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Associations of cumulative exposure and dynamic trajectories of the Modified Life's Essential 8 with incident cardiometabolic multimorbidity: a longitudinal analysis based on the China Health and Retirement Longitudinal Study (CHARLS)

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Abstract

Background

Life's Essential 8 (LE8) comprehensively assesses cardiovascular health, but previous studies have largely relied on a single measurement. Evidence linking cumulative exposure and sustained modified LE8 (mLE8) levels to incident cardiometabolic multimorbidity (CMM) remains limited in middle-aged and older Chinese adults.

Methods

Data were obtained from the China Health and Retirement Longitudinal Study. Baseline and longitudinal analyses included 8,815 and 5,394 participants, respectively. Cox models, restricted cubic splines, and k-means clustering assessed associations and longitudinal patterns. A prediction model was evaluated in both the training and validation cohorts using receiver operating characteristic curves, calibration curves, and decision curve analysis. Shapley additive explanations (SHAP) were used to further interpret the model.

Results

During follow-up, 812 participants (9.21%) developed CMM. Each 10-point increase in baseline mLE8 was associated with a 20% lower CMM risk (hazard ratio (HR) = 0.80, 95% confidence interval (CI) 0.76–0.85), and the HR for the highest versus lowest quartile was 0.47 (95% CI 0.37–0.59). Each 10-point increase in cumulative mLE8 (cumLE8) was associated with a 12% lower risk (HR, 0.88; 95% CI, 0.85–0.91). Compared with the persistently low-level group, the persistently moderate- and high-level groups had lower risks (HRs, 0.65 and 0.34, respectively). Baseline mLE8 showed an approximately linear inverse association with CMM, whereas cumLE8 showed a nonlinear inverse association. Adding mLE8 to conventional risk factors modestly improved prediction.

Conclusions

Higher baseline and cumLE8 levels and maintenance of higher mLE8 levels were associated with lower CMM risk. Longitudinal mLE8 monitoring may support CMM risk stratification and prevention.

Introduction

Cardiometabolic multimorbidity (CMM) is commonly defined as the coexistence of two or more cardiometabolic diseases (CMDs), including heart disease, stroke, and diabetes, within the same individual. With accelerated population aging and the continuing accumulation of chronic disease burden, the progression from a single CMD to CMM has become an increasing concern among middle-aged and older adults [1–3]. Compared with a single chronic condition, CMM is associated with more complicated disease management, greater healthcare utilization, poorer quality of life [4, 5], and an increased risk of disability and premature mortality. The coexistence of multiple CMDs may also lead to therapeutic conflicts, polypharmacy, and a substantial economic burden on patients and healthcare systems. Identifying modifiable health behaviors and metabolic factors before the development of CMM may therefore provide opportunities to delay disease progression and improve the coordinated prevention and management of cardiometabolic conditions [6–8].

Life's Essential 8 (LE8), proposed by the American Heart Association, is a comprehensive framework for evaluating cardiovascular health. It consists of four health behaviors: diet, physical activity, nicotine exposure, and sleep; and four health factors: body mass index, blood lipids, blood glucose, and blood pressure. Each component is scored on a scale ranging from 0 to 100, with a higher overall score representing a more favorable cardiovascular health status. Unlike the assessment of individual risk factors, LE8 integrates behavioral and biological dimensions and may provide a broader representation of an individual's overall cardiometabolic health [9–12]. Previous studies have linked higher LE8 scores to lower risks of cardiovascular disease, diabetes, stroke, and all-cause and cardiovascular mortality [13–16]. These findings suggest that maintaining favorable cardiovascular health across multiple domains may be relevant not only to the prevention of individual diseases but also to reducing the accumulation of cardiometabolic conditions.

Nevertheless, most previous studies have relied on LE8 measured at a single time point, which may be influenced by short-term variation and may not adequately reflect long-term cardiovascular health [17, 18]. Repeated assessments may provide complementary information by capturing cumulative exposure and the sustained maintenance of cardiovascular health. However, evidence linking these longitudinal mLE8 measures to incident CMM remains limited, particularly among middle-aged and older Chinese adults [19].

Based on longitudinal data from The China Health and Retirement Longitudinal Study (CHARLS), we evaluated mLE8 from three complementary perspectives: baseline level, cumulative exposure, and longitudinal patterns reflecting the sustained maintenance of cardiovascular health. We further examined their associations with incident CMM, nonlinear associations, subgroup differences, and the incremental predictive value of mLE8 beyond conventional risk factors [20].

Methods

Study design and population

Data were obtained from the China Health and Retirement Longitudinal Study (CHARLS), including the 2011–2012 baseline survey and follow-up waves in 2013, 2015, 2018, and 2020. Participants aged ≥ 45 years with preexisting CMM, incomplete follow-up information, or insufficient data to calculate baseline mLE8 were excluded, whereas those with only one component CMD at baseline remained eligible. Of 17,708 baseline participants, 8,815 were included in the baseline analysis and followed through 2020. Among them, 5,394 participants with complete mLE8 assessments in 2011–2012 and 2015 and without CMM during this period were included in the cumulative and longitudinal analyses from 2015 to 2020. The selection process is shown in Fig. 1. This study followed the STROBE reporting guidelines.

Data collection

At baseline, trained interviewers collected sociodemographic and health-related information using standardized questionnaires. Demographic characteristics included age, gender, marital status, and educational level. Health-related information included self-reported smoking and drinking status, physician-diagnosed hypertension, diabetes, dyslipidemia, heart disease and stroke, as well as the use of antihypertensive, antidiabetic, and lipid-lowering medications. Anthropometric and physiological measurements included height, weight, waist circumference (WC), body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP).

Fasting venous blood samples were collected for the measurement of fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), C-reactive protein (CRP), blood urea nitrogen (BUN), serum creatinine (Cr), and uric acid (UA).

Calculation of mLE8, longitudinal mLE8 patterns, and cumulative mLE8

Life's Essential 8 (LE8) comprises eight components: diet, physical activity, nicotine exposure, sleep health, BMI, blood lipids, blood glucose, and blood pressure. Each component is scored on a scale ranging from 0 to 100, with higher scores indicating more favorable cardiovascular health. Because detailed dietary information was unavailable in CHARLS, we constructed a modified Life's Essential 8 score based on the remaining seven components(Fig. S1). Apart from the exclusion of the diet component, each component was scored according to the official LE8 scoring criteria [21]. The overall mLE8 score was calculated as the mean of the seven component scores and ranged from 0 to 100, with higher scores representing better cardiovascular health.

cumulative mLE8 (cumLE8) was used to characterize long-term exposure to cardiovascular health status. It was calculated using mLE8 scores from the 2011–2012 baseline survey and the 2015 follow-up survey as follows:cumLE8 = [(mLE8_2011–2012 + mLE8_2015) / 2] × time interval (2015 − 2012).Longitudinal mLE8 patterns were identified using k-means clustering based on the two repeated mLE8 measurements. Participants were classified into three groups: Cluster 1, the persistently low-level group; Cluster 2, the persistently moderate-level group; and Cluster 3, the persistently high-level group.

Outcome definition and ascertainment

The primary outcome was incident CMM during follow-up. CMM was defined as the coexistence of at least two distinct CMDs, including diabetes, heart disease, and stroke [22]. Participants with only one CMD at baseline were retained in the study and were considered to have developed CMM if they experienced an additional CMD during follow-up.

Diabetes was identified on the basis of laboratory measurements, medication use, and self-reported physician diagnosis. Participants were classified as having diabetes if they met any of the following criteria: FPG ≥ 126 mg/dL, HbA1c ≥ 6.5%, current use of antidiabetic medication, or a self-reported physician diagnosis of diabetes.

Heart disease included coronary heart disease, angina, or heart failure and was identified primarily through self-reported physician diagnosis and the use of relevant cardiovascular medications. Stroke was identified according to a self-reported physician diagnosis.

Time to event was calculated from baseline to the survey wave at which CMM was first identified. Participants who did not develop CMM were censored at the date of their last available assessment.

Development and validation of the prediction model

Participants were randomly divided into a training cohort and a validation cohort at a ratio of 7:3 using stratified random sampling according to CMM event status to ensure a comparable event distribution between the two

cohorts. The training cohort was used for predictor screening and model development, whereas the held-out validation cohort was used exclusively to evaluate model performance. Candidate predictors were screened in a stepwise manner. First, baseline characteristics were compared between participants who developed CMM and those who remained free of CMM in the training cohort. Variables showing between-group differences at a two-sided P value < 0.05 were subsequently evaluated using univariable Cox proportional hazards regression. Variables associated with incident CMM at P < 0.05 in the univariable analyses were then entered into a multivariable Cox proportional hazards regression model. Variables that remained independently associated with incident CMM in the multivariable analysis were retained to construct the final prediction model. Model discrimination was assessed using time-dependent receiver operating characteristic curves and the corresponding area under the curve at 96 months in both the training and validation cohorts. Shapley additive explanations (SHAP) values were subsequently calculated to quantify the relative contribution of each predictor and improve the interpretability of the final model.

Statistical analysis

Continuous variables with normal distributions are reported as the means ± SD, whereas nonnormally distributed variables are expressed as medians (interquartile ranges, IQRs). Differences across groups were compared using the Kruskal-Wallis test. Categorical variables are presented as frequencies and percentages and were compared using the χ^2 test. k-means clustering based on Euclidean distance was applied to identify longitudinal mLE8 patterns using the mLE8 scores measured in 2011–2012 and 2015. The optimal number of clusters was determined using the elbow method, which supported a three-cluster solution (Fig. 3B). Each participant was assigned to the cluster with the nearest centroid. The resulting clusters represented persistently low, moderate, and high mLE8 levels.

Cox proportional hazards regression models were used to evaluate the associations of baseline mLE8, cumLE8, and longitudinal mLE8 patterns with incident CMM. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated. Four progressively adjusted models were constructed. Model 1 was unadjusted. Model 2 was adjusted for age, gender, marital status, and educational level. Model 3 was additionally adjusted for drinking status, hypertension, and dyslipidemia. Model 4 was further adjusted for BUN, serum creatinine, CRP, and UA. A multi-state model was constructed to evaluate the progression of cardiometabolic disease. Participants were categorized into three mutually exclusive states: State 0 (no cardiometabolic disease), State 1 (single cardiometabolic disease, including diabetes, heart disease, or stroke), and State 2 (cardiometabolic multimorbidity defined as the coexistence of at least two conditions). Allowed transitions included State 0→State 2, State 1→State 2. Transition-specific Cox proportional hazards models were used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals. All models were adjusted for the same covariates as in the fully adjusted Cox model (Model 4). Multicollinearity among covariates included in the primary Cox models was assessed using variance inflation factors (VIFs), with a VIF < 5 considered acceptable. Restricted cubic spline regression was used to examine the potential linear or nonlinear associations of baseline mLE8 and cumLE8 with incident CMM. Subgroup analyses were conducted according to age, gender, marital status, educational level, drinking status, hypertension, and dyslipidemia. All statistical analyses were performed using R software, version 4.5.1. All tests were two-sided P value < 0.05 was considered statistically significant.

Results

Population characteristics

Participants were categorized into quartiles according to baseline mLE8 scores (Table 1). Across increasing mLE8 quartiles, age, BMI, SBP, DBP, FPG, HbA1c, TC, TG, LDL-C, UA, and CRP levels progressively decreased, whereas HDL-C levels increased (all $P < 0.001$). Participants in the higher mLE8 quartiles were less likely to be male, smoke, or consume alcohol than those in the lower quartiles (all $P < 0.001$). The prevalence of hypertension, diabetes, dyslipidemia, stroke, and heart disease, as well as the use of glucose-lowering, lipid-lowering, and antihypertensive medications, also decreased with increasing mLE8 levels (all $P < 0.05$). Overall, higher baseline mLE8 scores were associated with a more favorable cardiometabolic profile.

Table 1
participants demographics and baseline characteristics

Variables	Q1 (n = 2214)	Q2 (n = 2209)	Q3 (n = 2243)	Q4 (n = 2149)	*P*
CMM	301 (13.60)	228 (10.32)	176 (7.85)	107 (4.98)	**< .001**
Age, years	61.00 (54.00,68.00)	59.00 (53.00,66.00)	58.00 (52.00,64.00)	56.00 (49.00,62.00)	**< .001**
SBP, mmHg	144.00 (131.00,159.00)	133.00 (121.00,148.00)	124.00 (114.00,138.00)	118.00 (110.00,129.00)	**< .001**
DBP, mmHg	83.00 (75.00,91.00)	78.00 (70.00,86.00)	74.00 (66.00,81.00)	70.00 (64.00,77.00)	**< .001**
Height, m	1.60 (1.53,1.66)	1.58 (1.52,1.64)	1.57 (1.52,1.63)	1.56 (1.51,1.62)	**< .001**
Weight, kg	61.50 (53.12,70.40)	58.60 (51.50,65.70)	56.40 (50.40,63.90)	54.90 (48.90,61.00)	**< .001**
WC, cm	88.40 (80.40,96.40)	85.80 (78.20,92.00)	83.20 (77.00,90.00)	81.00 (75.30,87.40)	**< .001**
BMI, kg/m2	24.41 (21.32,27.25)	23.23 (20.91,25.92)	22.80 (20.69,25.31)	22.35 (20.47,24.30)	**< .001**
BUN, mg/dL	15.46 (12.97,18.68)	15.29 (12.66,18.40)	15.10 (12.51,17.93)	14.73 (12.18,17.76)	**< .001**
Creatinine, mg/dL	0.80 (0.69,0.94)	0.77 (0.67,0.89)	0.75 (0.64,0.87)	0.71 (0.62,0.82)	**< .001**
CRP, mg/L	1.33 (0.71,2.83)	1.12 (0.58,2.33)	0.86 (0.50,1.76)	0.80 (0.45,1.67)	**< .001**
FPG, mg/dL	106.02 (96.84,120.24)	102.96 (95.04,113.04)	100.98 (93.78,109.26)	99.00 (92.34,107.28)	**< .001**
HbA1c, %	5.20 (4.90,5.60)	5.10 (4.90,5.40)	5.10 (4.90,5.40)	5.10 (4.80,5.30)	**< .001**
HDL-C, mg/dL	46.39 (37.89,56.73)	48.71 (40.21,59.92)	51.03 (41.75,61.47)	52.58 (43.69,62.24)	**< .001**
LDL-C, mg/dL	125.26 (102.45,150.68)	119.07 (97.42,141.88)	109.41 (90.85,131.44)	104.38 (87.76,123.71)	**< .001**
TC, mg/dL	204.90 (181.03,233.51)	195.23 (172.81,219.59)	184.41 (161.99,208.76)	176.68 (158.12,199.10)	**< .001**
TG, mg/dL	125.67 (87.61,186.74)	108.86 (77.88,161.07)	98.24 (70.36,140.71)	89.39 (66.38,124.79)	**< .001**
UA, mg/dL	4.68 (3.88,5.59)	4.42 (3.68,5.28)	4.20 (3.53,4.98)	3.96 (3.34,4.69)	**< .001**
Wave1-mLE8	51.43 (46.43,55.00)	62.86 (60.00,64.29)	71.43 (68.57,73.57)	82.14 (78.57,87.14)	**< .001**
Male, n (%)	1378 (62.24)	1127 (51.02)	984 (43.87)	650 (30.25)	**< .001**
Married, n (%)	1865 (84.24)	1920 (86.92)	2018 (89.97)	1954 (90.93)	**< .001**
Education, n (%)					**0.039**
< high school	1291 (58.31)	1302 (58.94)	1338 (59.65)	1339 (62.31)	

Variables	Q1 (n = 2214)	Q2 (n = 2209)	Q3 (n = 2243)	Q4 (n = 2149)	*P*
≥ high school	923 (41.69)	907 (41.06)	905 (40.35)	810 (37.69)	
Smoking, n (%)	1479 (66.80)	1001 (45.31)	703 (31.34)	289 (13.45)	**< .001**
Drinking, n (%)	1115 (50.36)	917 (41.51)	817 (36.42)	626 (29.13)	**< .001**
Hypertension, n (%)	911 (41.15)	622 (28.16)	419 (18.68)	223 (10.38)	**< .001**
Diabetes, n (%)	175 (7.90)	105 (4.75)	71 (3.17)	37 (1.72)	**< .001**
Dyslipidemia, n (%)	300 (13.55)	188 (8.51)	160 (7.13)	112 (5.21)	**< .001**
Heart disease, n (%)	253 (11.43)	248 (11.23)	225 (10.03)	172 (8.00)	**< .001**
Stroke, n(%)	46 (2.08)	29 (1.31)	35 (1.56)	17 (0.79)	**0.004**
Antidiabetic, n(%)	118 (5.33)	57 (2.58)	44 (1.96)	15 (0.70)	**< .001**
Lipid-lowering,n (%)	178 (8.04)	103 (4.66)	66 (2.94)	38 (1.77)	**< .001**
Antihypertensive, n (%)	714 (32.25)	458 (20.73)	296 (13.20)	134 (6.24)	**< .001**

SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; BMI, body mass index; BUN, blood urea nitrogen; Cr, serum creatinine; CRP, C-reactive protein; FPG, fasting plasma glucose;HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; UA, uric acid; CMM, cardiometabolic multimorbidity

Association between baseline mLE8 and incident CMM

Among the 8,815 participants, 812 (9.21%) developed CMM between 2013 and 2020 (Table 1). Figure 2A shows the Kaplan-Meier curves for CMM-free survival by mLE8 quartile. CMM-free survival increased progressively across higher mLE8 quartiles, and the differences among the four groups were statistically significant (log-rank $P < 0.001$).

The association between baseline mLE8 and incident CMM was further examined using Cox proportional hazards regression models (Table 2). In the unadjusted model, each 10-point increase in mLE8 was associated with a 26% lower risk of CMM (HR = 0.74, 95% CI: 0.70–0.78; $P < 0.001$). This association remained significant in the fully adjusted Model 4 (HR = 0.80, 95% CI: 0.76–0.85; $P < 0.001$).

Table 2
Association between the mLE8 and CMM incidence

Variables	Model1		Model2		Model3		Model4	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
mLE8 (per 10-point)	0.74 (0.70 ~ 0.78)	**< .001**	0.80 (0.75 ~ 0.84)	**< .001**	0.80 (0.75 ~ 0.84)	**< .001**	0.80 (0.76 ~ 0.85)	**< .001**
mLE8								
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	0.74(0.63–0.88)	**< .001**	0.70 (0.59–0.83)	**< .001**	0.84 (0.70–0.99)	**0.044**	0.84 (0.70-1.00)	**0.049**
Q3	0.56 (0.46–0.67)	**< .001**	0.50 (0.42–0.61)	**< .001**	0.69 (0.56–0.83)	**< .001**	0.69 (0.57–0.84)	**< .001**
Q4	0.35 (0.28–0.43)	**< .001**	0.30 (0.24–0.38)	**< .001**	0.46 (0.36–0.58)	**< .001**	0.47 (0.37–0.59)	**< .001**

HR: Hazard Ratio, CI: Confidence Interval

Model 1: Crude.

Model 2: Adjusted for age, gender, marriage, education.

Model 3: Adjusted for Model 2 + drinking, hypertension, dyslipidemia.

Model 4: Adjusted for Model 3 + BUN, Creatinine, CRP, UA.

When mLE8 was analyzed in quartiles, the fully adjusted HRs (95% CIs) for Q2, Q3, and Q4 were 0.84 (0.70-1.00), 0.69 (0.57–0.84), and 0.47 (0.37–0.59), respectively, compared with Q1. These findings indicated a graded decrease in CMM risk with increasing baseline mLE8 levels. Because several candidate covariates were components of mLE8 or closely overlapped with the health dimensions represented by mLE8, these exposure-related variables were not included in the primary models to reduce potential overadjustment.

Incidence of CMM according to longitudinal mLE8 patterns and cumLE8

A total of 5,394 participants with complete mLE8 data in both 2012 and 2015 were included in the longitudinal analyses of cumLE8 and longitudinal mLE8 patterns (Table S1). During the 5.0-year follow-up period, 346 participants (6.4%) developed CMM. Participants who developed CMM had lower cumLE8 levels than those who remained free of CMM [183.21 (159.64-207.85) vs. 202.49 (178.66-227.14); $P < 0.001$].

Based on mLE8 measurements in 2012 and 2015, k-means clustering identified three longitudinal patterns (Fig. 3C). Cluster 1 included 1,402 participants whose mean mLE8 score decreased from 52.56 to 51.79 and was characterized as the persistently low-level group. Cluster 2 included 2,429 participants whose mean score decreased from 67.18 to 65.97 and was defined as the persistently moderate-level group. Cluster 3 included 1,563 participants whose mean score decreased from 81.00 to 80.65 and was classified as the persistently high-level group.

The incidence of CMM showed a clear gradient across the three clusters, decreasing from 10.6% in Cluster 1 to 6.1% in Cluster 2 and 3.1% in Cluster 3 (Fig. 3D). Baseline characteristics according to longitudinal mLE8 patterns are presented in Table S2. From Cluster 1 to Cluster 3, age, SBP, DBP, body weight, WC, BMI, BUN, Cr, CRP, FPG, LDL-C, TC, TG, and UA progressively decreased, whereas HDL-C increased. The proportions of males, smokers, drinkers, participants with diabetes or dyslipidemia, and users of the corresponding medications also decreased across the clusters (all $P < 0.001$).

The Kaplan-Meier curves showed significant differences for CMM among the three longitudinal mLE8 groups (log-rank $P < 0.001$; Fig. 2B). Cluster 1 had the lowest survival probability, Cluster 2 had an intermediate probability, and Cluster 3 had the highest probability. The separation of the curves increased during follow-up, indicating a lower CMM risk among participants who consistently maintained higher mLE8 levels.

Table 3 summarizes the associations of cumLE8 and longitudinal mLE8 patterns with incident CMM. In the fully adjusted Model 4, each 10-point increase in cumLE8 was associated with a 12% lower risk of CMM (HR = 0.88, 95% CI: 0.85–0.91; $P < 0.001$). Compared with the lowest quartile of cumLE8, the adjusted HRs for Q2, Q3, and Q4 were 0.69 (95% CI: 0.53–0.90; $P = 0.007$), 0.57 (95% CI: 0.42–0.77; $P < 0.001$), and 0.28 (95% CI: 0.19–0.42; $P < 0.001$), respectively.

Table 3
Cox regression results for the association of mLE8 control level and cumulative mLE8 with CMM

Variables	Model 1		Model 2		Model 3		Model 4	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
CumLE8(per 10-point)	0.87 (0.84–0.89)	**< 0.001**	0.84 (0.82–0.87)	**< 0.001**	0.88 (0.85–0.91)	**< 0.001**	0.88 (0.85–0.91)	**< 0.001**
CumLE8								
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	0.63 (0.48–0.81)	**< 0.001**	0.57 (0.44–0.75)	**< 0.001**	0.69 (0.53–0.91)	**0.007**	0.69 (0.53–0.90)	**0.007**
Q3	0.50 (0.38–0.66)	**< 0.001**	0.42 (0.32–0.56)	**< 0.001**	0.57 (0.42–0.77)	**< 0.001**	0.57 (0.42–0.77)	**< 0.001**
Q4	0.24 (0.17–0.35)	**< 0.001**	0.19 (0.13–0.27)	**< 0.001**	0.28 (0.19–0.42)	**< 0.001**	0.28 (0.19–0.42)	**< 0.001**
Cluster group								
Cluster 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Cluster 2	0.58 (0.46–0.72)	**< 0.001**	0.51 (0.41–0.65)	**< 0.001**	0.65 (0.51–0.83)	**< 0.001**	0.65 (0.51–0.83)	**< 0.001**
Cluster 3	0.29 (0.21–0.40)	**< 0.001**	0.23 (0.16–0.32)	**< 0.001**	0.34 (0.24–0.49)	**< 0.001**	0.34 (0.24–0.49)	**< 0.001**

HR: Hazard Ratio, CI: Confidence Interval

Model 1: Crude.

Model 2: Adjusted for age, gender, marriage, education.

Model 3: Adjusted for Model 2 + drinking, hypertension, dyslipidemia.

Model 4: Adjusted for Model 3 + BUN, Creatinine, CRP, UA.

In the analysis of longitudinal patterns, participants in Cluster 2 and Cluster 3 had 35% and 66% lower risks of CMM, respectively, than those in Cluster 1. The corresponding HRs were 0.65 (95% CI: 0.51–0.83; P < 0.001) and 0.34 (95% CI: 0.24–0.49; P < 0.001).

Restricted cubic spline analyses were adjusted for the covariates included in Model 4. Baseline mLE8 was significantly associated with incident CMM overall (P for overall < 0.001), with no evidence of nonlinearity (P for nonlinearity = 0.184; Fig. 4A), indicating an approximately linear inverse association. cumLE8 was also significantly associated with CMM risk (P for overall < 0.001), and a significant nonlinear relationship was observed (P for nonlinearity < 0.001; Fig. 4B). In both analyses, CMM risk generally decreased with increasing mLE8 levels.

Multi-state analysis of cardiometabolic disease progression

In the multi-state model, higher mLE8 was consistently associated with a lower risk of cardiometabolic disease progression across different transition pathways. Specifically, each 10-point increase in mLE8 was associated with a significantly reduced risk of transitioning from no cardiometabolic disease to cardiometabolic multimorbidity (from State 0 to State 2 (CMM)) (HR = 0.85, 95% CI: 0.78–0.94, P = 0.001). A similar inverse association was observed among participants with one baseline cardiometabolic disease, where higher mLE8 was associated with a lower risk of progression to CMM (from State 1 to State 2 (CMM)) (HR = 0.88, 95% CI: 0.82–0.94, P < 0.001) (Table 4). These findings suggest that higher mLE8 is associated with a reduced risk of disease progression both in initially healthy individuals and in those with established single cardiometabolic disease.

Table 4
Transition-specific hazard ratios from multi-state model

Transition	HR (95% CI)	P value
State 0 → CMM	0.85 (0.78–0.94)	**0.001**
State 1 → CMM	0.88 (0.82–0.94)	**< 0.001**
HRs were estimated per 10-point increase in baseline mLE8.		

Subgroup analyses

Subgroup analyses showed that each 10-point increase in baseline and cumLE8 was associated with a lower risk of CMM in most participant subgroups (Fig. 5A and Fig. 5B). Significant interactions were observed between baseline mLE8 and age, marital status, drinking status, and hypertension status, with P values for interaction of 0.008, 0.025, 0.042, and < 0.001, respectively. The inverse association was more pronounced among participants aged 45 to < 60 years, those who were married, those who did not drink, and those without hypertension.

No significant interactions were observed between cumLE8 and any of the subgroup variables examined (all P for interaction > 0.05), indicating that the inverse association between cumLE8 and CMM risk was generally consistent across subgroups.

Sensitivity analyses

A series of sensitivity analyses were conducted to assess the stability of the primary findings. When all candidate covariates were included in the multicollinearity assessment, the VIFs for TC and LDL-C were 13.55 and 10.66, respectively, and the VIF for TG was 5.48, whereas all remaining variables had VIF values below 5 (Table S3). Because several candidate covariates were components of mLE8 or substantially overlapped with its underlying health dimensions, they were not included in the primary models to avoid potential overadjustment. As a supplementary analysis, variables with VIF values below 5 were added to the primary model, including WC, BMI, SBP, DBP, HDL-C, FPG, HbA1c, smoking, diabetes, heart disease, stroke, and the use of glucose-lowering, lipid-lowering, and antihypertensive medications (Table S4). After this extended adjustment, higher mLE8 remained associated with a lower risk of CMM. In Model 4, each 10-point increase in mLE8 was associated with a 12% lower risk (HR = 0.88, 95% CI: 0.82–0.95; P = 0.001). Compared with Q1, participants in Q4 had a 34% lower risk of CMM (HR = 0.66, 95% CI: 0.50–0.87; P = 0.004), whereas the associations for Q2 and Q3 did not reach statistical significance. Although the effect estimates were attenuated relative to the primary models, the overall inverse association remained observable.

Additional adjustment was also applied to the longitudinal analyses of cumLE8 and mLE8 clusters. Although the effect estimates were attenuated, cumLE8, the highest cumLE8 quartile, and Cluster 3 remained significantly associated with a lower risk of incident CMM (Table S5).

Schoenfeld residual testing indicated that the extended Cox model used in the supplementary analysis violated the proportional hazards assumption (global P < 0.001). After stratification by heart disease, stroke, antihypertensive medication use, and diabetes, the global test was no longer statistically significant (global P = 0.112), and mLE8 satisfied the proportional hazards assumption (P = 0.928; Table S6). In the multivariable stratified Cox model, mLE8 remained significantly associated with CMM risk (HR = 0.98, 95% CI: 0.97–0.99; P < 0.001; Table S7), corresponding to an approximately 2% reduction in risk per 1-point increase in mLE8.

Incremental predictive value of mLE8

To assess the incremental predictive value of mLE8, it was added to a baseline model comprising age, gender, hypertension, dyslipidemia, and diabetes. The C-index increased from 0.69 to 0.72 after the inclusion of mLE8. For the prediction of 96-month CMM risk, the continuous net reclassification improvement was 0.084 (95% CI: 0.042–0.136; P < 0.001), and the integrated discrimination improvement was 0.003 (95% CI: 0.000-0.006; P = 0.022) (Table S8). These findings suggested that mLE8 provided additional information for risk reclassification and discrimination beyond conventional risk factors.

The 8,815 participants were subsequently divided into a training cohort and a validation cohort at a ratio of 7:3 using stratified random sampling according to CMM status. The training cohort included 6,170 participants, and the validation cohort included 2,645 participants. Baseline characteristics were generally comparable between the two cohorts, with standardized mean differences below 0.1 for all variables (Table S9). In the training cohort, 18 variables with P values < 0.05 in comparisons between participants with and without CMM were selected as candidate predictors (Table S10). Multivariable Cox regression subsequently identified 10 independent predictors of incident CMM: diabetes, hypertension, heart disease, stroke, dyslipidemia, FPG, HbA1c, BMI, HDL-C, and mLE8 (Table 5).

Table 5
Univariate and multivariable Cox regression analyses for incident CMM in the training cohort.

Variables	Univariate Analysis		multivariate Cox regression	
	P value	HR	P value	HR
mLE8	**< 0.001**	0.96 (0.96–0.97)	**0.008**	0.99 (0.98–1.00)
Age	**0.0160**	1.01 (1.00–1.02)	0.95	1.00 (0.99–1.01)
SBP	**< 0.001**	1.01 (1.01–1.02)	0.21	1.00 (1.00–1.01)
DBP	**< 0.001**	1.02 (1.01–1.03)	0.61	1.00 (0.99–1.01)
BMI	**< 0.001**	1.10 (1.08–1.11)	**0.001**	1.04 (1.01–1.06)
FPG	**< 0.001**	1.01 (1.01–1.01)	**0.03**	1.00 (1.00–1.00)
HbA1c	**< 0.001**	1.47 (1.39–1.56)	**P < 0.001**	1.25 (1.12–1.39)
HDL-C	**< 0.001**	0.98 (0.97–0.99)	**0.009**	0.99 (0.98–1.00)
TC	**< 0.001**	1.00 (1.00–1.01)	0.49	1.00 (0.99–1.00)
TG	**< 0.001**	1.00 (1.00–1.00)	0.07	1.00 (0.99–1.00)
UA	**0.0031**	1.10 (1.03–1.17)	0.12	1.06 (0.99–1.13)
Male	**0.0031**	0.78 (0.66–0.92)	0.20	0.86 (0.68–1.08)
Smoking	**0.0033**	0.77 (0.65–0.92)	0.15	0.83 (0.64–1.07)
Hypertension	**< 0.001**	3.04 (2.58–3.59)	**P < 0.001**	1.62 (1.33–1.96)
Diabetes	**< 0.001**	4.05 (3.23–5.10)	**P < 0.001**	1.87 (1.37–2.55)
Dyslipidemia	**< 0.001**	3.69 (3.04–4.48)	**P < 0.001**	1.86 (1.50–2.30)
Heart disease	**< 0.001**	3.74 (3.11–4.49)	**P < 0.001**	3.84 (3.14–4.70)
Stroke	**< 0.001**	3.37 (2.18–5.21)	**P < 0.001**	4.00 (2.55–6.28)

At 96 months of follow-up, the model achieved an AUC of 0.81 (95% CI: 0.79–0.84) in the training cohort (Fig. 6A) and 0.80 (95% CI: 0.76–0.84) in the validation cohort (Fig. 6B). The 96-month calibration curves for the two cohorts are shown in Fig. S2A and Fig. S2B. In the training cohort, the 96-month Brier score was 0.0477 and the integrated Brier score from 1 to 96 months was 0.0208. The corresponding values in the validation cohort were 0.0469 and 0.0216. The similar scores in the two cohorts indicated relatively stable predictive performance.

Decision curve analysis showed that the model provided greater net benefit than the treat-all and treat-none strategies across a relatively wide range of threshold probabilities in both cohorts, supporting its potential clinical utility (Fig. S2C and Fig. S2D).

The multivariable Cox prediction model was further interpreted using SHAP values. The SHAP summary plot illustrates the distribution of SHAP values for the 10 clinical predictors, reflecting their direction, magnitude, and interindividual variation in contribution to predicted 96-month CMM risk (Fig. 6C). The presence of heart disease,

hypertension, dyslipidemia, diabetes, and stroke, together with higher HbA1c, BMI, and FPG levels, was generally associated with higher predicted risk. In contrast, higher mLE8 values generally showed negative SHAP contributions, indicating lower predicted CMM risk. Based on the mean absolute SHAP values, the three variables contributing most strongly to model prediction were heart disease, hypertension, and dyslipidemia, whereas mLE8 also provided additional predictive information (Fig. 6D).

Discussion

In this longitudinal cohort study of middle-aged and older Chinese adults, we found that higher modified Life's Essential 8 (mLE8) scores were consistently associated with a lower risk of incident cardiometabolic multimorbidity (CMM). Importantly, this inverse association was robust across multiple complementary analytical frameworks, including baseline exposure, cumulative exposure, longitudinal maintenance patterns, and multi-state transition models. Each 10-point increase in baseline mLE8 was associated with a 20% reduction in CMM risk, while higher cumLE8 and persistently favorable mLE8 levelswere associated with similarly lower risks. Furthermore, multi-state analyses extended these findings by showing that higher mLE8 was associated with a reduced risk of progression both from no cardiometabolic disease and from single cardiometabolic disease to multimorbidity, suggesting consistent inverse association across distinct stages of disease evolution. These findings collectively extend prior evidence based on single-time-point cardiovascular health measures and highlight the importance of long-term maintenance and dynamic assessment of cardiovascular health in preventing disease progression.

Our findings extend previous research on LE8 and cardiometabolic outcomes. LE8 incorporates health behaviors and biological factors into a comprehensive cardiovascular health framework and may provide broader information than individual risk factors. Higher LE8 scores have been associated with lower risks of cardiovascular disease [23], diabetes and stroke [24], as well as all-cause and cardiovascular mortality [25]. Favorable cardiovascular health may also be related to a lower probability of progression from a single cardiometabolic disease to CMM [26]. Cardiovascular health is not static. Blood pressure, glucose, lipid levels, body weight, and health behaviors may change with aging, disease progression, treatment, and lifestyle modification. A single measurement may therefore be affected by short-term variation and may not fully represent an individual's long-term health status. cumLE8, calculated from repeated measurements, may better approximate the average cardiovascular health level over a specified period. In the present study, participants who developed CMM had lower cumLE8 scores than those who remained free of CMM, and the risk of CMM decreased progressively across increasing cumLE8 quartiles. The clustering analysis showed a similar gradient, with the highest CMM incidence in the persistently low-level group and the lowest incidence in the persistently high-level group.

Previous cumulative exposure studies have shown that long-term maintenance of favorable blood pressure, glucose, and lipid levels is associated with a lower risk of cardiovascular events [27]. Individuals who maintain a favorable overall cardiovascular health status over time also tend to have a lower burden of metabolic diseases [28]. Our results are consistent with these observations and indicate that maintaining a high mLE8 level may be more informative than relying on a single assessment.

Restricted cubic spline analyses have shown that baseline mLE8 showed an approximately linear inverse association with CMM risk, indicating a gradual decrease in risk as cardiovascular health improved. In contrast,

cumLE8 exhibited a nonlinear relationship with CMM, suggesting that the magnitude of risk reduction may differ across cumulative score ranges.

Several biological and behavioral mechanisms may account for the association between mLE8 and CMM. A lower mLE8 score generally reflects the clustering of smoking, physical inactivity, poor sleep, obesity, hyperglycemia, dyslipidemia, and elevated blood pressure. Obesity and insulin resistance may promote chronic low-grade inflammation, oxidative stress, and endothelial dysfunction [29]. Elevated blood pressure may induce vascular remodeling, increase arterial stiffness, and impose additional cardiac workload [30]. Dyslipidemia contributes to the initiation and progression of atherosclerosis and may increase the risks of coronary heart disease and stroke [31]. Poor sleep may affect glucose and lipid metabolism through autonomic imbalance, neuroendocrine dysregulation, and inflammatory pathways [32]. Tobacco exposure may aggravate systemic inflammation, oxidative stress, and vascular endothelial injury [33]. These components are also interconnected. Regular physical activity may improve body weight, blood pressure, glucose regulation, and lipid profiles, whereas smoking cessation and improved sleep may produce benefits across several cardiometabolic dimensions [34].

In the subgroup analyses, significant interactions were identified between baseline mLE8 and age, marital status, drinking status, and hypertension. The inverse association appeared stronger among participants aged 45 to < 60 years, married participants, non-drinkers, and those without hypertension. These differences may be related to variations in disease stage, social support, lifestyle patterns, and the potential for risk-factor modification. Individuals without established hypertension may have greater opportunities to benefit from maintaining favorable cardiovascular health before substantial vascular damage develops. However, subgroup analyses involved multiple comparisons, and some strata may have included relatively few CMM events. These results should therefore be viewed as exploratory rather than definitive. No significant interactions were observed for cumLE8, suggesting that its inverse association with CMM was generally consistent across the examined subgroups.

Regarding predictive performance, adding mLE8 to a baseline model containing conventional risk factors increased the C-index and improved both the continuous net reclassification improvement and integrated discrimination improvement. The full prediction model achieved 96-month AUCs of 0.81 in the training cohort and 0.80 in the validation cohort, indicating relatively stable discrimination. SHAP analysis showed that heart disease, hypertension, and dyslipidemia made the largest contributions to model prediction, while higher mLE8 values were generally associated with negative SHAP values and a lower predicted CMM risk.

The high predictive contribution of preexisting cardiometabolic diseases should be interpreted in the context of the study design. Participants with one CMD at baseline were retained in the cohort. Consequently, those with heart disease, diabetes, or stroke required only one additional CMD during follow-up to meet the definition of CMM. These baseline diseases were therefore clinically closer to the outcome and were expected to receive relatively high importance in the prediction model. Although hypertension and dyslipidemia were not components of the CMM definition, they are common risk factors for diabetes, heart disease, and stroke and may also contribute strongly to risk prediction. SHAP values quantify the relative contribution of predictors within a particular model rather than their causal effects. The lower ranking of mLE8 therefore does not exclude its potential value. Instead, the improvement in discrimination and reclassification suggests that mLE8 may provide complementary information beyond disease history and conventional risk factors [35].

Strengths and limitations

A major strength of this study was the evaluation of cardiovascular health from three complementary perspectives, including baseline mLE8, cumulative exposure, and longitudinal patterns reflecting the sustained maintenance of mLE8 levels. The use of a large nationwide longitudinal cohort of middle-aged and older Chinese adults enabled us to extend previous findings derived mainly from single LE8 assessments. The consistency of the findings across Cox regression, restricted cubic spline analysis, k-means clustering, extended covariate adjustment, stratified Cox regression, and prediction analyses supports the stability of the main results. The use of SHAP analysis also improved the interpretability of the prediction model.

Several limitations should be considered. First, detailed dietary information was unavailable in CHARLS, and the mLE8 score used in this study did not include the diet component. It should therefore not be regarded as equivalent to the complete LE8 metric. Second, diabetes, heart disease, and stroke were identified partly from self-reported physician diagnoses, which may have introduced recall and misclassification bias. Future studies incorporating medical records, disease registries, or imaging findings may improve outcome ascertainment. Third, cumLE8 and longitudinal patterns were based on only two repeated assessments. Although these measures provide information on average and sustained cardiovascular health, they cannot fully capture complex changes over time. Fourth, despite adjustment for several potential confounders, residual confounding from unmeasured factors cannot be excluded, and the observational design does not permit causal inference. Finally, CHARLS mainly included Chinese adults aged 45 years or older. Further validation is required before these findings can be generalized to younger populations or other ethnic and geographic groups [36].

Conclusions

In this nationwide longitudinal cohort of middle-aged and older Chinese adults, higher baseline and cumLE8 levels and the sustained maintenance of higher mLE8 were consistently associated with a lower risk of incident CMM. These findings highlight the potential value of repeated cardiovascular health assessments and support repeated cardiovascular health assessment and the maintenance of favorable mLE8 levels as part of CMM prevention strategies.

Abbreviations

Abbreviations	Full English Name
AUC	Area under the curve
BMI	Body mass index
BUN	Blood urea nitrogen
CHARLS	China Health and Retirement Longitudinal Study
CI	Confidence interval
CMD	Cardiometabolic disease
CMM	Cardiometabolic multimorbidity
Cr	Serum creatinine
CRP	C-reactive protein
cumLE8	Cumulative modified Life's Essential 8
DBP	Diastolic blood pressure
FPG	Fasting plasma glucose
HbA1c	Glycated hemoglobin
HDL-C	High-density lipoprotein cholesterol
HR	Hazard ratio
IQR	Interquartile range
LDL-C	Low-density lipoprotein cholesterol
LE8	Life's Essential 8
mLE8	Modified Life's Essential 8
ROC	Receiver operating characteristic
SBP	Systolic blood pressure
SHAP	Shapley additive explanations
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TC	Total cholesterol
TG	Triglycerides
UA	Uric acid
VIF	Variance inflation factor
WC	Waist circumference

Declarations

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Availability of data and materials

The data used in this study were derived from the China Health and Retirement Longitudinal Study (CHARLS). These datasets can be accessed via the CHARLS official website (https://charls.pku.edu.cn/). Qualified researchers may obtain the data upon registration and approval, following the access procedures specified on the website.

Ethics statement

Ethical approval for the CHARLS study was granted by the Institutional Review Board of Peking University (IRB00001052-11015). Written informed consent was obtained from each participant prior to enrollment.

Author contributions

LWH conceived and designed the study and wrote the main manuscript. XZW and YZH analyzed the data. XXJ reviewed the manuscript. All authors approved the final manuscript.

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Conflict of interest

The authors declare no competing interests.

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Figures

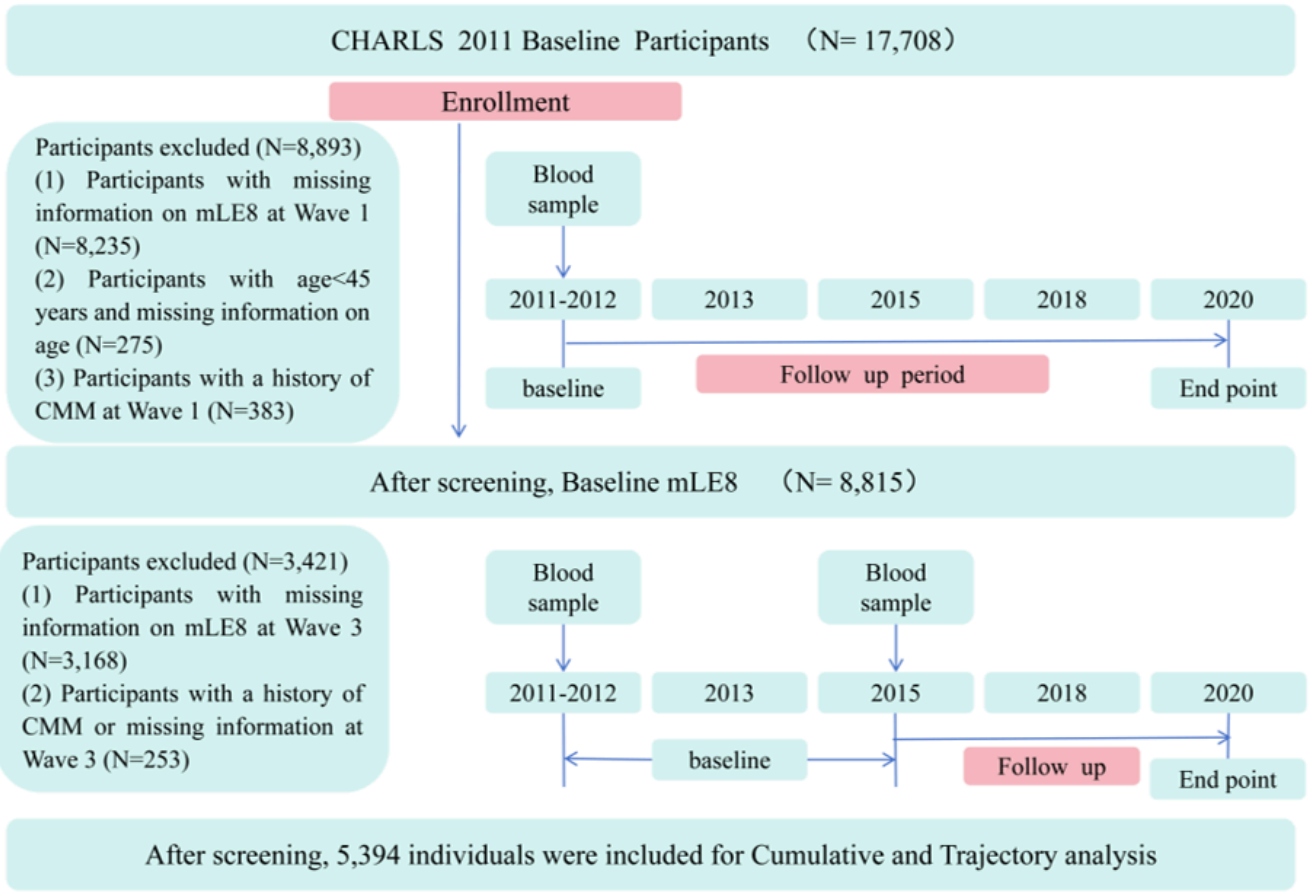

Figure 1

Flowchart of the study population

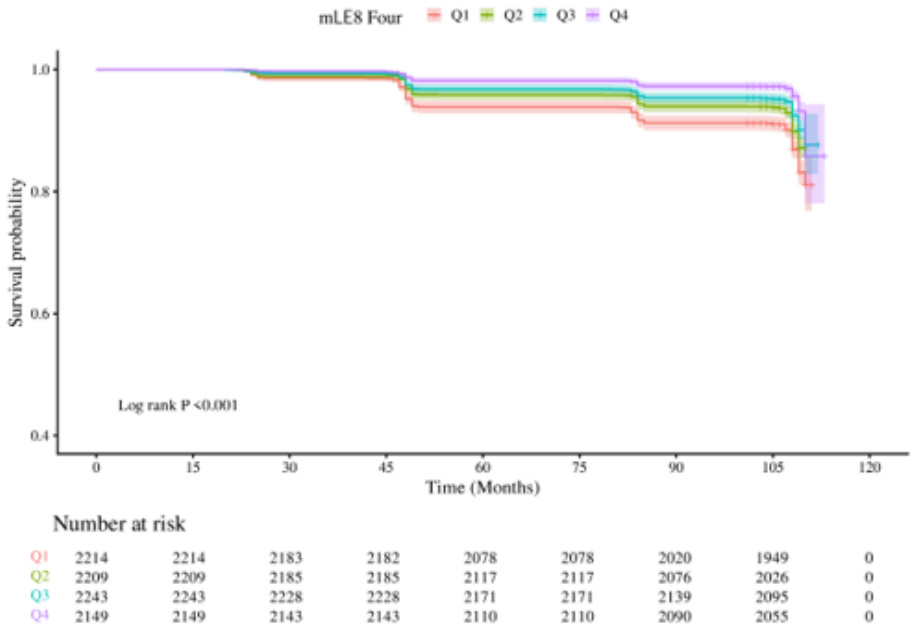

Fig.2A

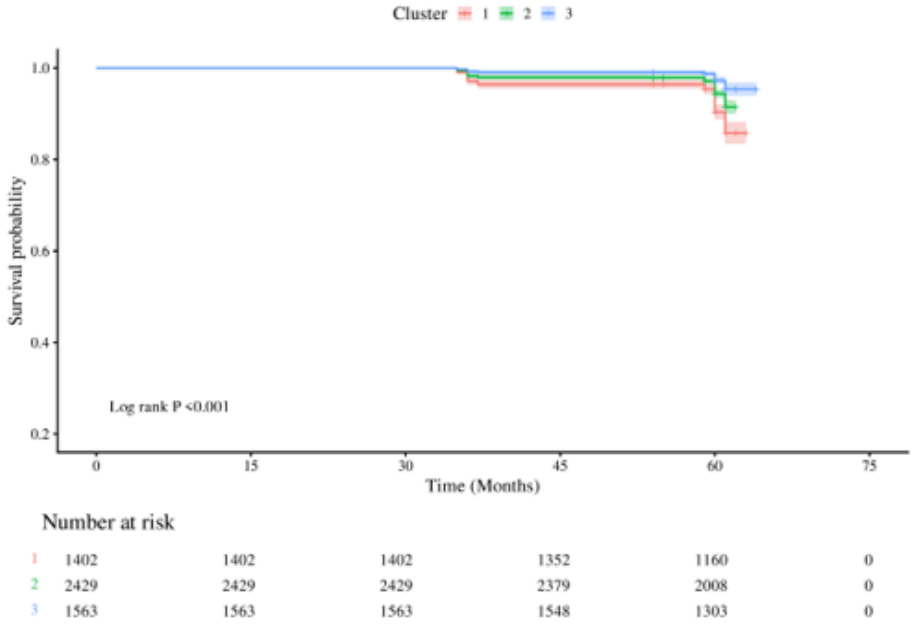

Fig.2B

Figure 2

A Kaplan–Meier analysis curves for CMM of baseline mLE8.

B Kaplan–Meier analysis curves for CMM of cluster group.

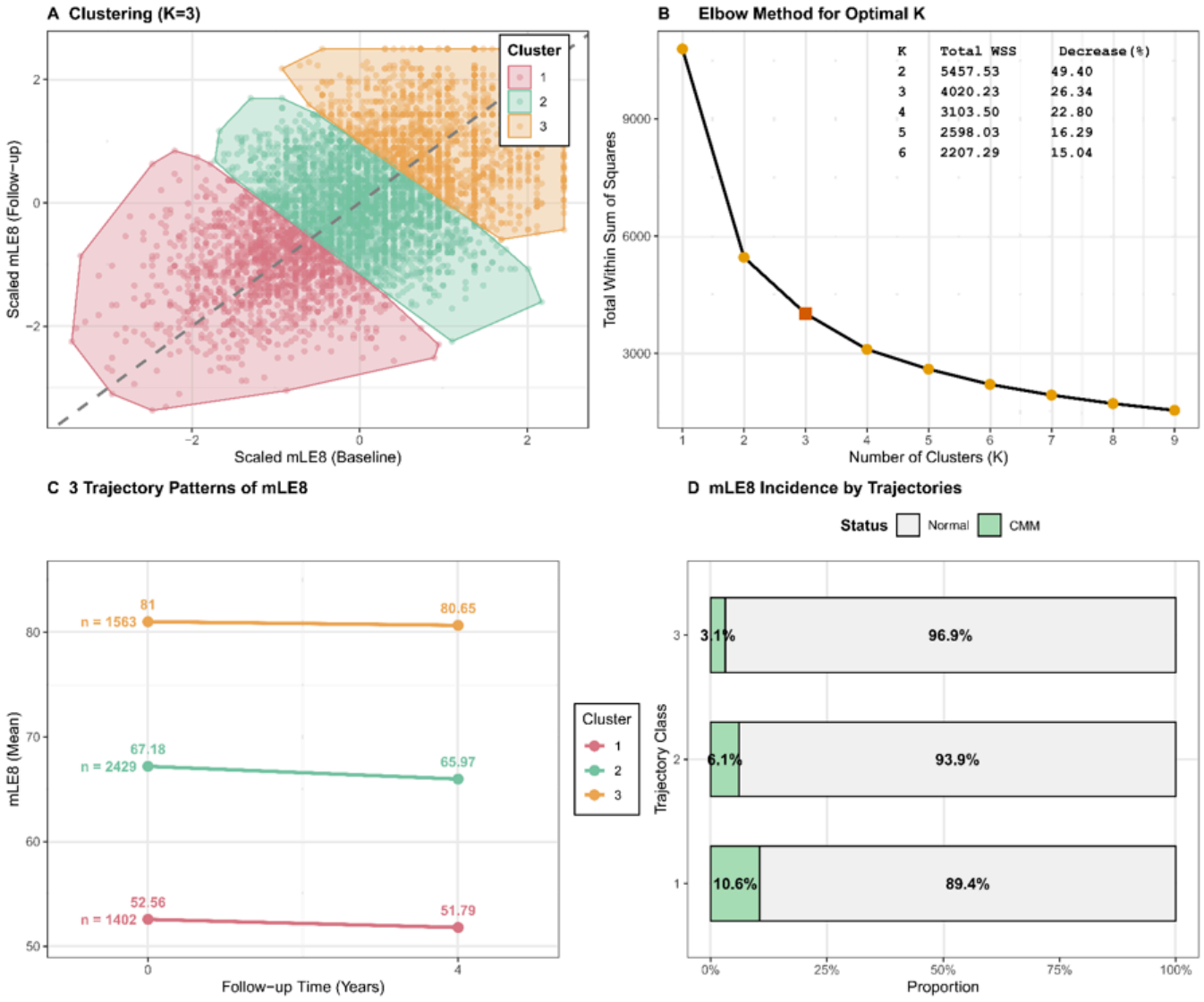

Figure 3

Results of mLE8 trajectory clustering and CMM incidence across different trajectory groups.A:Cluster distribution when K = 3; B:Optimal number of clusters determined by the elbow method; C:Three mLE8 trajectory patterns; D:Proportions of CMM incidence across different trajectory groups.

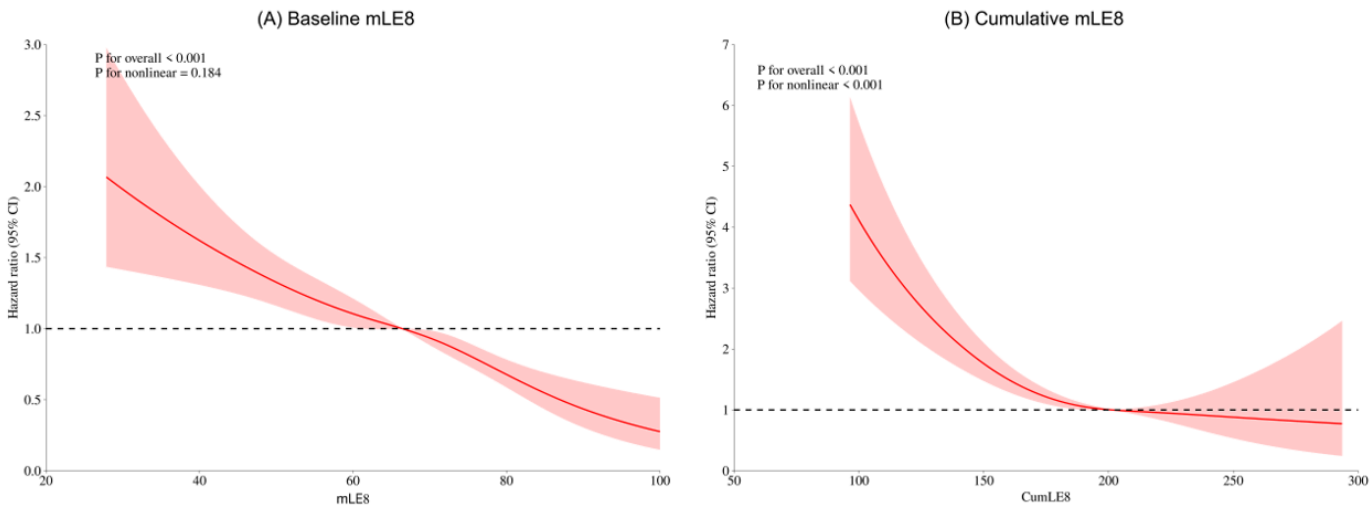

Figure 4

The RCS analysis of mLE8 and cumLE8 in the incidence of CMM.

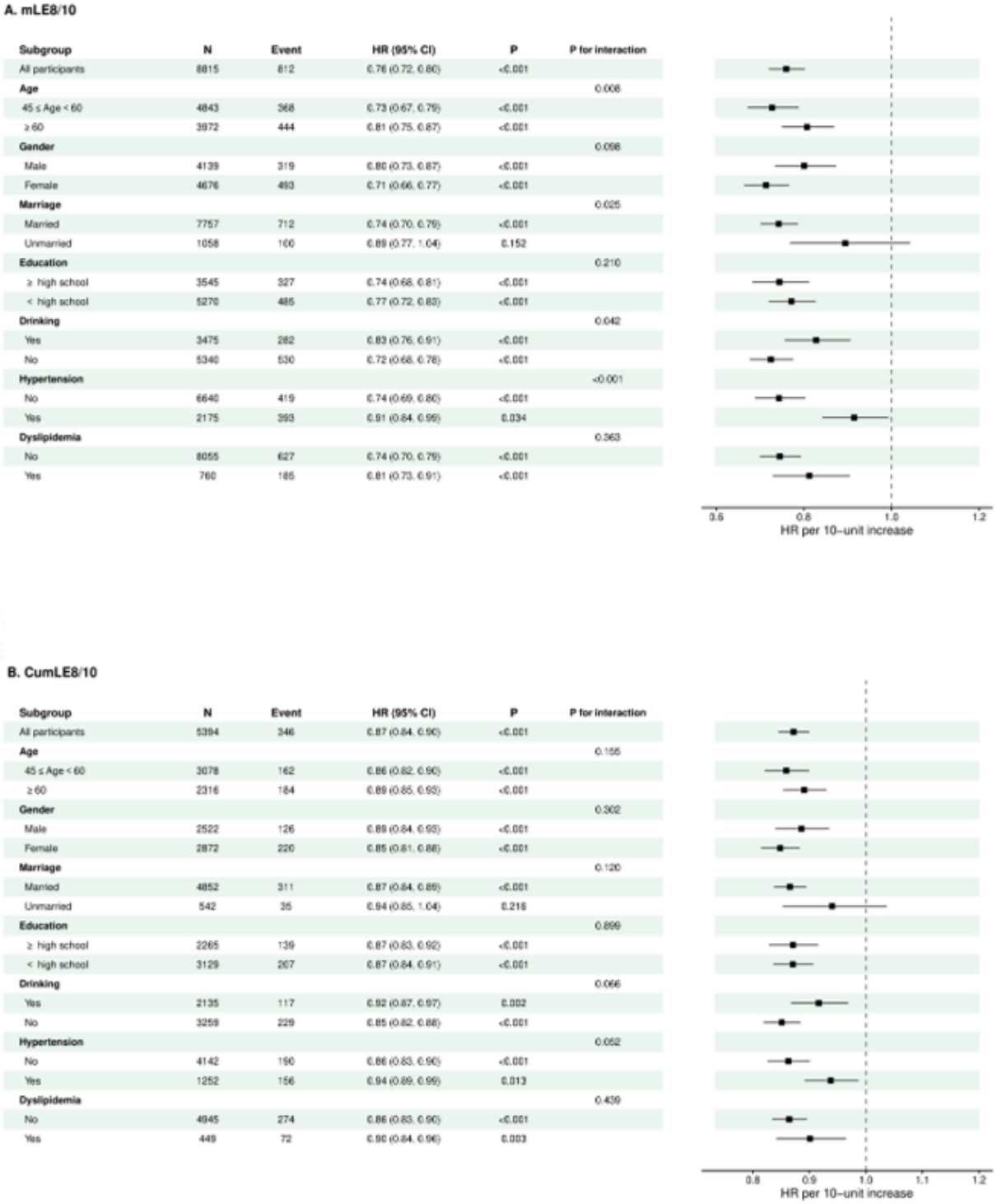

Figure 5

Subgroup analyses of the association of the mLE8 and cumLE8 with the risk of CMM.

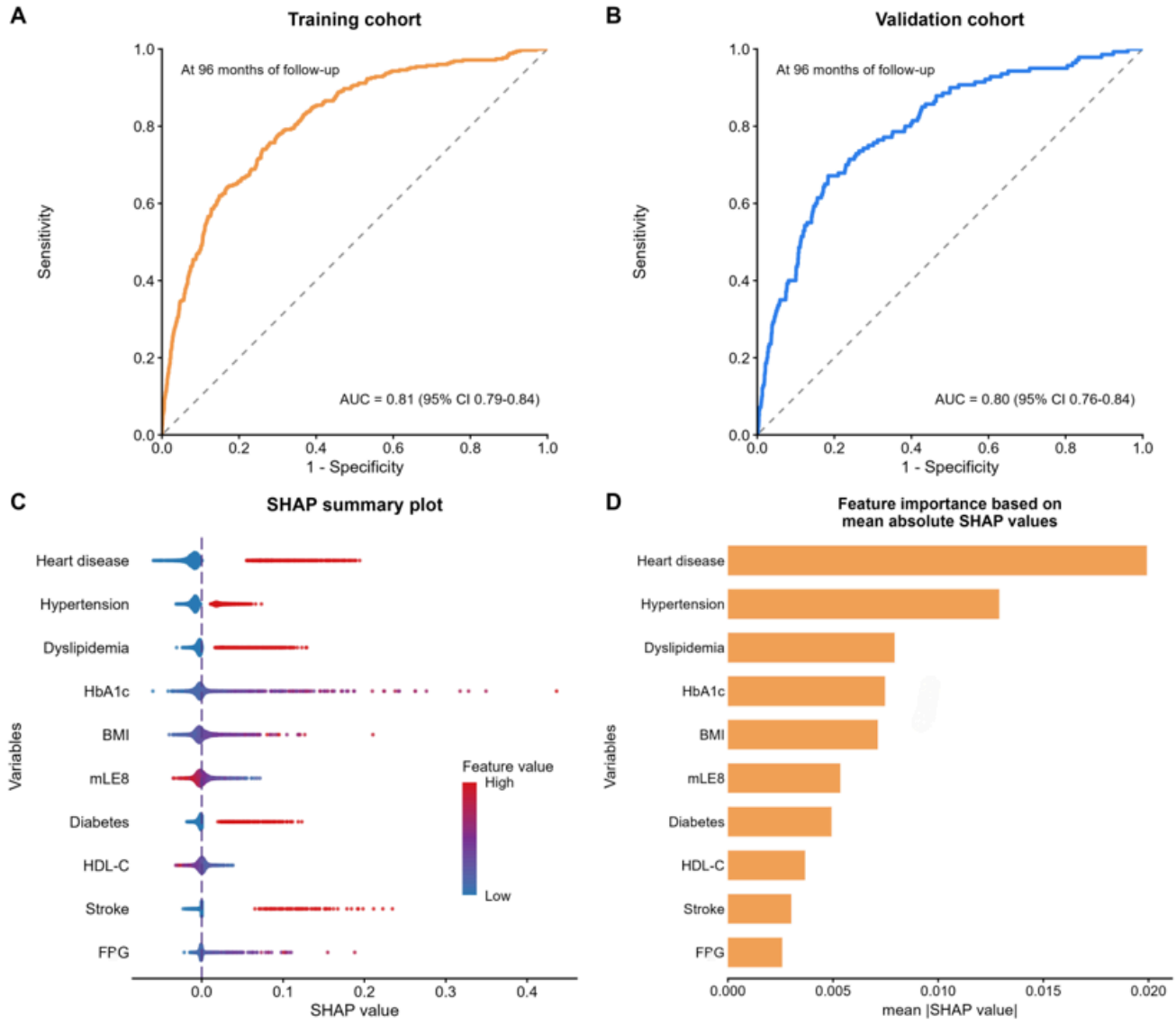

Figure 6

Time-dependent ROC curves and SHAP-based interpretation of the multivariable Cox prediction model in the training and validation cohorts.

Supplementary Files

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

- supplementary.docx