

Associations of depressive symptom trajectories with incident cardiometabolic multimorbidity: Evidence from longitudinal cohort studies in China and the United States

Jiahui Yang

Kunming Medical University

Wenhui Zhang

Kunming Medical University

Wen Zhang

Fuwai Yunnan Cardiovascular Hospital

Yajing Zhao

Fuwai Yunnan Cardiovascular Hospital

Wei Li

Qujing Central Hospital of Yunnan Province

Xiaoqing Zhang

zhangxiaoqing@kmmu.edu.cn

Kunming Medical University

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Abstract

Background

Depressive symptoms have been associated with incident cardiometabolic multimorbidity (CMM), but most studies relied on single-time assessments, which cannot capture the dynamic nature of depressive symptoms. We identified depressive symptom trajectories and examined their associations with incident CMM in China and the United States.

Methods

We included 8,952 participants from CHARLS (527 incident CMM events) and 10,812 from HRS (811 events), all free of CMM at baseline. Group-based trajectory modeling identified depressive symptom trajectories from three CES-D waves. Cox models estimated associations with incident CMM. Fine-Gray models and component outcome analyses were supplementary.

Results

Four trajectories were identified in both cohorts: low-stable, decreasing, increasing, and high-stable. In CHARLS, the decreasing (HR = 1.44, 95% CI: 1.14–1.82), increasing (HR = 1.64, 95% CI: 1.28–2.10), and high-stable (HR = 1.91, 95% CI: 1.41–2.59) groups had elevated CMM risk. In HRS, only high-stable remained significant (HR = 1.59, 95% CI: 1.21–2.07). Competing risk models were consistent. Component analyses showed the strongest association with heart disease.

Conclusions

Persistent high depressive symptoms were significantly associated with incident CMM in both cohorts, primarily driven by heart disease. Dynamic monitoring of depressive symptoms may improve risk stratification beyond single-time assessment.

Background

Cardiometabolic multimorbidity (CMM) is defined as the coexistence of two or more cardiometabolic conditions, including diabetes, heart disease, and stroke^{1,2}. With global population aging, the disease burden of CMM continues to rise, and CMM has become a major contributor to disability, cognitive decline, and mortality among middle-aged and older adults^{1–5}.

Depressive symptoms are common mental health problems in middle-aged and older populations. Previous studies have shown that depression is closely associated with the development and prognosis of diabetes^{6–8}, cardiovascular disease^{9–12}, and stroke^{13–15}, although the strength of association may differ across individual components. In addition, the association between depression and cardiometabolic multimorbidity has received increasing attention^{16,17}. However, most studies have relied on single-time assessments of depressive symptoms, which cannot distinguish persistent, intermittent, or remitted depression and may lead to biased effect estimates or inadequate risk stratification.

In recent years, group-based trajectory modeling (GBTM)^{18,19} has been increasingly used to identify longitudinal patterns of symptom evolution^{21,22}. Compared with single-time measures, depressive symptom trajectories can better capture the cumulative burden and dynamic changes of long-term exposure^{20–23}. However, studies examining the association between depressive symptom trajectories and CMM remain limited. Two important gaps exist. First, there is a lack of cross-cultural and cross-cohort comparative evidence²⁴. Second, most previous studies have used traditional Cox models without adequately accounting for death as a competing event^{25,26}.

The China Health and Retirement Longitudinal Study (CHARLS)²⁷ and the U.S. Health and Retirement Study (HRS)²⁸ are two structurally similar large longitudinal cohorts that provide representative data from middle-income and high-income countries, respectively. The differences in depression measurement instruments between the two cohorts offer a unique opportunity to examine the robustness of trajectory–outcome associations across measurement sensitivity. Using these two cohorts, this study aimed to identify depressive symptom trajectories, evaluate their associations with incident CMM, and further examine the influence of competing risks and component-specific associations.

Materials and Methods

Study Design and Data Sources

This study used a prospective cohort design. CHARLS covers 28 provinces in China and collects health and social information from adults aged 45 years and older²⁷; HRS covers U.S. adults aged 51 years and older²⁸. Both cohorts employed multistage probability sampling and collected comparable information.

Study Participants

Inclusion criteria were: age ≥ 51 years; completion of CES-D assessments at baseline and at least two follow-up waves; presence of 0 or 1 cardiometabolic condition at baseline; and complete CMM follow-up information. The final analytical samples included 8,952 participants from CHARLS (527 incident CMM cases during 2015–2020) and 10,812 participants from HRS (811 incident CMM cases during 2016–2022).

Depressive Symptom Assessment

CHARLS used the 10-item Center for Epidemiologic Studies Depression Scale (CES-D-10), with each item rated on a 0–3 scale and total scores ranging from 0 to 30²⁹. A cutoff of ≥ 10 was used to define depression^{30,31}. HRS used the 8-item CES-D (CES-D-8), with dichotomous items and total scores ranging from 0 to 8³². A cutoff of ≥ 4 was used to define depression^{33,34}. Both continuous scores and binary depression variables were used in the analyses.

Outcome Definition

Diabetes was defined as self-reported physician diagnosis or current use of antidiabetic medication. Heart disease was defined as self-reported physician diagnosis of coronary heart disease, myocardial infarction, or other heart disease. Stroke was defined as self-reported physician diagnosis of stroke. CMM was defined as the coexistence of at least two of the three conditions. Participants with prevalent CMM (≥ 2 conditions) at baseline were excluded. Incident CMM was defined as the transition from 0 or 1 condition at baseline to ≥ 2 conditions during follow-up, with

time to event defined as the interval from baseline to the diagnosis of the second distinct cardiometabolic condition.

Covariates

Covariates included demographic factors (age, sex, education, residence, marital status), health behaviors (smoking, drinking), functional status (ADL, IADL), and chronic conditions (hypertension, cancer, lung disease, arthritis, dyslipidemia). In sensitivity analyses, additional covariates included social activity, BMI, systolic blood pressure, diastolic blood pressure, hypertension medication, dyslipidemia medication, liver disease, kidney disease, stomach disease, and asthma.

Statistical Analysis

GBTM was implemented using the `hlme()` function from the R package `lcm`³⁵, with quadratic time polynomials to model longitudinal CES-D changes. Model selection criteria were: comparison of BIC across 1–5 class models; class proportion $\geq 5\%$; mean posterior probability > 0.75 ; and clinical interpretability of trajectory shapes^{36,37}. The four-class model was selected as the primary analysis in both cohorts, with the three-class model as a sensitivity analysis.

Because trajectory classes were derived from three CES-D assessments and were highly collinear with single-time CES-D scores, single-time measures and trajectory classes were modeled separately. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Three levels of adjustment were applied: Model 1, unadjusted; Model 2, adjusted for age, sex, education, residence, marital status, smoking, drinking, ADL, and IADL; Model 3, Model 2 plus hypertension, cancer, lung disease, arthritis, and dyslipidemia. The proportional hazards assumption was verified using Schoenfeld residual tests; all global P values were > 0.05 . Multicollinearity was assessed using generalized variance inflation factor (GVIF); all $GVIF^{1/(2 \times Df)}$ values were < 2 . Sensitivity analyses included: three-class trajectory models; extended covariate adjustment; CHARLS 8-item binary CES-D conversion; HRS complete-case analysis; Fine-Gray competing risk models; and component outcome analyses. Covariates with $< 20\%$ missingness were imputed using multiple imputation by chained equations (MICE)³⁸; variables with $> 20\%$ missingness were not included in primary analyses. All analyses were performed in R 4.5.1. Two-sided $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

Table 1 presents the baseline characteristics of participants by incident CMM status in both cohorts.

In CHARLS, 8,952 participants were included, of whom 527 (5.89%) developed incident CMM during follow-up. Compared with the no-CMM group, the CMM group had a higher median age (64.00 vs. 62.00 years, $P < 0.001$) and a higher proportion of women (63.00% vs. 51.91%, $P < 0.001$). The median CES-D score in the CMM group was 9.00, significantly higher than 6.00 in the no-CMM group ($P < 0.001$). The CMM group also had significantly higher ADL (0.67 ± 1.14 vs. 0.34 ± 0.86) and IADL (0.52 ± 0.93 vs. 0.29 ± 0.74) scores (both $P < 0.001$). The CMM group had a lower proportion of smokers (38.90% vs. 44.94%, $P = 0.007$), while drinking did not differ significantly. The CMM group had significantly higher prevalence of hypertension (64.52% vs. 31.79%), dyslipidemia (40.99% vs. 16.24%), lung disease (18.79% vs. 13.93%), and arthritis (57.50% vs. 45.66%) (all $P < 0.05$).

In HRS, 10,812 participants were included, of whom 811 (7.50%) developed incident CMM. The CMM group had a higher median age (69.00 vs. 66.00 years, $P < 0.001$). The median CES-D score was slightly but significantly higher in the CMM group ($P < 0.001$). The CMM group had significantly higher ADL (0.38 ± 0.91 vs. 0.23 ± 0.71) and IADL (0.27 ± 0.71 vs. 0.16 ± 0.52) scores (both $P < 0.001$). The CMM group had a higher proportion of smokers (58.82% vs. 53.32%, $P = 0.003$) and a lower proportion of drinkers (49.45% vs. 58.85%, $P < 0.001$). The CMM group had significantly higher prevalence of hypertension (79.04% vs. 58.09%), dyslipidemia (64.24% vs. 53.74%), lung disease (14.43% vs. 8.34%), and arthritis (71.15% vs. 58.62%) (all $P < 0.001$).

Table 1. Baseline characteristics of participants by incident cardiometabolic multimorbidity in CHARLS and HRS

Variable	Total (n = 10,812)	No CMM (n = 10,284)	CMM (n = 811)	Statistic	P
Panel A: CHARLS					
Variable	Total (n = 8,952)	No CMM (n = 8,425)	CMM (n = 527)	Statistic	P
Age, M (Q₁, Q₃)	62.00 (57.00, 68.00)	62.00 (57.00, 68.00)	64.00 (58.00, 69.00)	Z = -3.84	<0.001
Sex, n (%)				$\chi^2 = 24.48$	<0.001
Male	4,247 (47.44)	4,052 (48.09)	195 (37.00)		
Female	4,705 (52.56)	4,373 (51.91)	332 (63.00)		
Education, n (%)				$\chi^2 = 1.87$	0.393
Primary or below	8,031 (89.71)	7,551 (89.63)	480 (91.08)		
Secondary	821 (9.17)	781 (9.27)	40 (7.59)		
College or above	100 (1.12)	93 (1.10)	7 (1.33)		
Residence, n (%)				$\chi^2 = 7.89$	0.005
Urban	3,063 (34.22)	2,853 (33.86)	210 (39.85)		
Rural	5,889 (65.78)	5,572 (66.14)	317 (60.15)		
Marital status, n (%)				$\chi^2 = 0.26$	0.607
Married/partnered	7,678 (85.77)	7,230 (85.82)	448 (85.01)		
Unmarried/other	1,274 (14.23)	1,195 (14.18)	79 (14.99)		
CES-D score, M (Q₁, Q₃)	6.00 (3.00, 12.00)	6.00 (3.00, 11.00)	9.00 (5.00, 15.00)	Z = -8.21	<0.001
ADL, Mean $\pm$ SD	0.36 $\pm$ 0.88	0.34 $\pm$ 0.86	0.67 $\pm$ 1.14	t = -6.53	<0.001
IADL, Mean $\pm$ SD	0.31 $\pm$ 0.75	0.29 $\pm$ 0.74	0.52 $\pm$ 0.93	t = -5.56	<0.001
Smoking, n (%)				$\chi^2 = 7.32$	0.007
Non-smoker	4,961 (55.42)	4,639 (55.06)	322 (61.10)		
Smoker	3,991 (44.58)	3,786 (44.94)	205 (38.90)		
Drinking, n (%)				$\chi^2 = 3.33$	0.068
Non-drinker	4,888 (54.60)	4,580 (54.36)	308 (58.44)		
Drinker	4,064 (45.40)	3,845 (45.64)	219 (41.56)		
Hypertension, n (%)				$\chi^2 = 237.75$	<0.001
No	5,934 (66.29)	5,747 (68.21)	187 (35.48)		
Yes	3,018 (33.71)	2,678 (31.79)	340 (64.52)		

Variable	Total (n = 10,812)	No CMM (n = 10,284)	CMM (n = 811)	Statistic	P
Dyslipidemia, n (%)				$\chi^2 = 208.60$	<0.001
No	7,368 (82.31)	7,057 (83.76)	311 (59.01)		
Yes	1,584 (17.69)	1,368 (16.24)	216 (40.99)		
Cancer, n (%)				$\chi^2 = 0.10$	0.751
No	8,830 (98.64)	8,311 (98.65)	519 (98.48)		
Yes	122 (1.36)	114 (1.35)	8 (1.52)		
Lung disease, n (%)				$\chi^2 = 9.57$	0.002
No	7,679 (85.78)	7,251 (86.07)	428 (81.21)		
Yes	1,273 (14.22)	1,174 (13.93)	99 (18.79)		
Arthritis, n (%)				$\chi^2 = 27.93$	<0.001
No	4,802 (53.64)	4,578 (54.34)	224 (42.50)		
Yes	4,150 (46.36)	3,847 (45.66)	303 (57.50)		
Panel B: HRS					
Age, M (Q₁, Q₃)	67.00 (61.00, 76.00)	66.00 (60.00, 76.00)	69.00 (62.00, 77.00)	Z = -5.14	<0.001
Sex, n (%)				$\chi^2 = 7.35$	0.007
Male	4,184 (38.70)	3,834 (38.34)	350 (43.16)		
Female	6,628 (61.30)	6,167 (61.66)	461 (56.84)		
Education, n (%)				$\chi^2 = 18.48$	<0.001
Less than high school	1,653 (15.29)	1,498 (14.98)	155 (19.11)		
High school	6,352 (58.75)	5,863 (58.62)	489 (60.30)		
College or above	2,807 (25.96)	2,640 (26.40)	167 (20.59)		
Residence, n (%)				$\chi^2 = 0.73$	0.392
Urban	8,212 (75.95)	7,586 (75.85)	626 (77.19)		
Rural	2,600 (24.05)	2,415 (24.15)	185 (22.81)		
Marital status, n (%)				$\chi^2 = 0.92$	0.337
Married/partnered	6,782 (62.73)	6,286 (62.85)	496 (61.16)		
Unmarried/other	4,030 (37.27)	3,715 (37.15)	315 (38.84)		
CES-D score, M (Q₁, Q₃)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.50)	Z = -5.38	<0.001
ADL, Mean $\pm$ SD	0.24 $\pm$ 0.73	0.23 $\pm$ 0.71	0.38 $\pm$ 0.91	t = -4.61	<0.001

Variable	Total (n = 10,812)	No CMM (n = 10,284)	CMM (n = 811)	Statistic	P
IADL, Mean ± SD	0.17 ± 0.54	0.16 ± 0.52	0.27 ± 0.71	t = -4.46	<0.001
Smoking, n (%)				$\chi^2 = 9.10$	0.003
Non-smoker	5,002 (46.26)	4,668 (46.68)	334 (41.18)		
Smoker	5,810 (53.74)	5,333 (53.32)	477 (58.82)		
Drinking, n (%)				$\chi^2 = 27.29$	<0.001
Non-drinker	4,525 (41.85)	4,115 (41.15)	410 (50.55)		
Drinker	6,287 (58.15)	5,886 (58.85)	401 (49.45)		
Hypertension, n (%)				$\chi^2 = 136.73$	<0.001
No	4,361 (40.33)	4,191 (41.91)	170 (20.96)		
Yes	6,451 (59.67)	5,810 (58.09)	641 (79.04)		
Dyslipidemia, n (%)				$\chi^2 = 33.34$	<0.001
No	4,916 (45.47)	4,626 (46.26)	290 (35.76)		
Yes	5,896 (54.53)	5,375 (53.74)	521 (64.24)		
Cancer, n (%)				$\chi^2 = 0.49$	0.483
No	9,223 (85.30)	8,538 (85.37)	685 (84.46)		
Yes	1,589 (14.70)	1,463 (14.63)	126 (15.54)		
Lung disease, n (%)				$\chi^2 = 34.65$	<0.001
No	9,861 (91.20)	9,167 (91.66)	694 (85.57)		
Yes	951 (8.80)	834 (8.34)	117 (14.43)		
Arthritis, n (%)				$\chi^2 = 48.84$	<0.001
No	4,372 (40.44)	4,138 (41.38)	234 (28.85)		
Yes	6,440 (59.56)	5,863 (58.62)	577 (71.15)		

Notes: CMM, cardiometabolic multimorbidity; SD, standard deviation; M, median; Q₁, first quartile; Q₃, third quartile; CES-D, Center for Epidemiologic Studies Depression Scale; ADL, activities of daily living; IADL, instrumental activities of daily living.

Education and residence categories were aligned across the two cohorts to ensure comparability.

t, t-test; Z, Mann-Whitney U test; χ^2 , Chi-square test.

Depressive Symptom Trajectories

GBTM identified four distinct depressive symptom trajectories in both cohorts: low-stable, decreasing, increasing, and high-stable (Table 2, Supplementary Table 2).

In CHARLS, the low-stable group comprised 5,795 participants (64.73%), with mean CES-D scores of 5.21, 5.29, and 4.81 across the three waves. The decreasing group comprised 1,500 participants (16.76%), with the highest baseline score (16.09) declining to 11.42 and 9.36. The increasing group comprised 1,098 participants (12.26%), with scores rising from 8.36 to 10.66 and 16.95. The high-stable group comprised 559 participants (6.24%), with scores consistently maintained at a high level (19.44–20.80).

In HRS, the low-stable group comprised 8,311 participants (76.87%), with mean scores below 1 at all waves. The decreasing group comprised 1,201 participants (11.11%), with scores declining from 3.94 to 3.59 and 1.77. The increasing group comprised 719 participants (6.65%), with scores rising from 1.73 to 2.31 and 5.20. The high-stable group comprised 581 participants (5.37%), with scores consistently maintained between 5.80 and 6.08.

The three-class trajectory model was used as a sensitivity analysis (Supplementary Table 4).

Table 2. Mean CES-D scores across three waves by depressive symptom trajectory classes in CHARLS and HRS

Trajectory class	N	Wave 1 Mean (SD)	Wave 2 Mean (SD)	Wave 3 Mean (SD)
CHARLS		2011	2013	2015
Low-stable	5,795	5.21 (3.65)	5.29 (3.71)	4.81 (3.50)
Decreasing	1,500	16.09 (4.04)	11.42 (4.98)	9.36 (3.84)
Increasing	1,098	8.36 (3.93)	10.66 (4.77)	16.95 (3.80)
High-stable	559	19.44 (4.81)	19.14 (5.01)	20.80 (4.64)
HRS		2012	2014	2016
Low-stable	8,311	0.59 (0.89)	0.57 (0.88)	0.57 (0.85)
Decreasing	1,201	3.94 (1.98)	3.59 (2.04)	1.77 (1.20)
Increasing	719	1.73 (1.56)	2.31 (1.86)	5.20 (1.25)
High-stable	581	6.08 (1.64)	6.08 (1.56)	5.80 (1.63)

Notes: CHARLS used the 10-item CES-D (range 0–30); HRS used the 8-item CES-D (range 0–8).

Abbreviations: CHARLS, China Health and Retirement Longitudinal Study; HRS, Health and Retirement Study; CES-D, Center for Epidemiologic Studies Depression Scale; SD, standard deviation.

Depressive Symptoms and Incident CMM

Cox proportional hazards models were used to examine the associations of single-time depressive measures and depressive trajectories with incident CMM (Table 3).

In CHARLS, each 1-point increase in continuous CES-D score was associated with a 5% increased risk of CMM in Model 1 (HR = 1.05, 95% CI: 1.04–1.06), 4% in Model 2 (HR = 1.04, 95% CI: 1.03–1.05), and 3% in Model 3 (HR = 1.03, 95% CI: 1.02–1.05). Binary depression remained significant in Model 3 (HR = 1.44, 95% CI: 1.20–1.74). For trajectory classes, compared with the low-stable group, the decreasing, increasing, and high-stable groups had HRs of 1.65 (95% CI: 1.32–2.07), 2.00 (95% CI: 1.58–2.53), and 2.72 (95% CI: 2.07–3.56) in Model 1, showing a clear dose–response relationship. In Model 3, the decreasing (HR = 1.44, 95% CI: 1.14–1.82), increasing (HR = 1.64, 95% CI: 1.28–2.10), and high-stable (HR = 1.91, 95% CI: 1.41–2.59) groups all remained significantly elevated.

In HRS, continuous CES-D score was significantly associated with CMM risk in Model 1 (HR = 1.11, 95% CI: 1.08–1.15), decreasing to 1.06 (95% CI: 1.03–1.10) in Model 3 but remaining significant. Binary depression was significant in Model 3 (HR = 1.25, 95% CI: 1.02–1.52). Among trajectory classes, only the high-stable group remained significant in Model 3 (HR = 1.59, 95% CI: 1.21–2.07); the decreasing and increasing groups were significant in Model 1 but not after full adjustment.

Table 3. Associations of single-time depressive symptoms and depressive symptom trajectories with incident cardiometabolic multimorbidity in CHARLS and HRS

Panel A: CHARLS (n = 8,952; events = 527)

	Model1		Model2		Model3	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
CES-D score	1.05 (1.04 ~ 1.06)	<0.001	1.04 (1.03 ~ 1.05)	<0.001	1.03 (1.02 ~ 1.05)	<0.001
Binary depression						
Non-depressed	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Depressed	1.81 (1.52 ~ 2.15)	<0.001	1.53 (1.27 ~ 1.85)	<0.001	1.44 (1.20 ~ 1.74)	<0.001
4-class trajectory						
Low-stable	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Decreasing	1.65 (1.32 ~ 2.07)	<0.001	1.53 (1.21 ~ 1.93)	<0.001	1.44 (1.14 ~ 1.82)	0.002
Increasing	2.00 (1.58 ~ 2.53)	<0.001	1.77 (1.39 ~ 2.27)	<0.001	1.64 (1.28 ~ 2.10)	<0.001
High-stable	2.72 (2.07 ~ 3.56)	<0.001	2.13 (1.58 ~ 2.88)	<0.001	1.91 (1.41 ~ 2.59)	<0.001

Panel B: HRS (n = 10,812; events =811)

	Model1		Model2		Model3	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
CES-D score	1.11 (1.08 ~ 1.15)	<0.001	1.09 (1.05 ~ 1.13)	<0.001	1.06 (1.03 ~ 1.10)	<0.001
Binary depression						
Non-depressed	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Depressed	1.57 (1.31 ~ 1.88)	<0.001	1.35 (1.11 ~ 1.64)	0.003	1.25 (1.02 ~ 1.52)	0.029
4-class trajectory						
Low-stable	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Decreasing	1.33 (1.08 ~ 1.63)	0.008	1.27 (1.03 ~ 1.58)	0.028	1.17 (0.94 ~ 1.45)	0.153
Increasing	1.39 (1.07 ~ 1.79)	0.013	1.27 (0.98 ~ 1.66)	0.075	1.18 (0.91 ~ 1.55)	0.218

High-stable	2.09 (1.65 ~ 2.66)	<0.001	1.82 (1.39 ~ 2.37)	<0.001	1.59 (1.21 ~ 2.07)	<0.001
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Notes: Model 1␣ unadjusted. Model 2␣ adjusted for age, sex, education, residence, marital status, smoking, drinking, ADL, and IADL. Model 3␣ Model 2 plus hypertension, cancer, lung disease, arthritis, and dyslipidemia. Single-time measures and trajectory classes were modeled separately to avoid collinearity.

Abbreviations: CHARLS, China Health and Retirement Longitudinal Study; HRS, Health and Retirement Study; CES-D, Center for Epidemiologic Studies Depression Scale; HR, hazard ratio; CI, confidence interval.

Subgroup Analyses

In CHARLS, the association between depressive symptoms and CMM was stronger among participants without dyslipidemia (HR = 1.04, 95% CI: 1.03–1.06) than among those with dyslipidemia (HR = 1.02, 95% CI: 1.00–1.04), with a significant interaction (P for interaction = 0.029).

In HRS, the association was significant in women (HR = 1.07, 95% CI: 1.03–1.12) but not in men (HR = 1.04, 95% CI: 0.97–1.11) (P for interaction = 0.043). The association was significant among participants without cancer (HR = 1.08, 95% CI: 1.04–1.12) but not among those with cancer (HR = 0.98, 95% CI: 0.88–1.09) (P for interaction = 0.019). Other subgroup results are presented in Supplementary Table 9.

Table 4. Subgroup analyses of the association between continuous CES-D score and incident cardiometabolic multimorbidity in CHARLS and HRS

Subgroup	CHARLS				HRS			
	n (%)	HR (95%CI)	<i>P</i>	<i>P</i> for interaction	n (%)	HR (95%CI)	<i>P</i>	<i>P</i> for interaction
All participants	8,952 (100.00)	1.03 (1.02–1.05)	<0.001	—	10,812 (100.00)	1.06 (1.03–1.10)	<0.001	—
Sex				0.594				0.043
Male	4,247 (47.44)	1.03 (1.01–1.05)	0.014		4,184 (38.70)	1.04 (0.97–1.11)	0.268	
Female	4,705 (52.56)	1.04 (1.02–1.05)	<0.001		6,628 (61.30)	1.07 (1.03–1.12)	0.002	
Age, years				0.083				0.802
<65	5,526 (61.73)	1.04 (1.02–1.06)	<0.001		4,566 (42.23)	1.03 (0.97–1.10)	0.273	
≥65	3,426 (38.27)	1.02 (1.00–1.04)	0.031		6,246 (57.77)	1.08 (1.03–1.13)	<0.001	
Dyslipidemia				0.029				0.800
No	7,368 (82.31)	1.04 (1.03–1.06)	<0.001		4,916 (45.47)	1.05 (0.99–1.12)	0.117	
Yes	1,584 (17.69)	1.02 (1.00–1.04)	0.047		5,896 (54.53)	1.07 (1.02–1.12)	0.003	
Cancer				0.441				0.019
No	8,830 (98.64)	1.03 (1.02–1.05)	<0.001		9,223 (85.30)	1.08 (1.04–1.12)	<0.001	
Yes	122 (1.36)	1.17 (0.99–1.39)	0.065		1,589 (14.70)	0.98 (0.88–1.09)	0.734	

Notes:

HRs are from Cox proportional hazards models with continuous CES-D score as the exposure and incident CMM as the outcome. Models were adjusted for age, sex, education, residence, marital status, smoking, drinking, ADL, IADL, hypertension, cancer, lung disease, arthritis, and dyslipidemia. The stratifying variable was not adjusted for within its own subgroup.

Bold *P* for interaction values indicate statistical significance (*P* < 0.05).

CMM, cardiometabolic multimorbidity; CES-D, Center for Epidemiologic Studies Depression Scale; HR, hazard ratio; CI, confidence interval.

Sensitivity Analyses

The three-class trajectory model showed consistent results, with high-stable trajectories significantly associated with CMM in both cohorts (CHARLS: HR = 1.86, 95% CI: 1.36–2.53; HRS: HR = 1.64, 95% CI: 1.26–2.12) (Supplementary Table 5).

Extended covariate adjustment in CHARLS did not materially change the effect estimates (Supplementary Table 6). The HRS complete-case analysis also showed consistent findings (Supplementary Table 8).

After converting the CHARLS 10-item CES-D to an 8-item binary format, the four-class trajectory structure remained robust (Supplementary Table 3), and the high-stable group remained significantly associated with CMM (HR = 1.86, 95% CI: 1.38–2.51) (Supplementary Table 7).

Fine-Gray competing risk models showed that high-stable trajectories remained significantly associated with CMM after accounting for death as a competing event (CHARLS: sHR = 1.87, 95% CI: 1.37–2.55; HRS: sHR = 1.71, 95% CI: 1.30–2.25) (Supplementary Tables 10–11).

Component outcome analyses showed the strongest association with heart disease. In CHARLS, high-stable trajectories were significantly associated with heart disease (HR = 1.48), stroke (HR = 1.76), and diabetes (HR = 1.54). In HRS, only heart disease was significant (HR = 1.73) (Supplementary Tables 12–13).

Discussion

This study, based on two large longitudinal cohorts from China and the United States, found that persistent high depressive symptom trajectories were significantly associated with incident CMM, with consistent findings across multiple sensitivity analyses. Both cohorts showed a clear dose–response relationship, with the lowest risk in the low-stable group and the highest risk in the high-stable group.

Previous studies have established the associations of depression with diabetes^{6,7}, cardiovascular disease^{9,10}, and stroke¹³, but most relied on single-time assessments. Our trajectory-based approach showed that in HRS, only the high-stable group remained significant after full adjustment, supporting the "cumulative depression burden" hypothesis. Compared with previous studies limited to single countries or single outcomes^{21–23}, the present study enhanced cross-cultural comparability through parallel analyses in CHARLS and HRS. Previous studies on depression and CMM have mostly used single-time measures^{16,17}; our study extends this evidence by providing trajectory-level findings.

Fine-Gray models showed that the association between high-stable trajectories and CMM remained significant after accounting for death as a competing risk (CHARLS: sHR = 1.87; HRS: sHR = 1.71), with slightly higher effect estimates than the Cox models. This is consistent with the competing risk literature, which indicates that traditional Cox models may be biased when mortality risk differs between exposure groups^{25,26}.

The higher HR in CHARLS (1.91) than in HRS (1.59) may be explained by several factors. First, the 10-item CES-D used in CHARLS may capture depressive symptoms more comprehensively²⁹. Second, lower recognition and treatment rates of depression in China may result in longer untreated exposure. Third, differences in CMM diagnosis, healthcare access, and disease management between the two countries may affect outcome ascertainment^{24,27,28}.

Component analyses showed that the association with heart disease was strongest in both cohorts. In CHARLS, depressive trajectories were significantly associated with all three components, whereas in HRS, only heart disease

was significant. This is consistent with previous meta-analyses showing stronger associations of depression with coronary heart disease than with stroke or diabetes^{6,9,13}. Depression may exert more direct effects on the cardiovascular system than on cerebrovascular or metabolic systems.

Subgroup analyses showed a stronger association among participants without dyslipidemia in CHARLS, possibly because dyslipidemia itself is a strong risk factor for CMM, diluting the additional predictive value of depression^{20,21}. In HRS, stronger associations were observed in women and in those without cancer, but the statistical power of subgroup analyses is limited, and these findings should be interpreted cautiously.

Biologically, depression and CMM may be linked through multiple pathways. Long-term depression is closely associated with hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis^{16,39}. Older adults with depression often show elevated basal cortisol levels and abnormal dexamethasone suppression tests, indicating impaired HPA axis negative feedback^{39,40}. Chronic HPA axis activation may further lead to increased sympathetic tone, chronic low-grade inflammation, insulin resistance, and endothelial dysfunction^{10,12,16}. Persistent depression is also associated with unhealthy lifestyles, including physical inactivity, smoking, poor diet, and poor treatment adherence, all of which promote diabetes, hypertension, and atherosclerosis.

These findings suggest that clinical practice should not rely solely on single-time depression screening but should emphasize dynamic monitoring of depressive symptoms. Middle-aged and older adults with persistent high depressive symptoms should be considered a high-risk population for CMM and receive more proactive cardiometabolic risk monitoring and intervention. At the community and primary care level, establishing regular depression follow-up mechanisms may help identify high-risk individuals earlier¹⁷.

This study has several limitations. First, depressive symptoms and CMM components were self-reported and may be subject to recall and reporting biases, with potential cross-country differences in diagnostic standards and reporting habits. Second, only three waves of depression data were used, which may not fully capture the long-term dynamics of depressive symptoms. Third, despite adjustment for multiple covariates, residual confounding from genetic susceptibility, physical activity, psychotherapy, and antidepressant use cannot be excluded. Fourth, the two cohorts used different CES-D versions; although sensitivity analyses partially addressed this, direct cross-cohort comparisons of effect sizes should be interpreted cautiously. Fifth, although Fine-Gray models accounted for death as a competing risk, non-death censoring may still affect risk estimates. Sixth, although component-specific analyses were conducted, different disease combinations (e.g., diabetes plus heart disease vs. diabetes plus stroke) were not explored. Seventh, follow-up durations differed between CHARLS (approximately 5 years) and HRS (6 years), which may affect the comparability of effect estimates.

Conclusion

Based on two large longitudinal cohorts from China and the United States, this study found that persistent high depressive symptom trajectories were significantly associated with incident CMM in middle-aged and older adults. The association was primarily driven by heart disease and remained robust across multiple sensitivity and competing risk analyses. Dynamic monitoring of depressive symptoms may provide better risk stratification than single-time assessment, and individuals with persistent high depressive symptoms should be prioritized for CMM prevention.

Abbreviations

Abbreviation	Full Name
ADL	Activities of Daily Living
BMI	Body Mass Index
CES-D	Center for Epidemiologic Studies Depression Scale
CES-D-8	8-item Center for Epidemiologic Studies Depression Scale
CES-D-10	10-item Center for Epidemiologic Studies Depression Scale
CHARLS	China Health and Retirement Longitudinal Study
CI	Confidence Interval
CMM	Cardiometabolic Multimorbidity
DBP	Diastolic Blood Pressure
GBTM	Group-Based Trajectory Modeling
GVIF	Generalized Variance Inflation Factor
HPA	Hypothalamic–Pituitary–Adrenal
HR	Hazard Ratio
HRS	Health and Retirement Study
IADL	Instrumental Activities of Daily Living
LCMM	Latent Class Mixed Model
MICE	Multiple Imputation by Chained Equations
SBP	Systolic Blood Pressure
sHR	Subdistribution Hazard Ratio

Declarations

Ethics approval and consent to participate

The CHARLS study was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015), and all participants provided written informed consent. The HRS study was approved by the University of Michigan Health Sciences and Behavioral Sciences Institutional Review Board (HUM00061128), and all participants provided written informed consent. This study used de-identified publicly available data, and no additional ethical approval was required.

Clinical trial number: not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analysed during the current study are publicly available. CHARLS data can be obtained from <http://charls.pku.edu.cn/>, and HRS data can be obtained from <https://hrs.isr.umich.edu/>.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JY and XZ conceived and designed the study. JY performed the statistical analysis and drafted the manuscript. WL and WZ contributed to data interpretation and critically revised the manuscript for important intellectual content. YZ and WHZ contributed to literature review and data curation. XZ and WL supervised the study and provided overall guidance. All authors read and approved the final manuscript.

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Figures

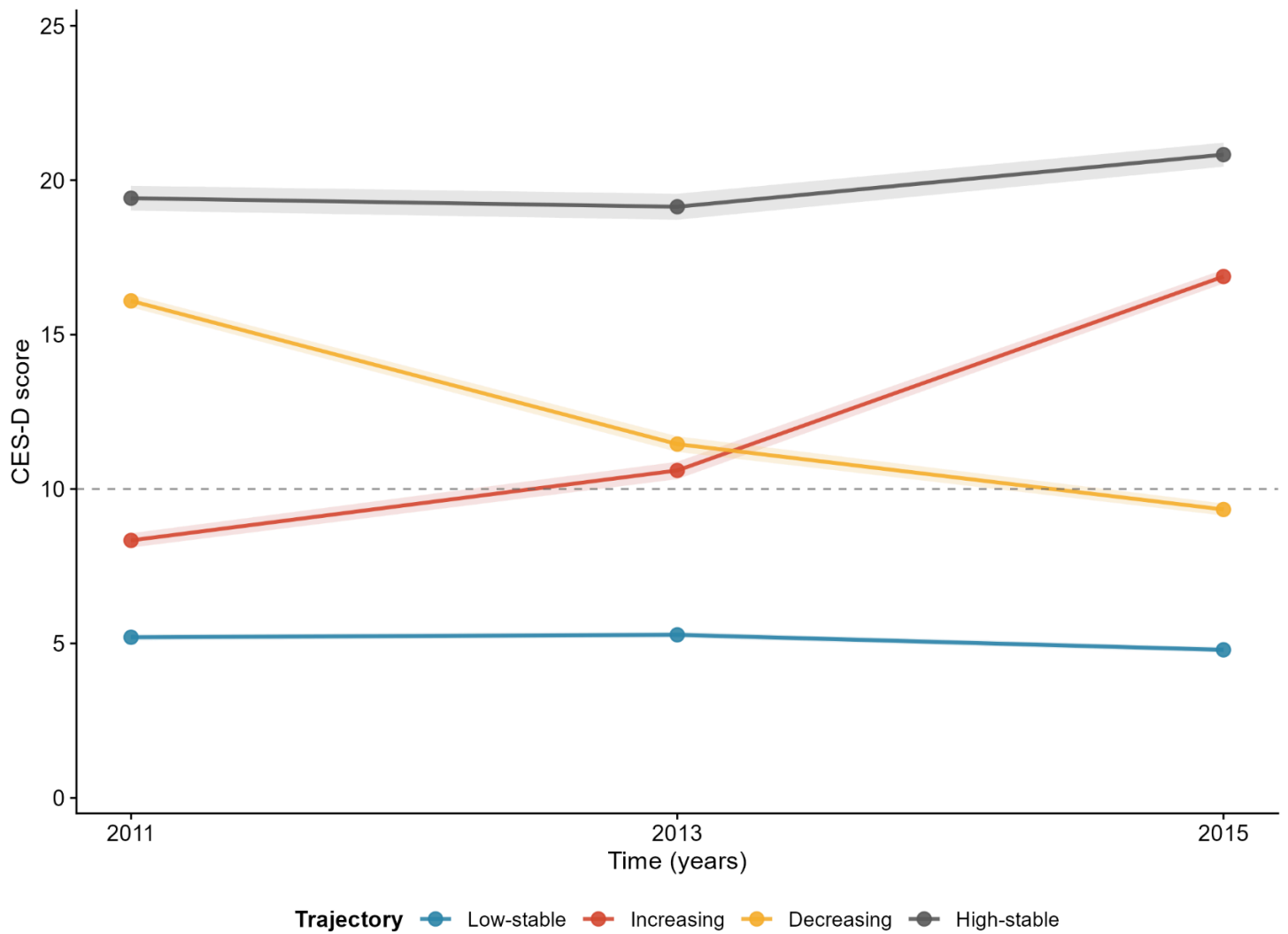


Figure 1

Trajectories of CES-D depressive symptoms, CHARLS cohort (2011-2015)

Figure legend: Depressive-symptom trajectories were fitted by latent class mixed model (LCMM). Four trajectory subgroups: low-stable, increasing, decreasing, high-stable. Shaded bands: 95% confidence intervals. Dashed horizontal line: CES-D clinical cutoff (≥ 10).

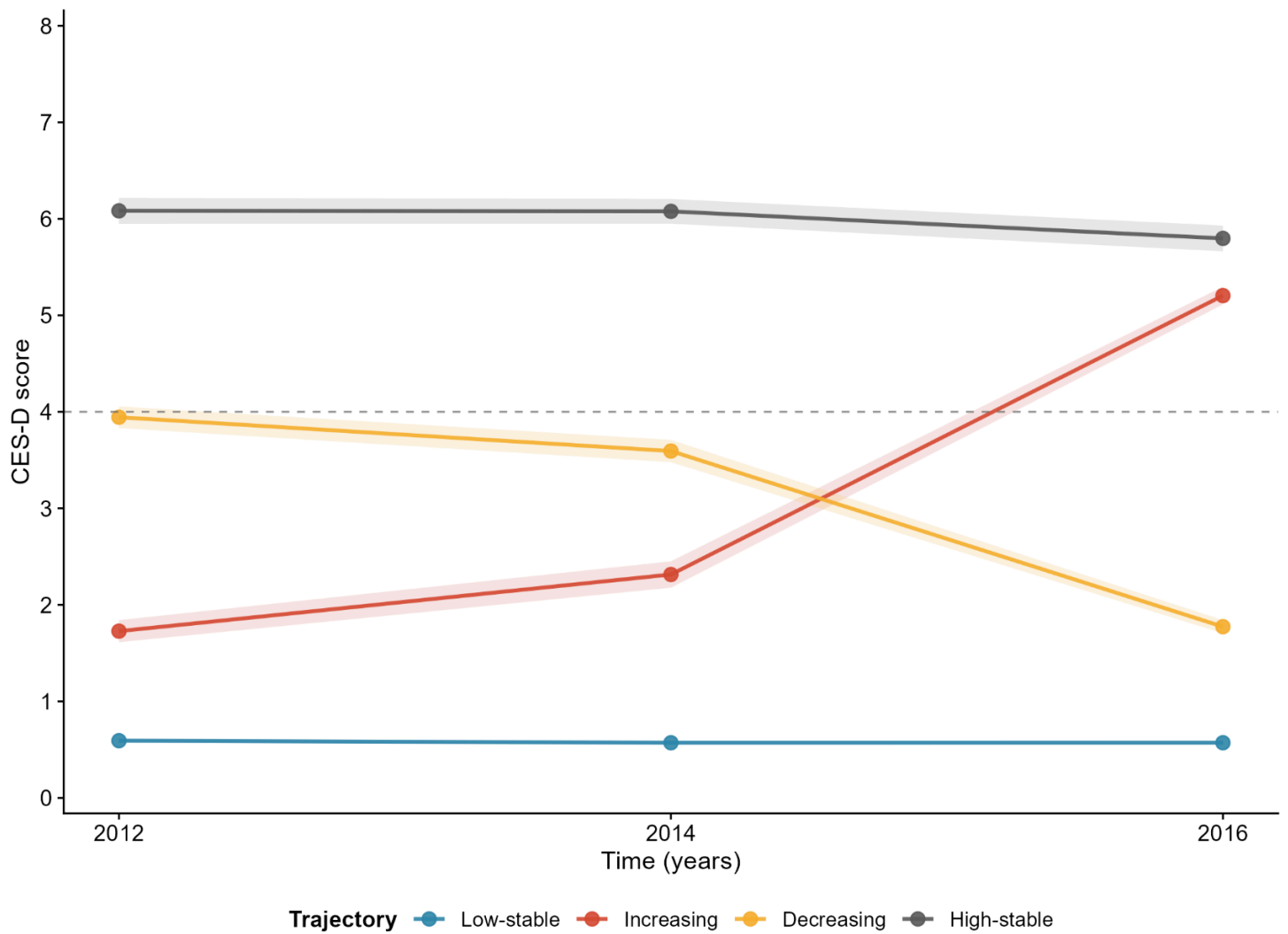


Figure 2

Trajectories of CES-D depressive symptoms, HRS cohort (2012-2016)

Figure legend: Depressive-symptom trajectories were fitted by latent class mixed model (LCMM). Four trajectory subgroups: low-stable, increasing, decreasing, high-stable. Shaded bands: 95% confidence intervals. Dashed horizontal line: CES-D clinical cutoff (≥ 4). Note: Different CES-D item sets were used in CHARLS and HRS, leading to distinct cutoff values.

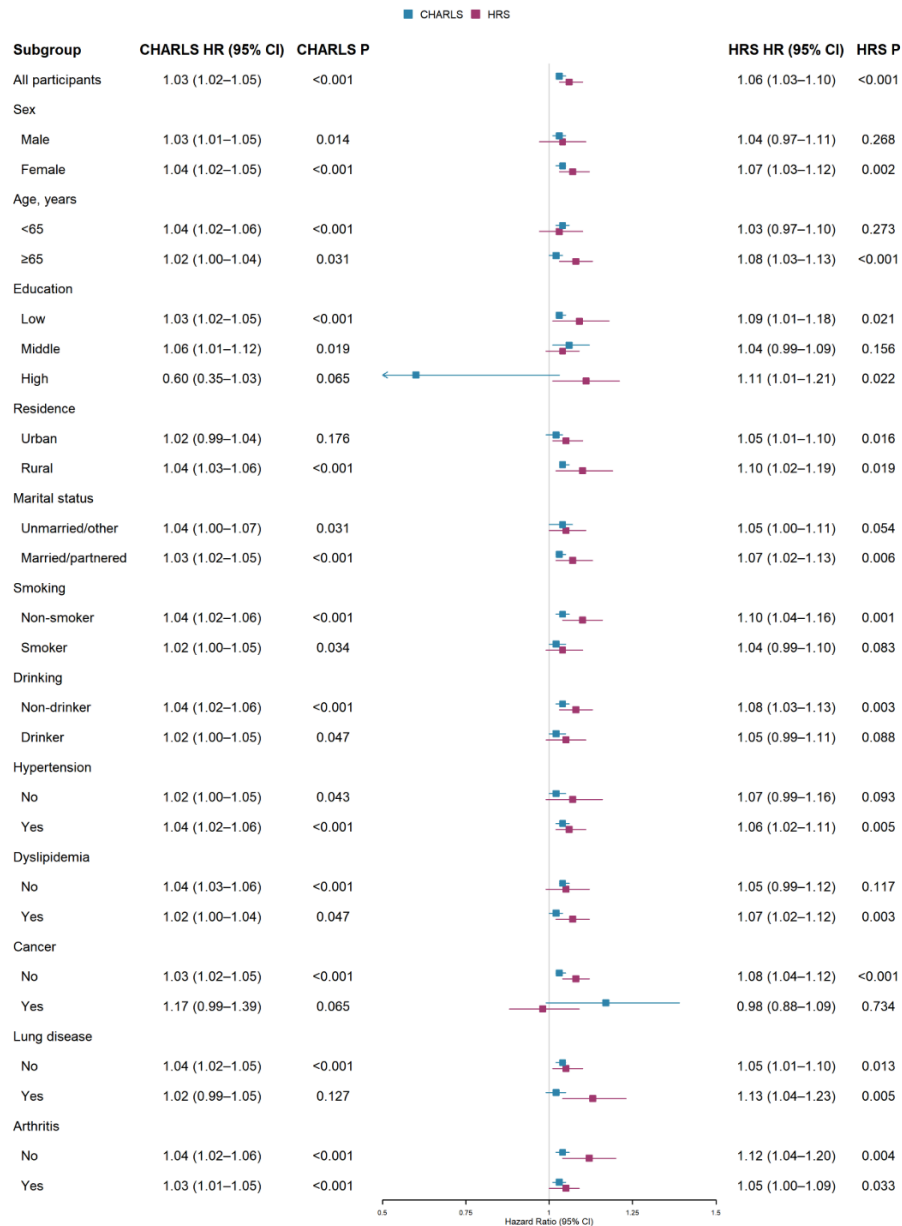


Figure 3

Subgroup analysis of depressive symptoms and incident cardiometabolic multimorbidity (CHARLS vs HRS)

Legend: HRs from Cox models (continuous CES-D, incident CMM). Adjusted for demographics, behaviors, ADL/IADL, and chronic diseases; stratifying variable excluded from its own subgroup. Age dichotomized at 65 years. $P < 0.05$ denote significant interaction. CMM, cardiometabolic multimorbidity; CES-D, Center for Epidemiologic Studies Depression Scale; HR, hazard ratio; CI, confidence interval.

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