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Associations of cumulative exposure and dynamic trajectories of the combined Chinese visceral adiposity index and frailty index with incident cardiometabolic multimorbidity: a longitudinal analysis based on CHARLS

Lifei Yao
Ji'an Central People's Hospital
Qiong Li
Ji'an Central People's Hospital
Kai Liu
Ji'an Central People's Hospital
Yi Yang
Ji'an Central People's Hospital
Xianyun Xu
xuxianyungmu20110126.com

Ji'an Central People's Hospital

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Abstract

Background

Visceral adiposity and frailty may jointly identify metabolic and physiologic vulnerability, but their longitudinal relationship with cardiometabolic multimorbidity (CMM) is uncertain. We examined initial, cumulative, and two-time-point profile measures of the Chinese visceral adiposity index (CVAI), a 32-deficit frailty index (FI), and their product in relation to incident CMM.

Methods

This landmark cohort study used China Health and Retirement Longitudinal Study data. CVAI and FI were measured in 2011 and 2015; participants with CMM by the 2015 landmark were excluded. CMM was defined as the coexistence of at least two of diabetes, heart disease, and stroke. Initial values, time-weighted cumulative exposure, and K-means two-time-point profiles were evaluated. Cox models estimated hazard ratios (HRs) after adjustment for sociodemographic, behavioral, anthropometric, kidney, lipid-treatment, hypertension, and medication variables. Restricted cubic splines, subgroup analyses, competing-risk and early-event exclusions, additional metabolic adjustment, and multiple-imputation analyses assessed robustness. Conventional receiver operating characteristic (ROC) and decision-curve analyses were exploratory descriptive assessments.

Results

Among 5,150 adults free of CMM at the 2015 landmark, 491 developed CMM over a median 5.08 years. In fully adjusted complete-case models, each 1-SD increment in initial CVAI, FI, and the CVAI-FI product was associated with HRs of 1.34 (95% CI, 1.15–1.56), 1.32 (1.21–1.45), and 1.27 (1.18–1.38), respectively. Corresponding HRs for cumulative measures were 1.43 (1.19–1.73), 1.47 (1.34–1.60), and 1.42 (1.30–1.54). Compared with the lowest product-profile class, the intermediate and highest classes had HRs of 2.74 (2.15–3.49) and 2.96 (2.07–4.23). Participants jointly in the highest CVAI and FI tertiles had an HR of 8.26 (3.49–19.53) versus those jointly in the lowest tertiles. Product associations were nonlinear. The cumulative product had an exploratory ordinary ROC area under the curve of 0.71 (0.69–0.74). Results were materially unchanged across sensitivity analyses and five imputed data sets.

Conclusions

Higher CVAI, frailty burden, and their co-occurrence before a 2015 landmark were associated with incident CMM. Repeated joint assessment may help characterize risk heterogeneity, but external validation and prediction-focused evaluation are required before clinical use.

Introduction

Cardiometabolic multimorbidity (CMM), commonly defined as the coexistence of at least two cardiometabolic diseases, represents a clinically important transition from a single chronic condition to a substantially more complex state. Diabetes, heart disease, and stroke share risk pathways, frequently cluster in later life, and impose interacting demands on medication use, self-management, functional reserve, and health-care delivery. Large collaborative analyses have linked cardiometabolic disease combinations to markedly increased mortality, and national Chinese data have shown that multimorbidity is not confined to high-income Western populations [1, 2]. Prospective studies further suggest that lifestyle behaviors and the accumulation of cardiometabolic disorders are intertwined [3–5]. Obesity is a major upstream determinant, but body mass index alone incompletely represents the distribution and metabolic consequences of adipose tissue [6]. Environmental, behavioral, psychological, and social factors also shape CMM risk [7–10]. This breadth motivates the use of markers that reflect more than one biological domain.

Visceral fat is metabolically active and has closer links to insulin resistance, ectopic lipid deposition, inflammation, and vascular injury than total body size. Lipid-related evidence, including work on remnant cholesterol and triglycerides, supports a causal or etiologic contribution of atherogenic lipid burden to cardiometabolic disease clustering [11]. Several practical anthropometric-metabolic indices have therefore been evaluated for CMM, including the cardiometabolic index, visceral adiposity index, triglyceride-glucose-related indices, and measures that combine waist or body-shape information with circulating lipids [12]. Chinese cohort studies have reported that visceral adiposity or abdominal obesity becomes more informative when considered together with muscle strength, sarcopenia, kidney function, or nontraditional lipid measures [13–17]. Longitudinal work on triglyceride-glucose and lipid-accumulation-product patterns also indicates that sustained exposure may carry information that a single measurement misses [18]. These studies motivate a repeated-measures approach but do not establish whether a population-specific visceral adiposity marker remains informative when the vulnerability of the whole organism is considered simultaneously.

The Chinese visceral adiposity index (CVAI) was developed for Chinese adults from age, body mass index, waist circumference, triglycerides, and high-density lipoprotein cholesterol [19]. In Chinese populations it has been associated with diabetes and has shown useful discrimination for metabolic risk [20]. Recent analyses have connected CVAI with CMM, compared it with other metabolic surrogates, and related it to cardiovascular or cardio-cerebrovascular events [21–24]. Its components are routinely collected, and the sex-specific formula partly accommodates population differences in body composition, making CVAI practical for population studies. Nevertheless, it remains a surrogate rather than a direct imaging measure of visceral fat, and its implications may depend on the host's resilience and accumulated health deficits.

Frailty offers a complementary perspective. The deficit-accumulation frailty index (FI) quantifies the proportion of health deficits present across symptoms, diseases, function, cognition, and other domains.

Rather than measuring a single disease, it summarizes diminished physiological reserve and vulnerability to additional stressors. Frailty and metabolic dysfunction may amplify one another: visceral adiposity can promote chronic inflammation, insulin resistance, mobility limitation, and muscle quality loss, whereas frailty can reduce physical activity, limit recovery, complicate disease management, and increase susceptibility to cardiometabolic transitions. A recent study combining frailty with an insulin-resistance surrogate reported a pronounced CMM gradient [25]. However, an apparently stronger gradient in a derived product does not by itself prove biological synergy or improved clinical prediction. This question requires separate evaluation of association, joint risk stratification, and exploratory discrimination.

We addressed this question using repeated assessments in the China Health and Retirement Longitudinal Study (CHARLS). The 2015 examination was treated as a landmark: CVAI and FI history from 2011 to 2015 was characterized before prospective ascertainment of new CMM. For each domain and their product, we evaluated three representations: the initial 2011 value, a time-weighted cumulative measure, and data-driven two-time-point profiles. We hypothesized that higher CVAI and FI would each be associated with incident CMM, that their combined product would identify a pronounced joint-risk gradient, and that cumulative and profile measures would reveal heterogeneity beyond a single initial value. Nonlinear associations, predefined subgroups, and a series of sensitivity analyses were also examined. Because the analysis was observational and internally evaluated, all discrimination and decision-curve results were considered exploratory rather than evidence of a deployable prediction model.

Methods

Study design and population

CHARLS is an ongoing, nationally representative longitudinal study of community-dwelling middle-aged and older adults in China. Its multistage probability sampling, field procedures, and core survey design have been described previously [26]. The present analysis used harmonized information from the 2011 baseline examination, the 2015 follow-up examination, and outcome follow-up through 2018–2020. We used a landmark design to preserve temporal ordering. The historical exposure window extended from 2011 to 2015; the 2015 visit was time zero for the outcome analysis; and only CMM occurring after that landmark contributed events.

The analytic cohort was assembled sequentially. From 25,586 records in the harmonized source data, 13,760 were removed because they were not in the audited wave-1 cohort, lacked required CMM information, or had prevalent CMM in 2011. A further 1,979 participants had prevalent CMM by 2015 or had 2015 CMM status that could not be ascertained. Of the 9,847 eligible at the landmark screen, 4,600 lacked one or more CVAI components at either 2011 or 2015, and 97 lacked the FI or core baseline information. The final exposure-complete cohort contained 5,150 participants. This count describes the cohort used for descriptive and exposure analyses; fully adjusted Cox models used model-specific

complete cases because several adjustment variables had residual missingness. The flow and timing are shown in Fig. 1.

Chinese visceral adiposity index

CVAI was calculated separately for men and women using the published sex-specific equations [19]. For men, CVAI = -267.93 + 0.68 x age + 0.03 x body mass index + 4.00 x waist circumference + 22.00 x log10(triglycerides) − 16.32 x high-density lipoprotein cholesterol. For women, CVAI = -187.32 + 1.71 x age + 4.23 x body mass index + 1.12 x waist circumference + 39.76 x log10(triglycerides) − 11.66 x high-density lipoprotein cholesterol. Age was measured in years, body mass index in kg/m2, waist circumference in cm, and lipids in mmol/L. Triglyceride and high-density lipoprotein cholesterol values recorded in mg/dL were converted to mmol/L by division by 88.57 before the formula was applied. Components were taken from the same wave so that 2011 and 2015 CVAI represented contemporaneous measurements. The equation has been evaluated in Chinese adults and subsequently used in studies of diabetes, CMM, and cardiovascular outcomes [20–24].

Frailty index

We constructed a 32-deficit FI using the deficit-accumulation approach. Candidate items covered chronic conditions, symptoms, self-rated health, cognition, activities and instrumental activities of daily living, mobility, and other age-related health deficits available at both assessments. Variables were coded from 0 (deficit absent) to 1 (deficit fully present), with intermediate values used for naturally ordered responses where appropriate. The FI was the sum of observed deficit scores divided by the number of nonmissing eligible deficits for that participant and wave. Construction followed established requirements that included multiple health domains, age association, non-saturation at early ages, and consistent direction of adverse coding [27–29]. We required sufficient observed items to calculate a stable individual score and applied the same deficit definitions at both waves. The FI is interpreted as a continuous proportion rather than a disease count. This approach is supported by longitudinal studies using FI change or profile information [30, 31].

Cardiometabolic multimorbidity outcome

The outcome was incident CMM after the 2015 landmark. Diabetes, heart disease, and stroke were ascertained from the harmonized disease indicators available in CHARLS. At each relevant wave, CMM was defined as the coexistence of at least two of these three conditions. Participants meeting that definition in 2011 or at the 2015 landmark were excluded. Follow-up began at the 2015 assessment and ended at the first post-landmark wave when CMM was identified or at the last available outcome assessment for participants who remained free of CMM. Follow-up time was calculated in years from the landmark date. This composite captures disease accumulation, but the analysis does not distinguish all possible sequences of the component diseases.

Covariates

Covariates were selected before outcome modeling based on plausible confounding and availability at the 2015 landmark. Model 1 included age, sex, and marital status. Model 2 additionally included rural residence, current drinking, current smoking, body mass index, education, kidney disease, dyslipidemia proxy, hypertension, antihypertensive medication, and glucose-lowering medication. Education was modeled in four categories. Kidney disease was defined by estimated glomerular filtration rate below 60 mL/min/1.73 m2. Hypertension incorporated the available blood-pressure and diagnosis information. Because the harmonized field used for the frozen analysis did not uniformly provide all laboratory measures needed to diagnose dyslipidemia, lipid-lowering medication use served as the operational dyslipidemia proxy; it was entered once and was not duplicated as a separate covariate. Body mass index remained in Model 2 despite its inclusion in CVAI because the aim was to examine whether CVAI-associated risk extended beyond overall body size. A sensitivity model further adjusted for waist circumference, triglycerides, and high-density lipoprotein cholesterol to test dependence on the components of CVAI.

Statistical analysis

Continuous variables were summarized as mean (SD) when approximately symmetric and as median (interquartile range) when skewed; categorical variables were summarized as number and percentage. Baseline characteristics were compared by incident CMM status using two-sample tests for continuous variables and chi-square or Fisher exact tests for categorical variables, as appropriate. These comparisons were descriptive and were not used to select covariates.

Associations with incident CMM were estimated with Cox proportional hazards regression. Separate models evaluated CVAI, FI, and the CVAI-FI product as standardized continuous measures and as tertiles. Standardization was performed within the analytic data set, so each continuous HR represents a 1-SD increment. We reported crude, Model 1, and Model 2 estimates with 95% confidence intervals (CIs). For the two-time-point profiles, class 1 was the reference. We also cross-classified CVAI and FI tertiles into nine groups to display joint risk, using low CVAI/low FI as the reference. Cumulative hazard curves and risk tables were generated for the tertile and profile measures, with log-rank tests used for unadjusted comparisons.

Potential nonlinearity in the product measure was examined with restricted cubic splines using four knots placed at the 5th, 35th, 65th, and 95th percentiles. The median exposure was the reference. Likelihood-ratio and Wald decomposition procedures provided tests for overall and nonlinear association. Subgroup analyses were conducted by age (< 60 or > = 60 years), sex, drinking, smoking, hypertension, kidney disease, dyslipidemia proxy, glucose-lowering medication, and antihypertensive medication. Multiplicative interaction terms were tested in models that omitted the stratifying variable from the adjustment set. These analyses were exploratory; no multiplicity correction was applied, and isolated interaction P values were interpreted cautiously.

Several sensitivity analyses evaluated robustness. First, Fine-Gray competing-risk regression treated death before observed CMM as a competing event. Second, participants developing CMM within the first year were excluded to reduce the possibility that subclinical disease affected baseline exposure measurements. Third, models additionally adjusted for waist circumference, triglycerides, and high-density lipoprotein cholesterol. Fourth, CVAI was anchored explicitly to the 2011 measurement to assess consistency with the initial-value formulation. Fifth, multiple imputation by chained equations created five completed data sets using the exposure, outcome, follow-up, and covariate information. The imputation analysis was conducted in 5,162 individuals with 493 events who met the broader exposure-outcome criteria; estimates from each completed data set were displayed to show between-imputation stability. The imputed results were treated as a sensitivity analysis rather than substituted for the prespecified complete-case primary model.

Conventional ROC curves summarized how each continuous exposure separated participants with and without an observed CMM event over the available follow-up. Areas under the curve (AUCs), empirical confidence intervals, Youden thresholds, sensitivity, and specificity were calculated. Decision-curve analysis displayed standardized net benefit over a range of thresholds. These analyses did not fix a common prediction horizon, did not use cross-validation or external validation, and did not evaluate a full clinical risk model. These results are reported only as exploratory descriptive discrimination and utility analyses, not as evidence that the CVAI-FI product improves validated risk prediction.

All tests were two-sided. P values below 0.05 were considered statistically significant for the primary association analyses, while subgroup interaction results were treated as hypothesis-generating. Analyses were performed in R version 4.5.2 using survival 3.8-6, ggplot2 4.0.2, pROC 1.19.0.1, mice 3.19.0, and related packages.

Results

Study population and participant characteristics

The final exposure-complete cohort included 5,150 participants free of CMM at the 2015 landmark (Fig. 1). Over a median follow-up of 5.08 years, 491 participants developed CMM. Participants who developed CMM were older and had higher body mass index, CVAI, FI, and CVAI-FI product values at both exposure assessments. Initial mean CVAI was 125.32 (SD, 37.00) among those who later developed CMM and 103.84 (37.03) among those who did not. Median initial FI was 0.19 (interquartile range, 0.11–0.28) versus 0.13 (0.07–0.21), and median initial product was 22.06 (12.70-35.74) versus 12.17 (6.49–21.22). Cumulative measures showed similarly separated distributions. Incident cases were more often women and more often had hypertension or medication indicators of dyslipidemia and diabetes. They were less often current drinkers or smokers, a pattern that may reflect age, illness-related behavior change, selection, or residual confounding rather than protection. Detailed characteristics and variable-specific denominators are presented in Table 1.

Table 1
Participant Characteristics According to Incident Cardiometabolic Multimorbidity Status

Variable	No incident CMM	Incident CMM	P value
Age, y	62.27 (8.56)	63.79 (7.59)	< 0.001
Body mass index, kg/m2	23.59 (3.60)	25.16 (3.79)	< 0.001
CVAI, 2011	103.84 (37.03)	125.32 (37.00)	< 0.001
CVAI, 2015	112.55 (37.95)	131.48 (39.89)	< 0.001
Cumulative CVAI	431.15 (143.58)	513.00 (147.93)	< 0.001
Frailty index, 2011	0.13 (0.07–0.21)	0.19 (0.11–0.28)	< 0.001
Frailty index, 2015	0.15 (0.09–0.24)	0.23 (0.14–0.34)	< 0.001
Cumulative frailty index	0.56 (0.34–0.91)	0.89 (0.55–1.23)	< 0.001
CVAI-FI product, 2011	12.17 (6.49–21.22)	22.06 (12.70-35.74)	< 0.001
CVAI-FI product, 2015	15.34 (8.31–27.40)	27.53 (17.38–44.50)	< 0.001
Cumulative CVAI-FI product	56.71 (32.12–95.99)	105.87 (65.66-154.04)	< 0.001
Exposure interval, y	3.98 (0.10)	3.99 (0.09)	0.01
Sex: female	2448 (52.5)	308 (62.7)	< 0.001
Married	4020 (86.3)	414 (84.3)	0.26
Rural residence	3164 (67.9)	328 (66.8)	0.65
Current drinking	1589 (34.1)	128 (26.1)	< 0.001
Current smoking	1302 (28.0)	90 (18.4)	< 0.001
Kidney disease (eGFR < 60)	443 (9.5)	45 (9.2)	0.87
Dyslipidemia (lipid-lowering Rx)	237 (5.4)	107 (24.3)	< 0.001
Hypertension	1444 (31.5)	286 (59.0)	< 0.001
Antihypertensive Rx	974 (21.8)	228 (49.0)	< 0.001
Glucose-lowering Rx	129 (2.8)	57 (12.4)	< 0.001

Values are mean (SD), median (interquartile range), or No. (%). P values are descriptive. CMM indicates cardiometabolic multimorbidity; CVAI, Chinese visceral adiposity index; FI, frailty index; Rx, medication use.

Initial and cumulative measures

Higher initial CVAI, FI, and the CVAI-FI product were each associated with incident CMM (Table 2). In Model 2, HRs per 1-SD increment were 1.34 (95% CI, 1.15–1.56) for CVAI, 1.32 (1.21–1.45) for FI, and

1.27 (1.18–1.38) for the product. Compared with the lowest tertile, the highest tertile HRs were 1.85 (1.27–2.68), 2.38 (1.80–3.15), and 3.08 (2.24–4.25), respectively. The tertile findings show a particularly pronounced contrast for the joint product even though per-SD effect sizes should not be compared as though they share an identical scale or variance structure.

Table 2
Associations of Initial CVAI, Frailty Index, and the CVAI-FI Product With Incident Cardiometabolic Multimorbidity

Exposure	Model	HR (95% CI)	P value
CVAI			
CVAI (per SD increase)	Crude model	1.68 (1.55–1.83)	< 0.01
CVAI tertiles			
T1	Crude model	Reference	
T2	Crude model	1.99 (1.51–2.61)	< 0.01
T3	Crude model	3.62 (2.81–4.66)	< 0.01
CVAI			
CVAI (per SD increase)	Model 1	1.68 (1.54–1.83)	< 0.01
CVAI tertiles			
T1	Model 1	Reference	
T2	Model 1	1.86 (1.41–2.45)	< 0.01
T3	Model 1	3.35 (2.59–4.34)	< 0.01
CVAI			
CVAI (per SD increase)	Model 2	1.34 (1.15–1.56)	< 0.01
CVAI tertiles			
T1	Model 2	Reference	
T2	Model 2	1.56 (1.12–2.16)	< 0.01
T3	Model 2	1.85 (1.27–2.68)	< 0.01
Frailty index			
Frailty index (per SD increase)	Crude model	1.45 (1.35–1.55)	< 0.01
Frailty index tertiles			
T1	Crude model	Reference	
T2	Crude model	1.47 (1.14–1.91)	< 0.01

Values are HRs (95% CIs) from Cox models. Model 1 adjusted for age, sex, and marital status. Model 2 additionally adjusted for residence, drinking, smoking, body mass index, education, kidney disease, dyslipidemia proxy, hypertension, antihypertensive medication, and glucose-lowering medication. Continuous exposures are per 1 SD. Model 2 used 4,499 complete cases with 390 events.

Exposure	Model	HR (95% CI)	P value
CVAI			
T3	Crude model	2.85 (2.25–3.61)	< 0.01
Frailty index			
Frailty index (per SD increase)	Model 1	1.39 (1.29–1.49)	< 0.01
Frailty index tertiles			
T1	Model 1	Reference	
T2	Model 1	1.40 (1.08–1.82)	0.01
T3	Model 1	2.57 (2.02–3.27)	< 0.01
Frailty index			
Frailty index (per SD increase)	Model 2	1.32 (1.21–1.45)	< 0.01
Frailty index tertiles			
T1	Model 2	Reference	
T2	Model 2	1.45 (1.08–1.95)	0.01
T3	Model 2	2.38 (1.80–3.15)	< 0.01
CVAI-FI product			
CVAI-FI product (per SD increase)	Crude model	1.54 (1.46–1.63)	< 0.01
CVAI-FI product tertiles			
T1	Crude model	Reference	
T2	Crude model	1.83 (1.37–2.44)	< 0.01
T3	Crude model	4.37 (3.37–5.65)	< 0.01
CVAI-FI product			
CVAI-FI product (per SD increase)	Model 1	1.50 (1.41–1.60)	< 0.01
CVAI-FI product tertiles			
T1	Model 1	Reference	
T2	Model 1	1.76 (1.32–2.35)	< 0.01

Values are HRs (95% CIs) from Cox models. Model 1 adjusted for age, sex, and marital status. Model 2 additionally adjusted for residence, drinking, smoking, body mass index, education, kidney disease, dyslipidemia proxy, hypertension, antihypertensive medication, and glucose-lowering medication. Continuous exposures are per 1 SD. Model 2 used 4,499 complete cases with 390 events.

Exposure	Model	HR (95% CI)	P value
CVAI			
T3	Model 1	4.03 (3.08–5.26)	< 0.01
CVAI-FI product			
CVAI-FI product (per SD increase)	Model 2	1.27 (1.18–1.38)	< 0.01
CVAI-FI product tertiles			
T1	Model 2	Reference	
T2	Model 2	1.77 (1.27–2.47)	< 0.01
T3	Model 2	3.08 (2.24–4.25)	< 0.01

Values are HRs (95% CIs) from Cox models. Model 1 adjusted for age, sex, and marital status. Model 2 additionally adjusted for residence, drinking, smoking, body mass index, education, kidney disease, dyslipidemia proxy, hypertension, antihypertensive medication, and glucose-lowering medication. Continuous exposures are per 1 SD. Model 2 used 4,499 complete cases with 390 events.

Cumulative exposure measures produced consistent and in several comparisons stronger gradients (Table 3). Fully adjusted HRs per 1-SD increment were 1.43 (1.19–1.73) for cumulative CVAI, 1.47 (1.34–1.60) for cumulative FI, and 1.42 (1.30–1.54) for the cumulative product. Highest-versus-lowest tertile HRs were 1.72 (1.16–2.55), 3.42 (2.52–4.65), and 3.86 (2.75–5.41), respectively. Cumulative hazard curves separated across tertiles for all three measures (all log-rank P < 0.0001; Fig. 3).

Table 3
Associations of Cumulative CVAI, Frailty Index, and the CVAI-FI Product With Incident Cardiometabolic Multimorbidity

Exposure	Model	HR (95% CI)	P value
Cumulative CVAI			
Cumulative CVAI (per SD increase)	Crude model	1.69 (1.55–1.84)	< 0.01
Cumulative CVAI tertiles			
T1	Crude model	Reference	
T2	Crude model	2.03 (1.54–2.66)	< 0.01
T3	Crude model	3.62 (2.81–4.67)	< 0.01
Cumulative CVAI			
Cumulative CVAI (per SD increase)	Model 1	1.68 (1.54–1.83)	< 0.01
Cumulative CVAI tertiles			
T1	Model 1	Reference	
T2	Model 1	1.89 (1.43–2.48)	< 0.01
T3	Model 1	3.34 (2.58–4.32)	< 0.01
Cumulative CVAI			
Cumulative CVAI (per SD increase)	Model 2	1.43 (1.19–1.73)	< 0.01
Cumulative CVAI tertiles			
T1	Model 2	Reference	
T2	Model 2	1.55 (1.11–2.15)	< 0.01
T3	Model 2	1.72 (1.16–2.55)	< 0.01
Cumulative frailty index			
Cumulative frailty index (per SD increase)	Crude model	1.56 (1.46–1.67)	< 0.01
Cumulative frailty index tertiles			
T1	Crude model	Reference	
T2	Crude model	1.77 (1.34–2.34)	< 0.01
T3	Crude model	3.93 (3.05–5.06)	< 0.01

Values are HRs (95% CIs) from Cox models with the same adjustment sets as Table 2. Cumulative measures equal the mean of the 2011 and 2015 values multiplied by participant-specific elapsed time. Model 2 used 4,499 complete cases with 390 events.

Exposure	Model	HR (95% CI)	P value
Cumulative CVAI			
Cumulative frailty index			
Cumulative frailty index (per SD increase)	Model 1	1.51 (1.41–1.63)	< 0.01
Cumulative frailty index tertiles			
T1	Model 1	Reference	
T2	Model 1	1.69 (1.28–2.24)	< 0.01
T3	Model 1	3.60 (2.77–4.67)	< 0.01
Cumulative frailty index			
Cumulative frailty index (per SD increase)	Model 2	1.47 (1.34–1.60)	< 0.01
Cumulative frailty index tertiles			
T1	Model 2	Reference	
T2	Model 2	1.73 (1.26–2.39)	< 0.01
T3	Model 2	3.42 (2.52–4.65)	< 0.01
Cumulative CVAI-FI product			
Cumulative CVAI-FI product (per SD increase)	Crude model	1.65 (1.56–1.75)	< 0.01
Cumulative CVAI-FI product tertiles			
T1	Crude model	Reference	
T2	Crude model	1.91 (1.41–2.60)	< 0.01
T3	Crude model	5.57 (4.24–7.31)	< 0.01
Cumulative CVAI-FI product			
Cumulative CVAI-FI product (per SD increase)	Model 1	1.63 (1.53–1.73)	< 0.01
Cumulative CVAI-FI product tertiles			
T1	Model 1	Reference	
T2	Model 1	1.87 (1.38–2.56)	< 0.01
T3	Model 1	5.35 (4.03–7.10)	< 0.01

Values are HRs (95% CIs) from Cox models with the same adjustment sets as Table 2. Cumulative measures equal the mean of the 2011 and 2015 values multiplied by participant-specific elapsed time. Model 2 used 4,499 complete cases with 390 events.

Exposure	Model	HR (95% CI)	P value
Cumulative CVAI			
Cumulative CVAI-FI product			
Cumulative CVAI-FI product (per SD increase)	Model 2	1.42 (1.30–1.54)	< 0.01
Cumulative CVAI-FI product tertiles			
T1	Model 2	Reference	
T2	Model 2	1.73 (1.21–2.46)	< 0.01
T3	Model 2	3.86 (2.75–5.41)	< 0.01
Values are HRs (95% CIs) from Cox models with the same adjustment sets as Table 2. Cumulative measures equal the mean of the 2011 and 2015 values multiplied by participant-specific elapsed time. Model 2 used 4,499 complete cases with 390 events.			

Two-time-point profiles and joint tertile groups

The three-class solutions identified low, intermediate, and high two-time-point profiles for each exposure family (Fig. 2). For the CVAI-FI product, class 1 included 3,265 participants, with an observed CMM proportion of 5.0%. Class 2 included 1,547 participants and had a proportion of 16.2%, whereas class 3 included 338 participants and had a proportion of 23.4%. In fully adjusted models, product-profile class 2 had an HR of 2.74 (2.15–3.49) and class 3 an HR of 2.96 (2.07–4.23) relative to class 1 (Table 4). Corresponding highest-profile HRs were 1.91 (1.24–2.94) for CVAI and 2.77 (2.05–3.75) for FI. The profile results were also apparent in cumulative hazard curves with numbers at risk (Fig. 3).

Table 4
Associations of Two-Time-Point Profile Classes With Incident Cardiometabolic Multimorbidity

Exposure	Model	HR (95% CI)	P value
CVAI two-time-point profile class			
CVAI two-time-point profile			
Class 1	Crude model	Reference	
Class 2	Crude model	2.11 (1.62–2.76)	< 0.01
Class 3	Crude model	4.03 (3.09–5.25)	< 0.01
CVAI two-time-point profile class			
CVAI two-time-point profile			
Class 1	Model 1	Reference	
Class 2	Model 1	1.95 (1.50–2.55)	< 0.01
Class 3	Model 1	3.72 (2.84–4.87)	< 0.01
CVAI two-time-point profile class			
CVAI two-time-point profile			
Class 1	Model 2	Reference	
Class 2	Model 2	1.57 (1.13–2.20)	< 0.01
Class 3	Model 2	1.91 (1.24–2.94)	< 0.01
Frailty index two-time-point profile class			
Frailty index two-time-point profile			
Class 1	Crude model	Reference	
Class 2	Crude model	2.14 (1.75–2.63)	< 0.01
Class 3	Crude model	3.59 (2.82–4.58)	< 0.01
Frailty index two-time-point profile class			
Frailty index two-time-point profile			
Class 1	Model 1	Reference	
Class 2	Model 1	2.01 (1.64–2.48)	< 0.01

Values are HRs (95% CIs) from Cox models. Class 1 is the reference. With two assessments, classes summarize paired exposure profiles and are not interpreted as fully observed trajectories. Model 2 used 4,499 complete cases with 390 events.

Exposure	Model	HR (95% CI)	P value
CVAI two-time-point profile class			
CVAI two-time-point profile			
Class 3	Model 1	3.19 (2.47–4.11)	< 0.01
Frailty index two-time-point profile class			
Frailty index two-time-point profile			
Class 1	Model 2	Reference	
Class 2	Model 2	1.87 (1.47–2.37)	< 0.01
Class 3	Model 2	2.77 (2.05–3.75)	< 0.01
CVAI-FI product two-time-point profile class			
CVAI-FI product two-time-point profile			
Class 1	Crude model	Reference	
Class 2	Crude model	3.50 (2.87–4.26)	< 0.01
Class 3	Crude model	5.47 (4.18–7.16)	< 0.01
CVAI-FI product two-time-point profile class			
CVAI-FI product two-time-point profile			
Class 1	Model 1	Reference	
Class 2	Model 1	3.40 (2.77–4.17)	< 0.01
Class 3	Model 1	5.20 (3.91–6.91)	< 0.01
CVAI-FI product two-time-point profile class			
CVAI-FI product two-time-point profile			
Class 1	Model 2	Reference	
Class 2	Model 2	2.74 (2.15–3.49)	< 0.01
Class 3	Model 2	2.96 (2.07–4.23)	< 0.01

Values are HRs (95% CIs) from Cox models. Class 1 is the reference. With two assessments, classes summarize paired exposure profiles and are not interpreted as fully observed trajectories. Model 2 used 4,499 complete cases with 390 events.

Cross-classification supported a strong joint gradient. Participants in the highest CVAI and FI tertiles had an HR of 8.26 (3.49–19.53) compared with participants in the lowest tertiles. Confidence intervals were wide in extreme cross-classified groups, so the magnitude should be interpreted as evidence of risk concentration rather than a precise estimate of multiplicative biological interaction. The product, tertile cross-classification, and profile results were directionally coherent: participants with higher visceral adiposity together with greater deficit accumulation consistently had the greatest observed risk.

Nonlinearity, subgroup analyses, and exploratory discrimination

Restricted cubic splines showed evidence of overall and nonlinear associations for both initial and cumulative CVAI-FI products (all overall and nonlinear $P < 0.001$; Fig. 4). Risk increased more steeply across parts of the upper product distribution, although uncertainty widened at distributional extremes. This shape supports flexible modeling and cautions against interpreting a single HR as constant over the entire exposure range.

Most subgroup estimates were positive and directionally similar (Table 5). The cumulative-product association appeared stronger in participants younger than 60 years than in older participants (P for interaction = 0.02). Interactions were also observed for hypertension, the dyslipidemia proxy, and antihypertensive medication (P for interaction < 0.01 for initial and cumulative products). Associations were numerically stronger among participants without hypertension, without the dyslipidemia proxy, and without antihypertensive treatment. Sex, drinking, smoking, kidney disease, and glucose-lowering medication did not show clear interaction. Because many subgroup tests were performed without multiplicity correction, these differences should not be treated as confirmed effect modification.

Table 5
Subgroup Analyses of Initial and Cumulative CVAI-FI Products

Subgroup	Level	Baseline CVAI-FI product HR (95% CI)	Cumulative CVAI-FI product HR (95% CI)	P for interaction Baseline	P for interaction Cumulative
Age, y	<60	1.43 (1.23–1.67)	1.68 (1.40–2.03)	0.06	0.02
	>=60	1.23 (1.12–1.35)	1.35 (1.22–1.50)		
Sex	Female	1.27 (1.11–1.45)	1.35 (1.16–1.57)	0.65	0.92
	Male	1.26 (1.14–1.39)	1.45 (1.30–1.61)		
Drinking status	No	1.27 (1.16–1.39)	1.42 (1.29–1.57)	0.99	0.84
	Current	1.27 (1.07–1.52)	1.43 (1.19–1.72)		
Smoking status	No	1.27 (1.17–1.39)	1.46 (1.32–1.60)	0.79	0.46
	Current	1.35 (1.08–1.69)	1.32 (1.04–1.69)		
Hypertension	No	1.56 (1.37–1.79)	1.72 (1.49–1.98)	< 0.01	< 0.01
	Yes	1.16 (1.04–1.28)	1.27 (1.13–1.42)		
Kidney disease	No	1.26 (1.15–1.37)	1.40 (1.28–1.54)	0.34	0.47
	Yes	1.33 (0.97–1.82)	1.40 (1.04–1.89)		
Dyslipidemia	No	1.36 (1.24–1.49)	1.51 (1.37–1.66)	< 0.01	< 0.01
	Yes	1.05 (0.89–1.24)	1.14 (0.95–1.37)		
Glucose-lowering medication use	No	1.28 (1.18–1.40)	1.42 (1.30–1.56)	0.13	0.16

Values are Model 2 HRs (95% CIs) per 1-SD increase. Models omitted the stratifying variable and used available model-specific complete cases. Interaction tests were multiplicative, exploratory, and not adjusted for multiple comparisons.

Subgroup	Level	Baseline CVAI-FI product HR (95% CI)	Cumulative CVAI-FI product HR (95% CI)	P for interaction Baseline	P for interaction Cumulative
	Yes	1.25 (0.97–1.62)	1.39 (1.06–1.83)		
Antihypertensive medication use	No	1.49 (1.32–1.69)	1.62 (1.42–1.84)	< 0.01	< 0.01
	Yes	1.15 (1.03–1.28)	1.27 (1.12–1.43)		

Values are Model 2 HRs (95% CIs) per 1-SD increase. Models omitted the stratifying variable and used available model-specific complete cases. Interaction tests were multiplicative, exploratory, and not adjusted for multiple comparisons.

In conventional ROC analyses, the initial product had an AUC of 0.69 (0.66–0.71), compared with 0.66 (0.64–0.69) for initial CVAI and 0.64 (0.61–0.66) for initial FI. The cumulative product had the highest descriptive AUC, 0.71 (0.69–0.74), with a Youden threshold of 79.34, sensitivity of 0.67, and specificity of 0.67 (Table 6 and Fig. 5). Decision curves suggested potential net benefit over selected thresholds. These ordinary ROC and decision curves do not constitute internally validated time-to-event prediction analyses and should not be used to infer clinical transportability.

Table 6
Exploratory Ordinary ROC Discrimination of Initial and Cumulative Exposure Measures

Predictor	AUC (95% CI)	Best threshold	Specificity	Sensitivity
Baseline CVAI	0.66 (0.64–0.69)	109.46	0.59	0.65
Baseline frailty index	0.64 (0.61–0.66)	0.17	0.64	0.59
Baseline CVAI-FI product	0.69 (0.66–0.71)	20.39	0.73	0.56
Cumulative CVAI	0.66 (0.63–0.68)	406.99	0.46	0.78
Cumulative CVAI-FI product	0.71 (0.69–0.74)	79.34	0.67	0.67
Cumulative frailty index	0.67 (0.64–0.69)	0.83	0.70	0.56

Ordinary ROC analyses classify observed events over available follow-up and do not account for censoring at a fixed prediction horizon. Thresholds use the original exposure scale. These results are descriptive and not a validated prediction analysis.

Sensitivity analyses

Results were stable across sensitivity analyses. The fully adjusted subdistribution HR for a 1-SD increment in the cumulative product was 1.40 (1.29–1.53) when death was treated as a competing event. After exclusion of CMM events within the first year, the corresponding Cox HR was 1.42 (1.30–1.54). Additional adjustment for waist circumference, triglycerides, and high-density lipoprotein cholesterol yielded an HR of 1.26 (1.17–1.37) for the initial product. When CVAI was anchored to its 2011 value, its per-SD HR was 1.51 (1.34–1.69).

Across five imputed data sets, product estimates varied minimally. Initial-product HRs ranged from 1.28 to 1.29, and cumulative-product HRs ranged from 1.39 to 1.40. For the product profiles, class-2 HRs ranged from 2.53 to 2.58 and class-3 HRs from 3.03 to 3.09 (Table 7). Similar estimates in the broader imputation cohort reduce concern that complete-case selection alone explains the observed associations, although imputation cannot recover information that was never measured or eliminate nonrandom missingness.

Table 7
Sensitivity Analyses Across Five Imputed Data Sets

Exposure	Imputed data set 1	Imputed data set 2	Imputed data set 3	Imputed data set 4	Imputed data set 5
Baseline CVAI (per SD increase)	1.34 (1.17–1.54)	1.35 (1.17–1.55)	1.34 (1.17–1.53)	1.33 (1.16–1.53)	1.33 (1.16–1.53)
Baseline frailty index (per SD increase)	1.33 (1.23–1.44)	1.33 (1.23–1.43)	1.33 (1.24–1.44)	1.33 (1.23–1.44)	1.33 (1.23–1.44)
Baseline CVAI-FI product (per SD increase)	1.29 (1.20–1.38)	1.28 (1.20–1.38)	1.29 (1.21–1.38)	1.29 (1.20–1.38)	1.29 (1.21–1.38)
Cumulative CVAI (per SD increase)	1.42 (1.20–1.68)	1.43 (1.21–1.69)	1.42 (1.20–1.69)	1.42 (1.19–1.68)	1.41 (1.19–1.68)
Cumulative CVAI-FI product (per SD increase)	1.39 (1.29–1.50)	1.40 (1.30–1.50)	1.39 (1.29–1.50)	1.40 (1.30–1.51)	1.40 (1.30–1.51)
Cumulative frailty index (per SD increase)	1.45 (1.34–1.57)	1.45 (1.34–1.56)	1.45 (1.34–1.56)	1.45 (1.34–1.57)	1.45 (1.34–1.57)
CVAI two-time-point profile class - Class 1	Reference	Reference	Reference	Reference	Reference
CVAI two-time-point profile class - Class 2	1.44 (1.07–1.93)	1.45 (1.08–1.94)	1.44 (1.07–1.93)	1.42 (1.06–1.91)	1.42 (1.06–1.91)
CVAI two-time-point profile class - Class 3	1.88 (1.28–2.75)	1.87 (1.28–2.75)	1.89 (1.29–2.76)	1.83 (1.25–2.68)	1.85 (1.26–2.70)
Frailty index two-time-point profile class - Class 1	Reference	Reference	Reference	Reference	Reference
Frailty index two-time-point profile class - Class 2	1.88 (1.52–2.32)	1.90 (1.54–2.35)	1.90 (1.54–2.35)	1.89 (1.53–2.33)	1.88 (1.53–2.33)
Frailty index two-time-point profile class - Class 3	2.61 (2.00-3.41)	2.59 (1.98–3.38)	2.59 (1.98–3.38)	2.60 (1.99–3.40)	2.58 (1.98–3.38)
CVAI-FI product two-time-point profile class - Class 1	Reference	Reference	Reference	Reference	Reference
CVAI-FI product two-time-point profile class - Class 2	2.53 (2.04–3.14)	2.58 (2.08–3.20)	2.55 (2.06–3.16)	2.53 (2.04–3.14)	2.55 (2.05–3.16)

Values are Model 2 HRs (95% CIs) estimated separately in five completed data sets. The imputation analysis included 5,162 participants and 493 events and is a sensitivity analysis.

Exposure	Imputed data set 1	Imputed data set 2	Imputed data set 3	Imputed data set 4	Imputed data set 5
CVAI-FI product two-time-point profile class - Class 3	3.09 (2.27–4.21)	3.07 (2.25–4.18)	3.05 (2.24–4.16)	3.06 (2.24–4.17)	3.03 (2.22–4.13)
Values are Model 2 HRs (95% CIs) estimated separately in five completed data sets. The imputation analysis included 5,162 participants and 493 events and is a sensitivity analysis.					

Discussion

Principal findings

In this national cohort of Chinese middle-aged and older adults, higher CVAI, greater deficit-accumulation frailty, and their joint product before a 2015 landmark were consistently associated with incident CMM. Initial CVAI and FI each carried independent prognostic information in covariate-adjusted association models. The cumulative measures, which integrated 2011 and 2015 exposure with elapsed time, showed gradients with subsequent CMM. Simple two-time-point profiles separated groups with markedly different event proportions and adjusted hazards, especially for the CVAI-FI product. Participants jointly in the highest CVAI and FI tertiles had the most concentrated risk. Spline and sensitivity analyses were consistent with the central association, while the exploratory discrimination analyses suggested only moderate separation and do not justify a clinical prediction claim.

Previous studies have associated triglyceride-glucose, abdominal obesity, lipid parameters, muscle strength, sarcopenia, kidney measures, and other modifiable factors with CMM [8, 10–18, 25]. Work using CVAI has shown associations with diabetes and cardiometabolic outcomes and has compared its performance with other adiposity surrogates [19–24]. Here, repeated FI information was incorporated within a landmark design that preceded outcome ascertainment. Separating exposure history from outcome ascertainment helps distinguish antecedent vulnerability from consequences of already established multimorbidity.

Comparison with previous work

Longitudinal patterns of metabolic indices have been associated with cardiovascular outcomes [32]. The results are also consistent with emerging studies that combine a metabolic or atherogenic index with frailty. A triglyceride-glucose-frailty index has been associated with incident CMM in CHARLS, while combined triglyceride-glucose and frailty measures have predicted cardiovascular disease and stroke in prospective cohorts [25, 33]. Studies of an atherogenic index plus FI, joint triglyceride-glucose and frailty exposure, a cholesterol-high-density-lipoprotein-glucose frailty index, and a combined atherogenic-frailty index have also reported that participants with high burden in both domains fare worst [34–37]. The cited studies describe metabolic load and reduced reserve as separate, overlapping dimensions of vulnerability.

Our work differs in the metabolic construct and in how exposure history was represented. CVAI incorporates age, body mass index, waist circumference, triglycerides, and high-density lipoprotein cholesterol through sex-specific formulas designed for Chinese adults [19]. It therefore captures central adiposity and lipid phenotype more directly than fasting-glucose-based insulin-resistance surrogates. The FI, in contrast, aggregates manifestations across organ systems and functional domains. Their product is consequently interpretable as an empirical cross-domain co-burden score. We deliberately avoid labeling it a mechanistically validated index: multiplication changes the distribution, creates scale dependence, and can amplify upper-tail contrasts even in the absence of statistical interaction. The concordant results from separate CVAI and FI models, cross-classified tertiles, the product, and profile classes are more informative than the product alone.

Longitudinal studies have increasingly examined cumulative exposure and dynamic categories. Two-wave and multiwave patterns of metabolic indices have been associated with cardiovascular outcomes, while FI patterns and changes have been linked to physical decline and cardiovascular disease [30–32, 38–41]. Long-term insulin resistance has likewise been connected to frailty progression and cardiovascular disease [38]. Our two-point cumulative measure is transparent and preserves the exposure-time window; it should not be confused with a lifetime cumulative dose. The K-means groups summarize paired measurements, not fully observed trajectories. Two participants with identical endpoints but different intermediate paths cannot be distinguished when only 2011 and 2015 are observed.

The observed FI findings fit extensive evidence that frailty is related to adverse metabolic and cardiovascular transitions. Frailty has been associated with progression from prediabetes to diabetes, cardiovascular disease, and mortality; changes in frailty have predicted incident cardiovascular disease across cohorts [39, 40]. Mendelian-randomization evidence has also been used to explore possible causal directions between FI and cardiovascular disease, although genetic-instrument assumptions and lifelong effects differ from the present observational estimand [41]. Frailty is common across countries and reflects systemic deficit accumulation rather than a single organ diagnosis [42–45]. Genome-wide work further suggests that its biology spans multiple pathways, including neurological and aging-related processes [46]. This evidence makes frailty relevant to studies of cardiometabolic disease accumulation, but does not establish that reducing an FI value will necessarily lower CMM risk.

Potential mechanisms

Several pathways may explain why CVAI and FI jointly mark CMM risk. Visceral adipose tissue releases free fatty acids and adipokines, promotes ectopic fat deposition, and contributes to hepatic and peripheral insulin resistance. Dysregulated lipid flux, endothelial dysfunction, oxidative stress, and low-grade inflammation can accelerate diabetes, atherosclerotic heart disease, and cerebrovascular injury. CVAI combines central size and lipid information and may therefore reflect this metabolic environment more closely than body mass index alone. The persistence of an association after adjustment for body mass index is consistent with, but does not prove, information beyond generalized adiposity.

Frailty may intensify these processes through reduced skeletal-muscle mass or quality, lower activity, autonomic dysregulation, endocrine changes, poor nutrition, and limited capacity to recover from illness. Skeletal muscle is a major site of glucose disposal; declining muscle function can worsen insulin sensitivity and reduce the ability to offset excess energy stores. Conversely, chronic metabolic inflammation and microvascular injury may impair muscle and neurological function, increase fatigue, and accelerate deficit accumulation. Medication burden, depression, mobility restriction, and socioeconomic adversity may further couple the two domains. High CVAI with high FI could indicate both a strong cardiometabolic stressor and limited multisystem reserve.

The nonlinear product associations are plausible under a threshold or saturation framework. At low values, increments in one domain may be partly tolerated. Once metabolic load and deficits both become substantial, compensatory capacity may diminish and small further increases may coincide with steeper risk. Spline curvature can also arise from the product's skewed distribution, residual confounding, influential observations, or differential measurement error. The wider confidence bands at the extremes emphasize that the curve should guide flexible modeling rather than define clinical cut points.

The subgroup patterns require similar restraint. Stronger relative associations among participants without hypertension or antihypertensive treatment could reflect a larger contrast among individuals not already identified as high risk, treatment-related risk attenuation, index-event bias, or differences in baseline hazard. A lower relative HR among treated or hypertensive participants does not imply lower absolute risk. The dyslipidemia interaction is especially sensitive to the operational definition based on lipid-lowering medication. The age interaction for cumulative product may reflect survival, competing risk, selective participation, or a larger relative impact of premature co-burden in younger participants. Replication with prespecified interaction hypotheses and absolute-risk estimates is needed.

Clinical and public-health implications

Waist circumference and routine lipids capture a modifiable metabolic phenotype, while the FI describes accumulated vulnerability that may be visible through function, symptoms, cognition, and chronic disease. Repeatedly high values in both domains could identify people who merit careful assessment of blood pressure, glycemia, lipids, physical function, nutrition, medication management, and barriers to activity. Functional reserve and deficit burden may influence risk and the feasibility of intervention even when the primary goal is to prevent diabetes or vascular events.

This analysis does not establish a screening threshold. The cumulative product's ordinary AUC of 0.71 is moderate, and the comparison did not include a fully specified clinical risk model evaluated at a fixed horizon. Because CVAI includes variables already available to clinicians and the FI requires multiple items, implementation would need to demonstrate incremental value over simpler alternatives, reliable data capture, calibration, and equitable performance. A future prediction study should prespecify a landmark and horizon, use fold-local preprocessing, compare nested models, quantify calibration and

Brier score, and perform internal-external or external validation. Decision-curve analysis would then be interpretable in relation to a validated probability model and a defined clinical action.

The results are currently more applicable to etiologic and risk-stratification questions. They suggest that a high visceral-adiposity phenotype and deficit accumulation are not redundant. The nine-group tertile analysis, although imprecise at some extremes, makes the joint gradient tangible without requiring acceptance of the product's exact scale. The two-time-point profiles likewise show that repeated measurement can separate persistently low from higher-burden groups. In practice, attention to direction and persistence may be more reliable than adopting the numerical product cut point from one cohort.

Strengths and limitations

Strengths include the national CHARLS setting, repeated metabolic and frailty measurements, explicit 2015 landmark, incident CMM outcome, and parallel evaluation of initial, cumulative, cross-classified, and profile measures. The landmark design reduces future-information leakage because post-2015 outcomes were not used to construct the exposure history. The FI was based on a broad deficit set rather than a single self-reported frailty item. Findings were consistent in competing-risk, early-event-exclusion, additional-adjustment, alternate-anchoring, and multiple-imputation analyses. Composite figures display risk tables and exposure distributions alongside the main analytic contrasts.

Several limitations remain. First, this is an observational analysis, and residual or unmeasured confounding is likely. Diet, physical activity detail, inflammatory biomarkers, medication adherence, access to care, and socioeconomic circumstances may not be fully captured. Reverse causation may persist despite the landmark and early-event exclusion because subclinical cardiometabolic disease can influence weight, lipids, function, or behavior before diagnosis. The results should therefore be interpreted as associations rather than causal effects.

Second, diabetes, heart disease, and stroke were based on harmonized survey indicators, which may be affected by recall, diagnostic access, and interval censoring. The exact onset date was not continuously observed; follow-up was aligned to survey waves. The composite outcome does not differentiate the sequence, severity, or phenotype of component diseases. Death can preclude observed CMM, and although the competing-risk analysis was consistent, incomplete death information or informative loss to follow-up may remain.

Third, CVAI is a surrogate and is partly age-dependent by construction. It is not equivalent to computed tomography or magnetic-resonance imaging of visceral fat. Adjusting for age and body mass index helps address confounding but also complicates interpretation because age and body mass index are components of the exposure. Additional adjustment for waist and lipids may represent overadjustment if these variables are integral to the CVAI construct; we therefore treated that model as a sensitivity analysis. The product with FI is scale-dependent, has no established clinical unit, and may be influenced by skewness. External work is required to determine whether another joint formulation is more stable or interpretable.

Fourth, the main cohort required exposure completeness at two visits, creating potential selection bias toward healthier survivors with repeated biomarker data. Fully adjusted models additionally relied on model-specific complete cases (4,499 participants and 390 events), so their estimand applies to participants with observed covariates. The imputation analysis included 5,162 participants and 493 events and produced similar estimates, but missing-at-random assumptions cannot be verified. The difference in analytic denominators is disclosed to prevent the cohort count from being mistaken for the exact sample size of every model.

Fifth, only two exposure assessments were available for the frozen analysis. K-means classes summarize paired levels and should not be interpreted as rich trajectories. Cluster choice is data-dependent, alternative standardization or clustering methods could yield different groups, and the three-class solution requires replication. Cumulative measures assume linear interpolation between visits and cannot capture short-term variability or unobserved changes.

Sixth, multiple exposure formulations, subgroup analyses, and interactions increase the chance of false-positive findings. The subgroup results were not multiplicity-adjusted and are explicitly exploratory. The apparent attenuation in participants with treated hypertension or dyslipidemia may reflect confounding by indication or differences in relative rather than absolute risk. Finally, the ROC analysis ignored censoring and variable follow-up, and no resampling or external validation was used. It describes separation in this data set but cannot support a claim of improved five-year prediction or clinical readiness.

Future research

Replication should begin with a transportable exposure definition and a prespecified analysis contract. Cohorts with at least three repeated assessments could distinguish stable-high, increasing, decreasing, and fluctuating patterns more convincingly. Imaging or dual-energy X-ray measures would allow evaluation of how much of CVAI's association is attributable to actual visceral fat. Mediation could be examined with repeated inflammatory, metabolic, muscle, and functional biomarkers without treating the present product as a mechanistic construct. Transition-specific analyses could determine whether the joint phenotype is more strongly related to diabetes-first, heart-disease-first, or stroke-first pathways.

Clinical prediction studies should compare a parsimonious reference model with models that add CVAI, FI, or their joint representation, using fixed time zero, fixed horizon, appropriate survival metrics, calibration, decision analysis, and external validation. Net reclassification measures should be used only with clear risk categories and clinical consequences. The value of repeated measurement should be judged by whether it changes decisions or outcomes, not solely by whether it yields a statistically significant HR.

Conclusions

Across the 2011–2015 exposure window in CHARLS, higher CVAI and frailty burden were associated with incident CMM after the 2015 landmark. Risk was greatest when both domains were elevated, whether exposure was represented by initial values, cumulative measures, cross-classified tertiles, or two-time-point profiles. The observational results favor repeated assessment of visceral adiposity and physiologic vulnerability, but the CVAI-FI product remains a research co-burden marker rather than a validated clinical prediction tool. Implementation requires replication, fixed-horizon validation, and comparison with simpler risk models.

Declarations

Ethics approval and consent to participate

The original CHARLS protocol was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015), and all participants provided informed consent.

Clinical trial number

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

CHARLS data are available to qualified researchers through the official CHARLS data portal subject to registration and the study's data-use conditions. Analysis scripts and derived non-identifiable outputs for this manuscript are retained in the local project archive.

Competing interests

The authors declare that there are no competing interests.

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Authors’ contributions

Conceptualization, methodology, supervision, and project administration: LY, QL, and XX;

Software: LY, QL, and KL;

Formal analysis and validation: LY and YY;

Data curation: LY and YY;

Investigation, resources and material collection: LY, QL and KL;

Writing-original draft preparation: LY, QL, KL, and YY;

Writing-reviewing and editing: XX.

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Figures

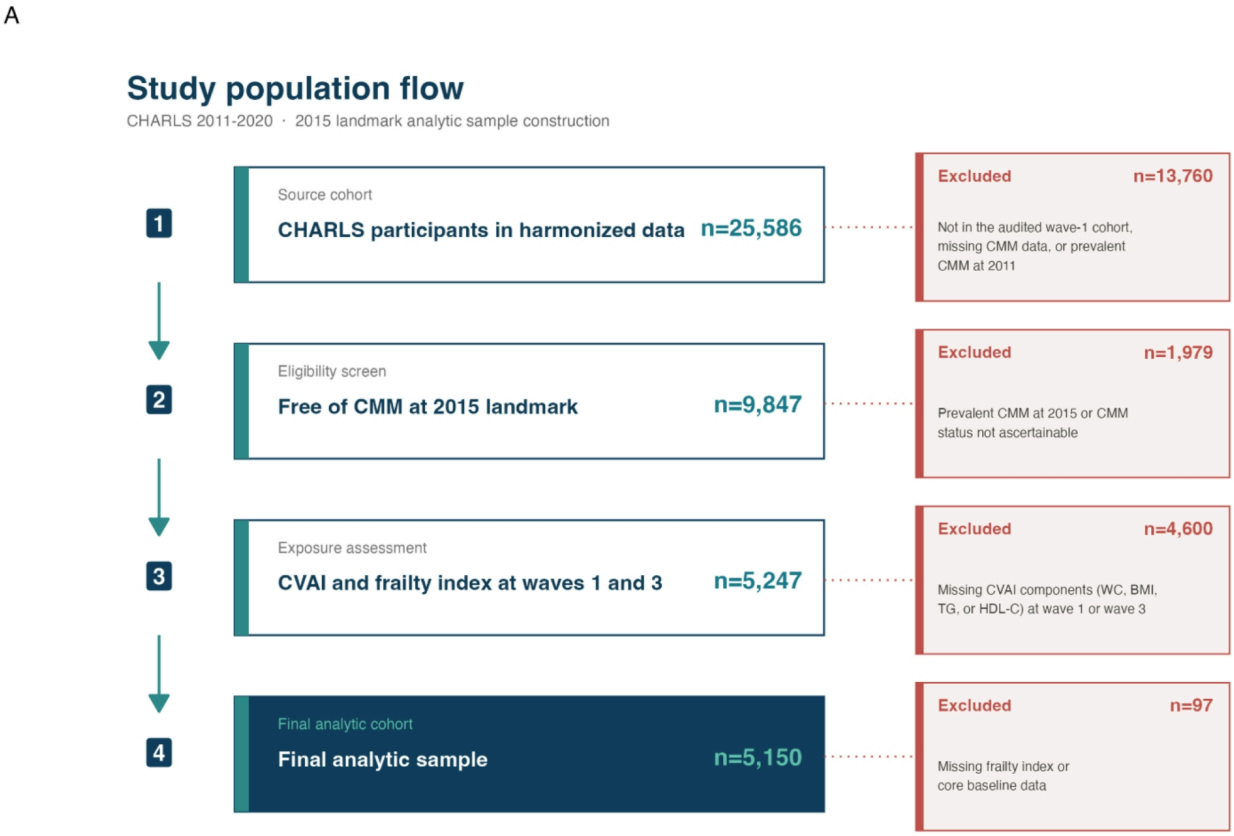


Figure 1

Study population flow and landmark timeline.

Panel A shows sequential construction of the exposure-complete cohort. Panel B shows the 2011-2015 historical exposure window, the 2015 landmark, and post-landmark ascertainment of incident CMM3. Fully adjusted models use model-specific complete cases. CMM3 indicates coexistence of at least two of diabetes, heart disease, and stroke; CVAI, Chinese visceral adiposity index; FI, frailty index.

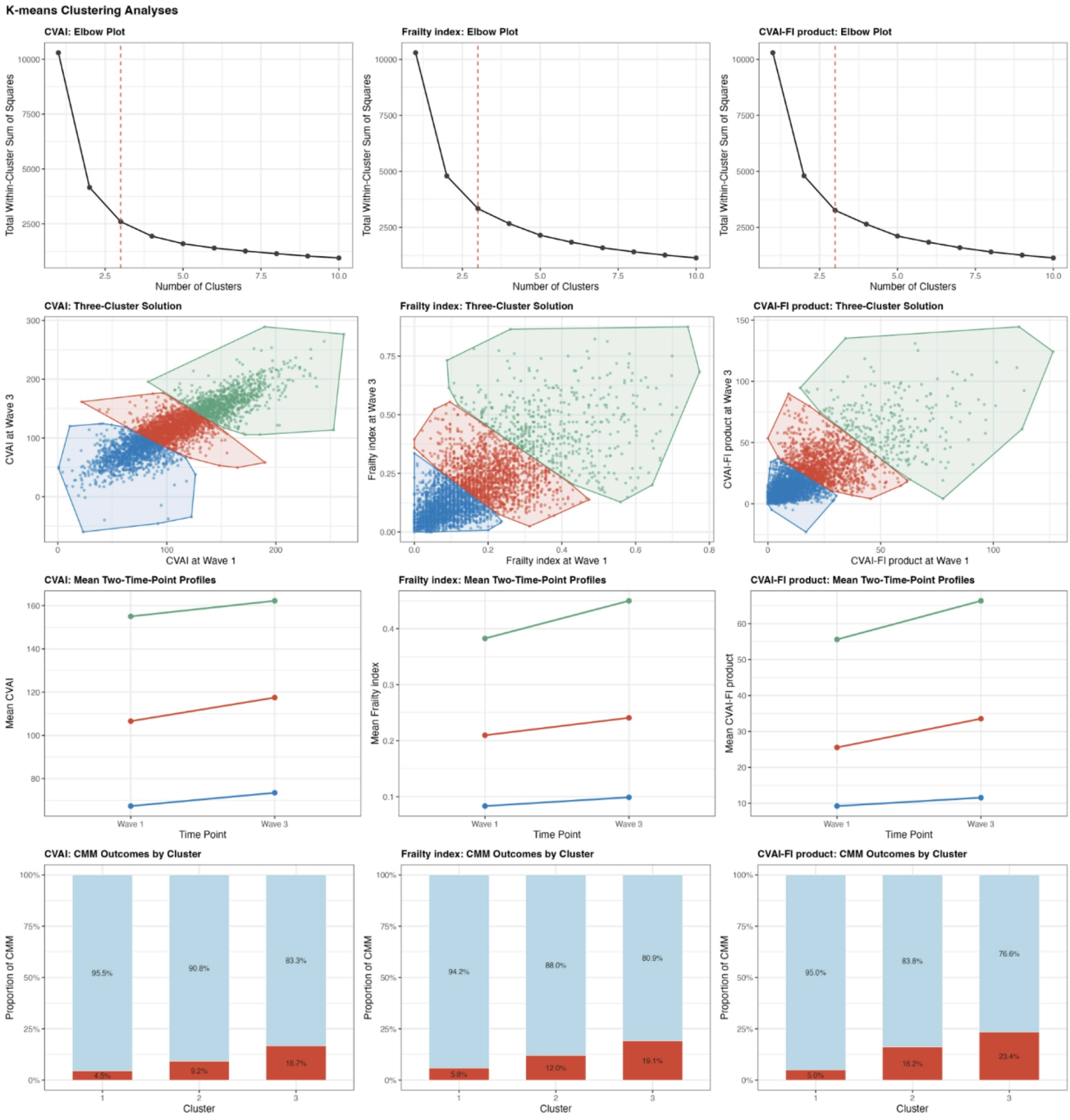


Figure 2

K-means clustering of paired CVAI, frailty index, and CVAI-FI product measurements.

Panels A-C show elbow plots supporting a three-class solution; panels D-F show paired-value distributions and cluster envelopes; panels G-I show mean two-time-point profiles; and panels J-L show observed CMM status by class. With only two assessments, classes are interpreted as profiles rather than full trajectories.

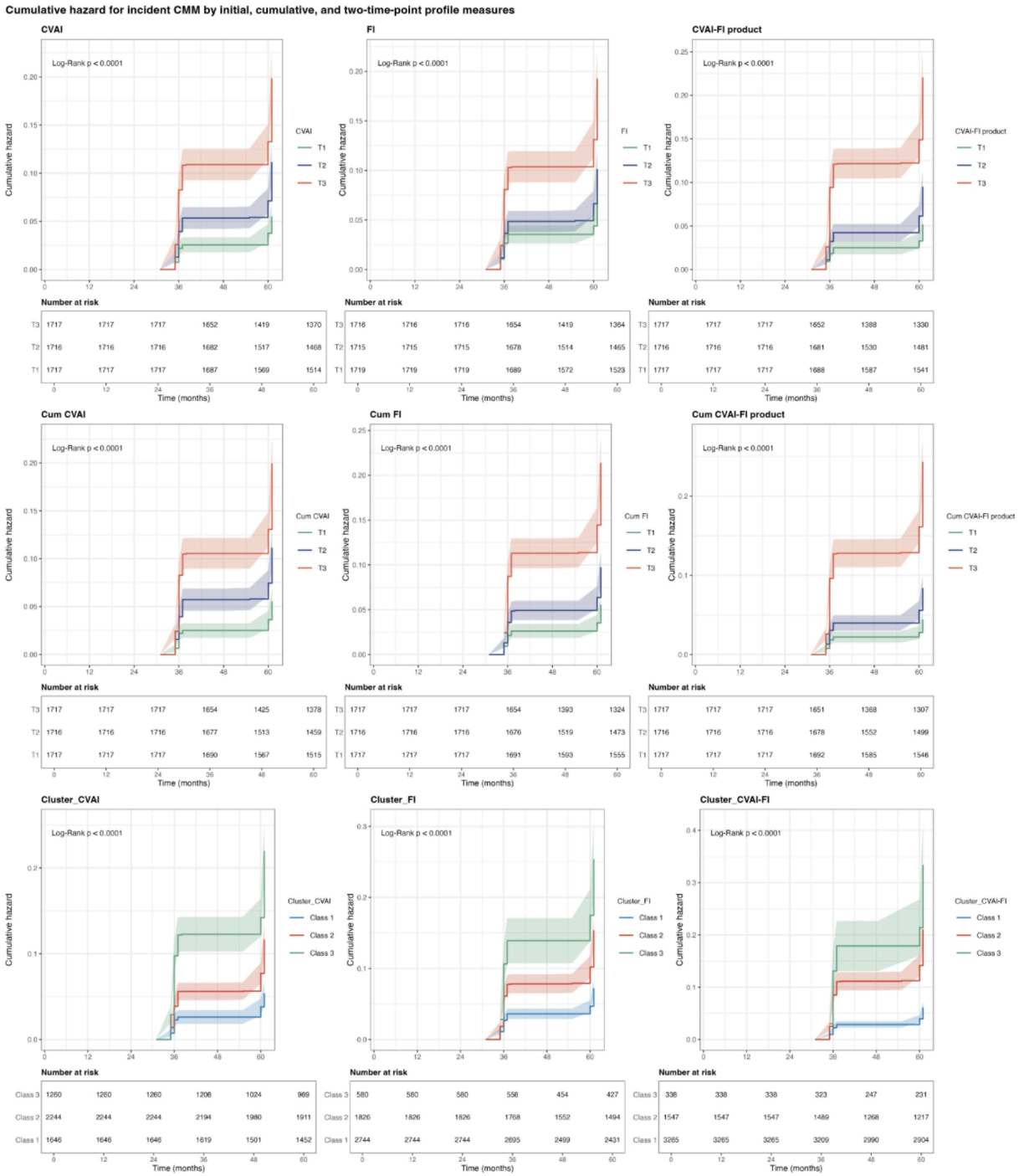


Figure 3

Cumulative hazard curves for incident CMM by initial, cumulative, and two-time-point profile measures.

Columns show CVAI, FI, and the CVAI-FI product; rows show initial tertiles, cumulative tertiles, and profile classes. Numbers at risk and unadjusted log-rank P values are displayed.

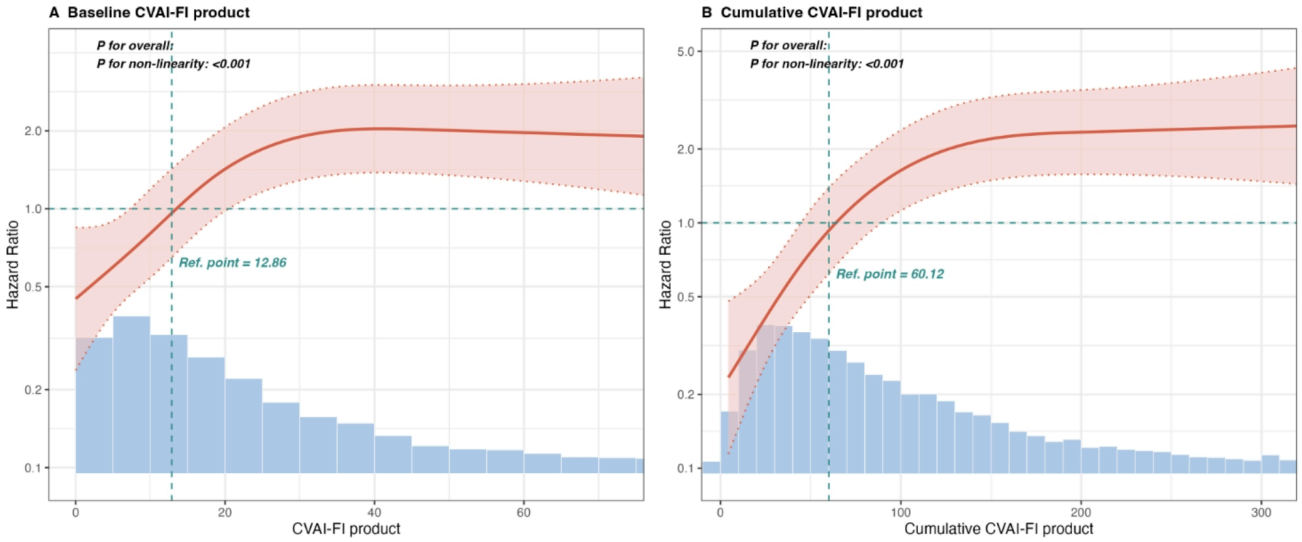


Figure 4

Restricted cubic spline associations of the CVAI-FI product with incident CMM.

Panel A shows the initial 2011 product and panel B the cumulative product. Solid curves are adjusted HRs, shaded regions are 95% CIs, histograms show exposure distributions, vertical dashed lines mark reference values, and the horizontal dashed line indicates HR=1.

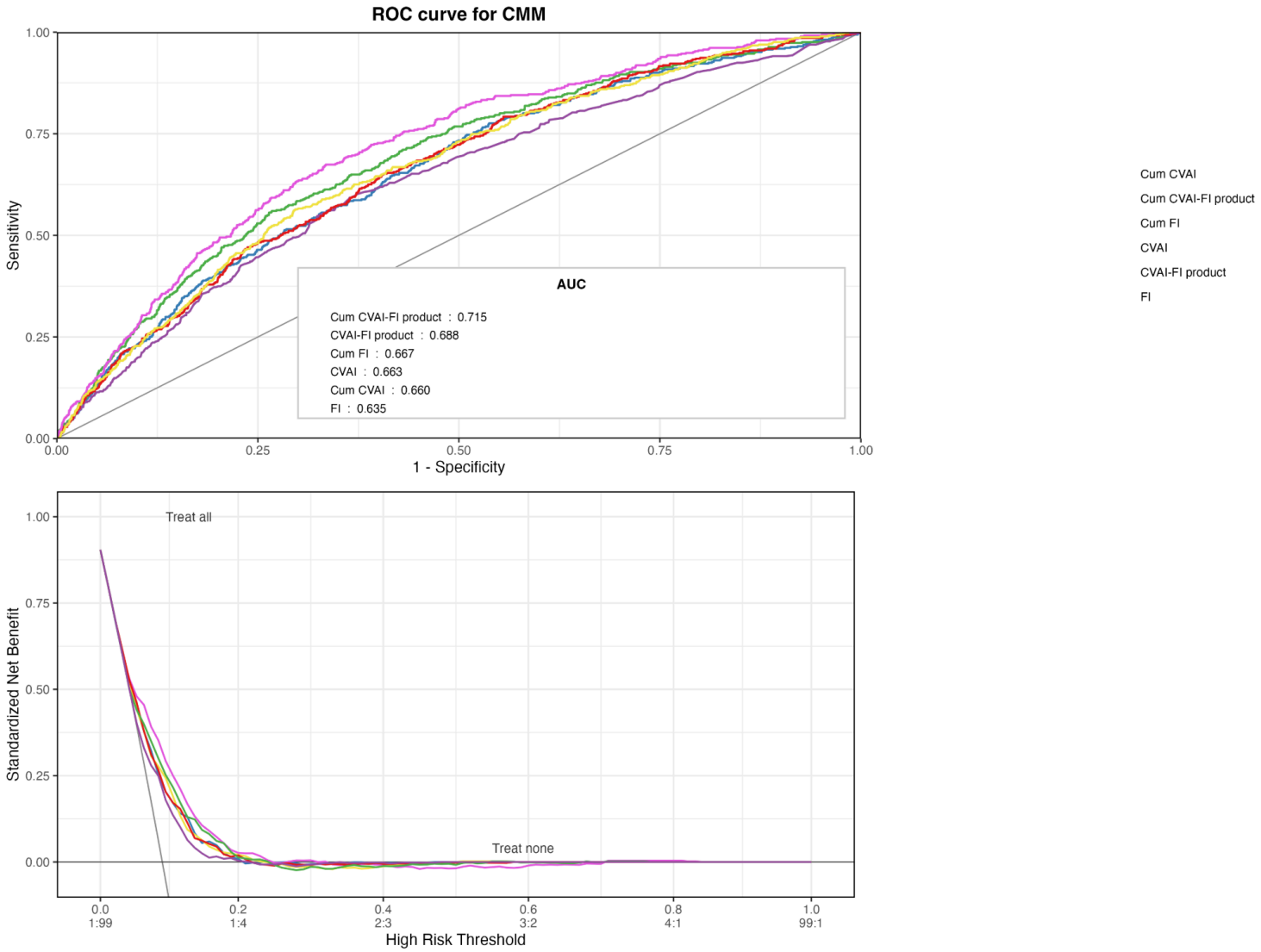


Figure 5

Exploratory ordinary ROC curves and decision-curve analysis.

Panel A compares observed-event discrimination for initial and cumulative CVAI, FI, and product measures. Panel B displays standardized net benefit across thresholds. The analyses do not use a fixed survival horizon or external validation and are not a validated clinical prediction model.