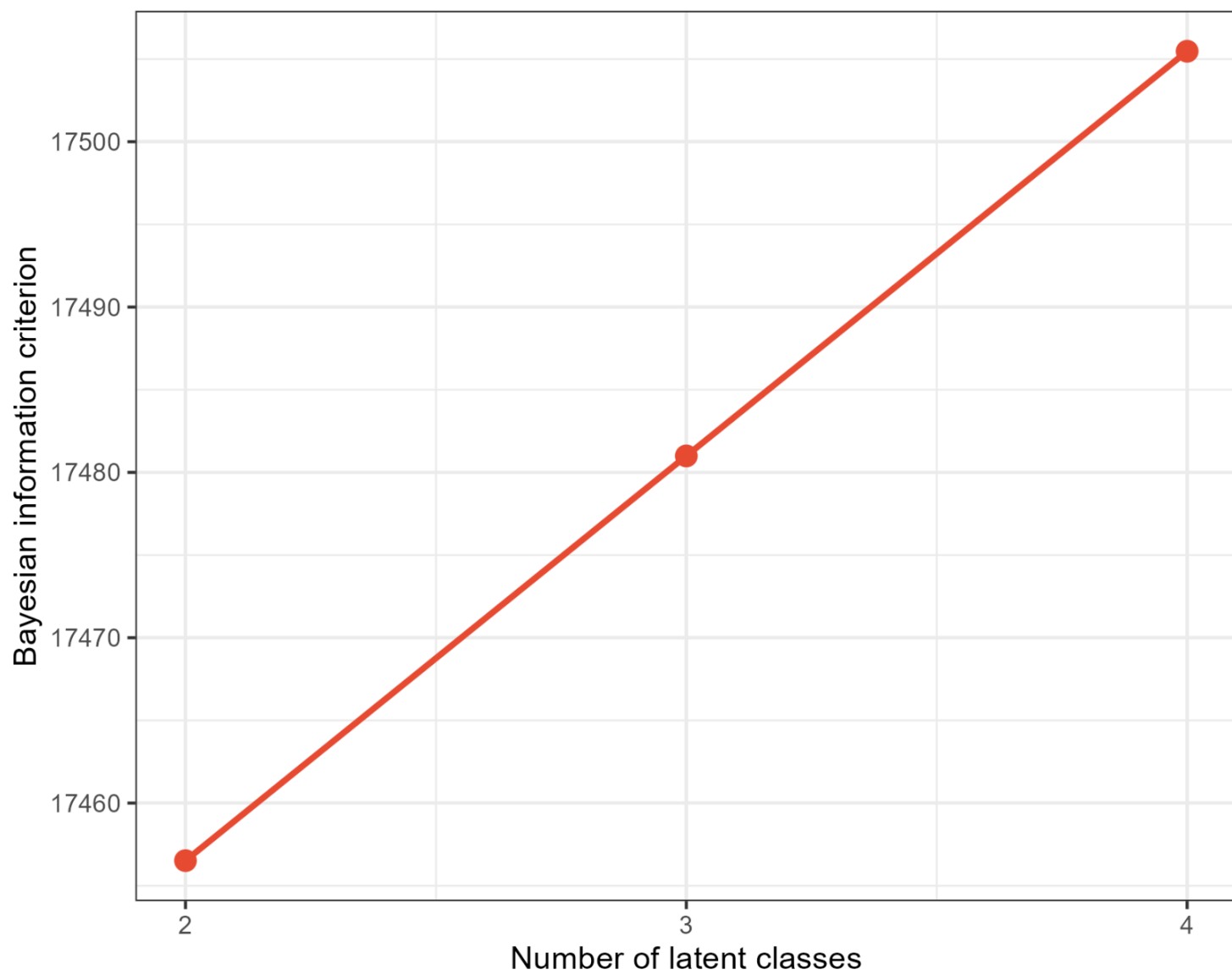


Figure 2

Figure 3A. Bayesian information criterion for GBTM model selection.

B. GBTM-derived CMIFI trajectories

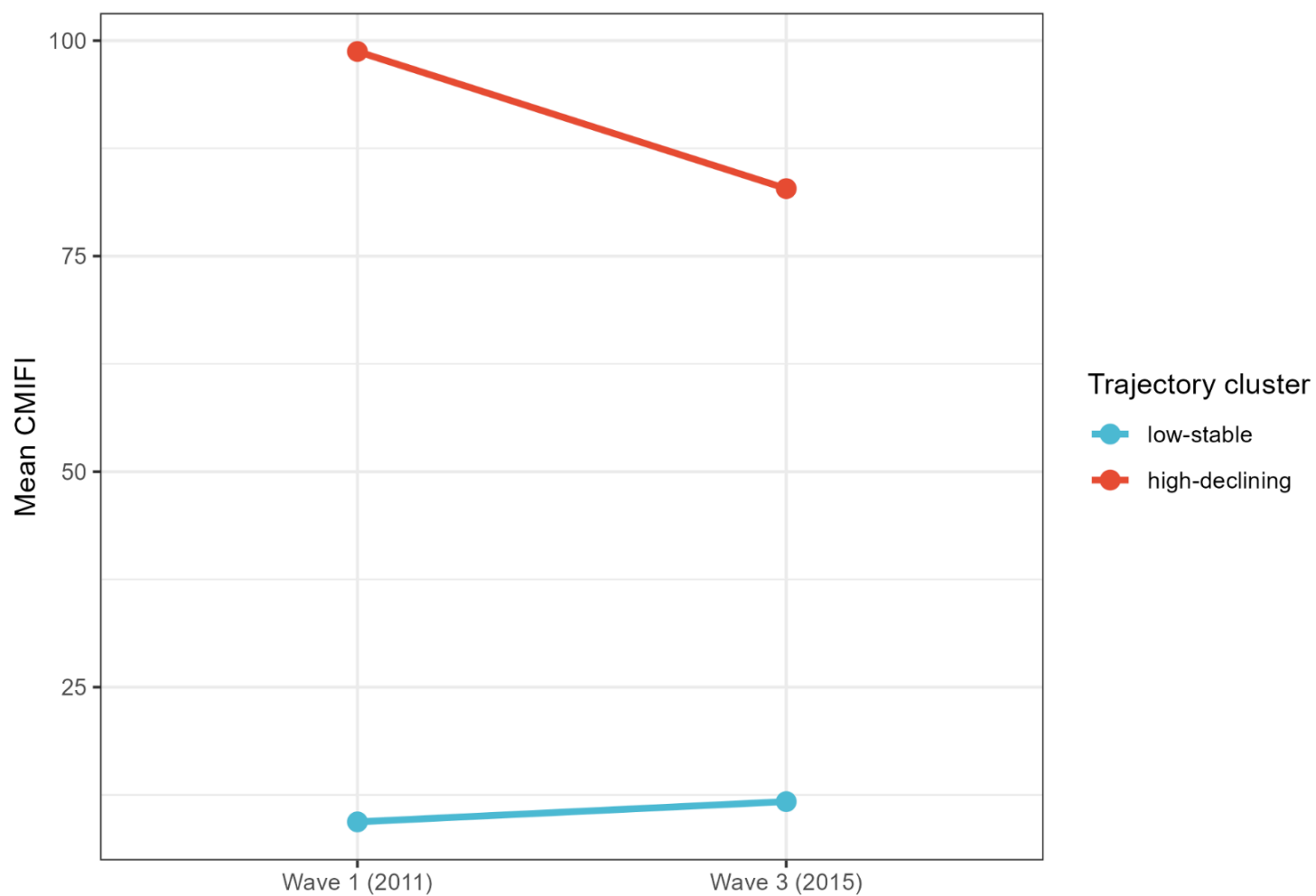


Figure 3

Figure 3B. Mean CMIFI trajectories identified by GBTM.

A. Baseline CMIFI

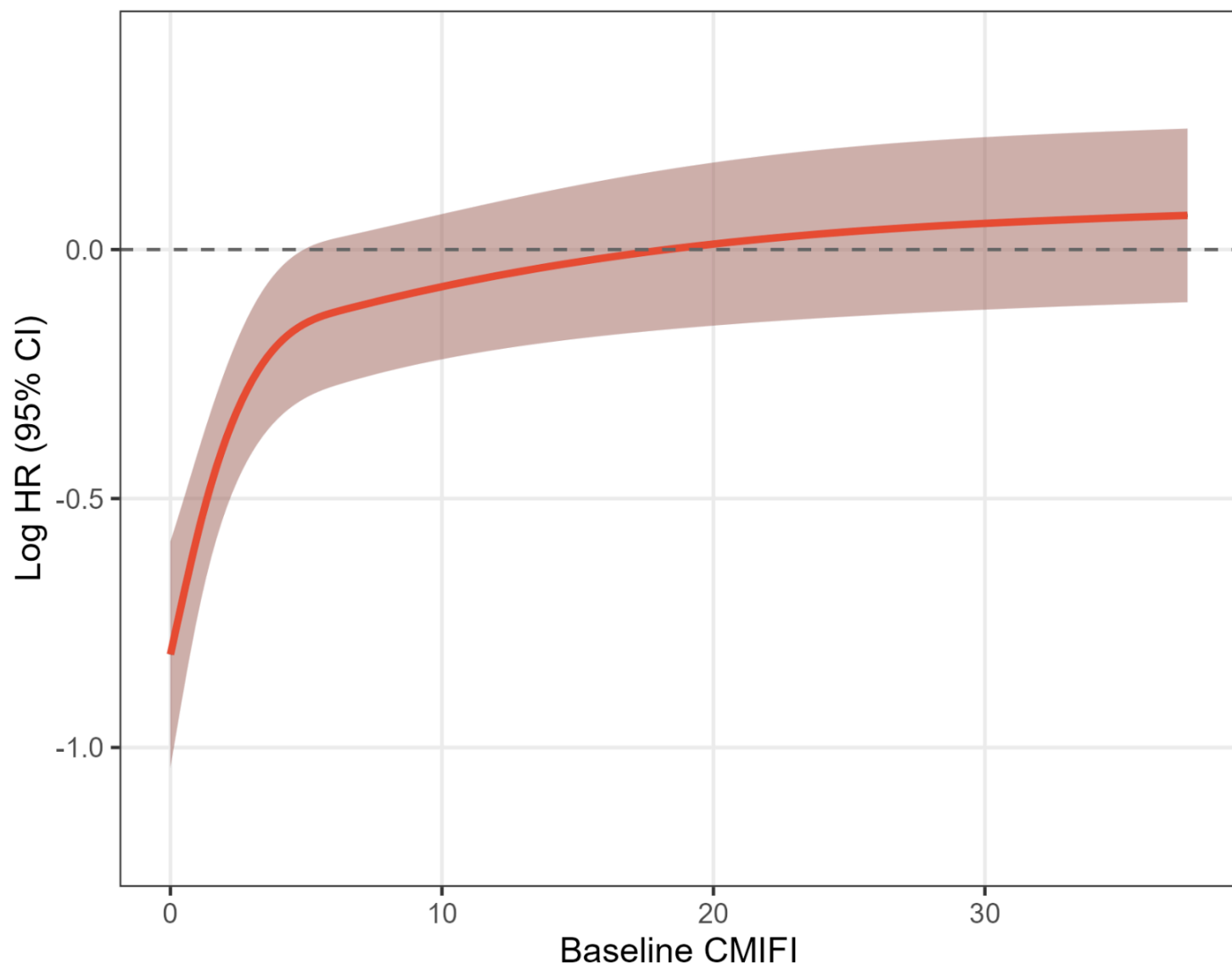


Figure 4

Figure 4A. Restricted cubic spline analysis of baseline CMIFI and incident CVD.

B. Cumulative CMIFI

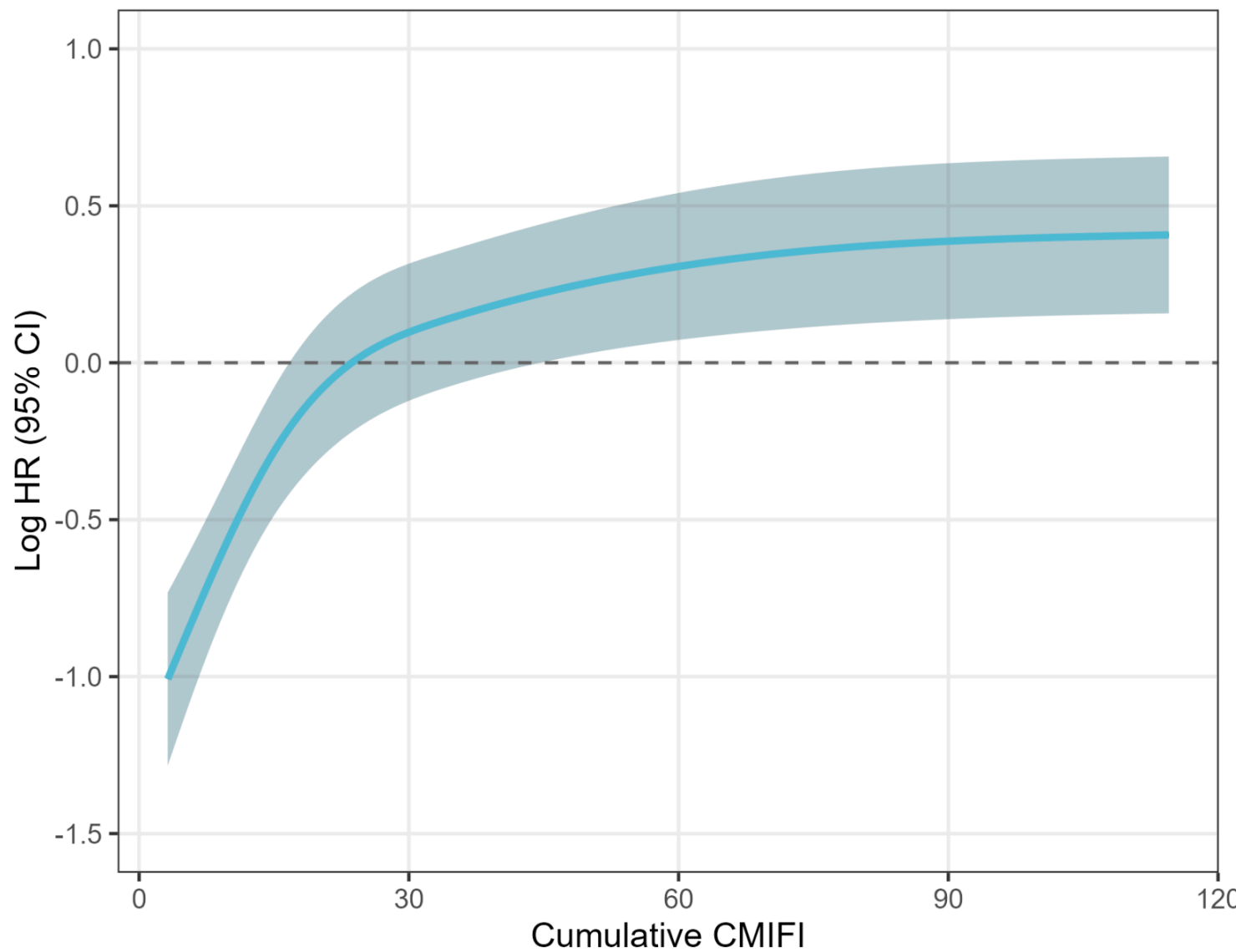


Figure 5

Figure 4B. Restricted cubic spline analysis of cumulative CMIFI and incident CVD.

Subgroup	N	Events	HR (95% CI)	P value
Overall	7748	1750	1.09 (1.06-1.13)	<0.001
Age <65	5751	1232	1.11 (1.08-1.15)	<0.001
Age ≥65	1997	518	1.05 (0.97-1.14)	0.196
Male	3678	736	1.15 (1.09-1.23)	<0.001
Female	4070	1014	1.07 (1.02-1.12)	0.002
No Diabetes	7356	1623	1.12 (1.08-1.16)	<0.001
Diabetes	392	127	1.05 (0.98-1.12)	0.168
No Hypertension	5985	1145	1.10 (1.03-1.18)	0.007
Hypertension	1763	605	1.05 (1.01-1.08)	0.006
No Dyslipidemia	7186	1522	1.11 (1.06-1.16)	<0.001
Dyslipidemia	562	228	1.03 (0.96-1.12)	0.415

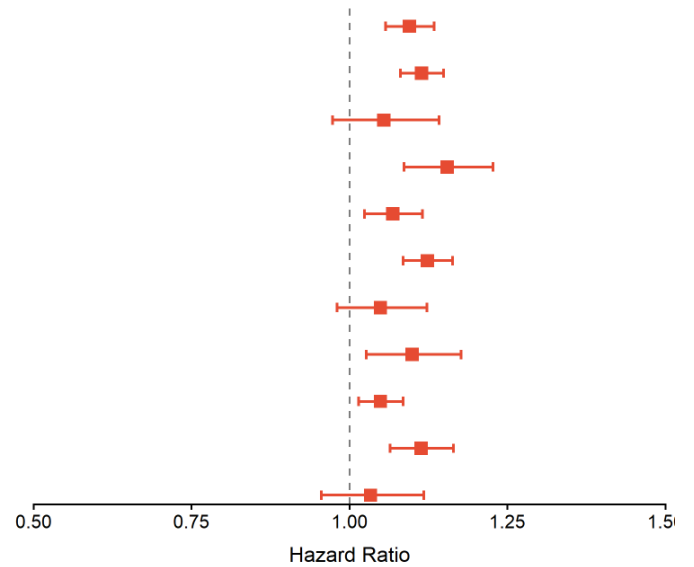


Figure 6

Figure 5. Subgroup analyses for the association between baseline CMIFI (per 1-SD) and incident CVD.

Decision curve analysis at 5 years

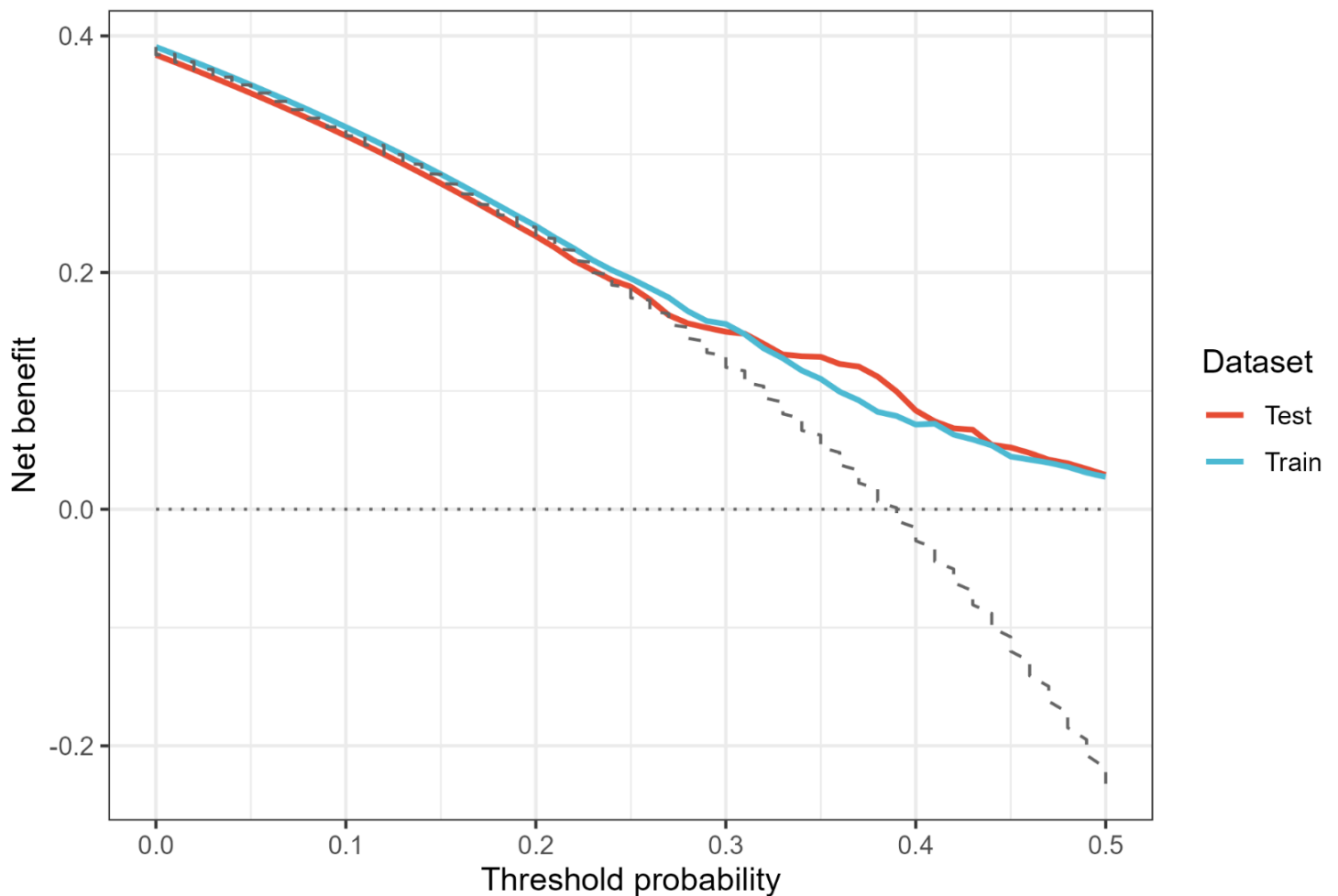


Figure 7

Figure 6. Decision curve analysis comparing the model with traditional risk factors plus CMIFI versus treat-all and treat-none strategies in the training and validation sets.

Supplementary Files

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