Cardiometabolic multimorbidity and depressive symptom trajectories in middle-aged and older adults with chronic pain: evidence from the CHARLS and ELSA cohorts

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Abstract

Introduction: The co-occurrence of chronic pain and cardiometabolic multimorbidity (CMM) is increasingly prevalent among middle-aged and older adults, yet the extent to which CMM shapes the longitudinal course of depressive symptomatology in this population remains poorly understood.
Material and methods: Data were drawn from the China Health and Retirement Longitudinal Study (CHARLS; participants aged 45 years and older) and the English Longitudinal Study of Ageing (ELSA; participants aged 50 years and older). Group-based trajectory modeling (GBTM) was applied to identify distinct depressive symptom trajectories, and multinomial logistic regression was used to examine associations between CMM and trajectory group membership, with subgroup analyses conducted to assess potential effect modification.
Results: Three stable depressive symptom trajectories were identified in both cohorts: persistently low-, moderate-, and high-symptom groups. In ELSA, CMM was significantly associated with both moderate- (OR = 1.56, 95% CI: 1.24–1.96) and high-symptom trajectories (OR = 2.20, 95% CI: 1.61–3.02) after full covariate adjustment. In CHARLS, the association was confined to the high-symptom trajectory (OR = 1.39, 95% CI: 1.03–1.86). Subgroup analyses indicated a more pronounced association among female participants in CHARLS and among those younger than 65 years in ELSA.
Conclusions: CMM is significantly associated with more severe depressive symptom trajectories among middle-aged and older adults with chronic pain, with cross-cohort heterogeneity reflecting differences in population characteristics and sociocultural context. These findings suggest that consideration of CMM may be useful in the clinical assessment of individuals with chronic pain and may help identify individuals at elevated risk for adverse psychological outcomes.

Key words: cardiometabolic multimorbidity, chronic pain, depressive disorder, longitudinal cohort study, comorbidity.

Introduction

Against the backdrop of accelerating global population aging, the prevalence of chronic noncommunicable diseases continues to rise worldwide [1]. When two or more cardiometabolic conditions – such as diabetes mellitus, cardiovascular disease, or hypertension – co-occur in

a single individual, this constitutes cardiometabolic multimorbidity (CMM), a clinically complex state encompassing cardiovascular, metabolic, and inflammatory dysregulation with profound bidirectional interactions among its components. The global burden attributable to CMM is substantial and continues to grow [2, 3]. Estimates indicate that approximately 37% of adults worldwide live with multimorbidity (defined as ≥ 2 chronic conditions), with prevalence exceeding 50% among individuals aged 60 years and older; among common clustering patterns, cardiometabolic combinations – including diabetes mellitus, hypertension, and cardiovascular disease – are the most frequently observed [4]. In low- and middle-income countries, the pooled prevalence of noncommunicable disease multimorbidity approximates 36%, with cardiometabolic and cardiopulmonary-metabolic clusters predominating, and with older age, female sex, urban residence, and higher socioeconomic status identified as associated factors [5]. Importantly, individuals with CMM are at substantially elevated risk for a range of adverse outcomes, including depressive disorders and cognitive impairment [6–8].

Emerging evidence indicates that the number of chronic pain sites is closely associated with CMM risk; individuals reporting pain at four or more anatomical sites demonstrate a 1.82-fold increased risk of developing CMM [9]. The co-occurrence of chronic pain and CMM exerts a compounding adverse effect on patients' daily functioning and health-related quality of life, while simultaneously imposing a considerable economic burden through both direct healthcare expenditures and indirect costs arising from functional dependency and caregiving needs [10, 11]. Beyond its role as a somatic symptom, chronic pain is itself a well-established risk factor for the onset and exacerbation of depressive disorders [12, 13]. Notably, the relationship between CMM and depressive symptomatology appears to be bidirectional, with proposed biological mechanisms encompassing immune dysregulation, metabolic dysfunction, and genetic predisposition [14, 15].

Despite growing evidence linking chronic pain to depressive disorders, and cardiometabolic disease to depression independently, the role of CMM in shaping the longitudinal trajectory of depressive symptomatology among individuals with chronic pain remains poorly characterized. Existing evidence is largely derived from studies focusing on single disease states and predominantly cross-sectional in design, precluding the identification of dynamic patterns of symptom evolution over time. Whether CMM exerts a differential influence on the progression of depressive symptomatology in individuals with chronic pain, therefore, warrants systematic investigation.

To address this gap, the present study leverages data from two large, nationally representative longitudinal aging cohorts: the China Health and Retirement Longitudinal Study (CHARLS) and the English Longitudinal Study of Ageing (ELSA) [16, 17]. The complementary use of these two cohorts – drawn from distinct sociocultural and healthcare contexts – enables robust longitudinal analysis of the association between CMM and depressive symptom trajectories among individuals with chronic pain, and allows comparison of these associations across cohorts. Accordingly, this study applies group-based trajectory modeling to integrated longitudinal data from CHARLS and ELSA to elucidate the dynamic course of depressive symptomatology in the context of CMM among individuals with chronic pain. It is anticipated that these findings will provide an evidence base to inform the development of integrated intervention strategies encompassing cardiometabolic disease management, functional rehabilitation, and psychological support, with the ultimate aim of improving overall health outcomes and health-related quality of life in this high-risk population.

Material and methods

Study population

Data were obtained from two nationally representative, community-based longitudinal aging cohorts: the China Health and Retirement Longitudinal Study (CHARLS) and the English Longitudinal Study of Ageing (ELSA). Detailed descriptions of both cohorts have been reported elsewhere. The ELSA protocol was approved by the London Multicentre Research Ethics Committee, and CHARLS received approval from the Institutional Review Board of Peking University. Written informed consent was obtained from all participants prior to enrollment.

For CHARLS, the 2011 survey wave served as baseline, with follow-up assessments conducted in 2013, 2015, and 2018. For ELSA, the 2008 wave served as baseline, with follow-up data collected in 2010, 2012, and 2014. Participants were excluded if they reported no chronic pain at baseline, were younger than 45 years of age, or had missing data on depressive symptomatology or CMM status at baseline or during follow-up. The age range of participants included in CHARLS was 45 to 91 years (mean ± SD: 58.7 ±8.5 years), and that in ELSA was 50 to 90 years (mean ± SD: 65.2 ±9.0 years). These age criteria are consistent with the population inclusion criteria adopted in previous longitudinal studies utilizing the CHARLS and ELSA databases [18, 19]. After applying these criteria, 3,633 CHARLS participants and 2,979 ELSA participants were retained for analysis (Figure 1).

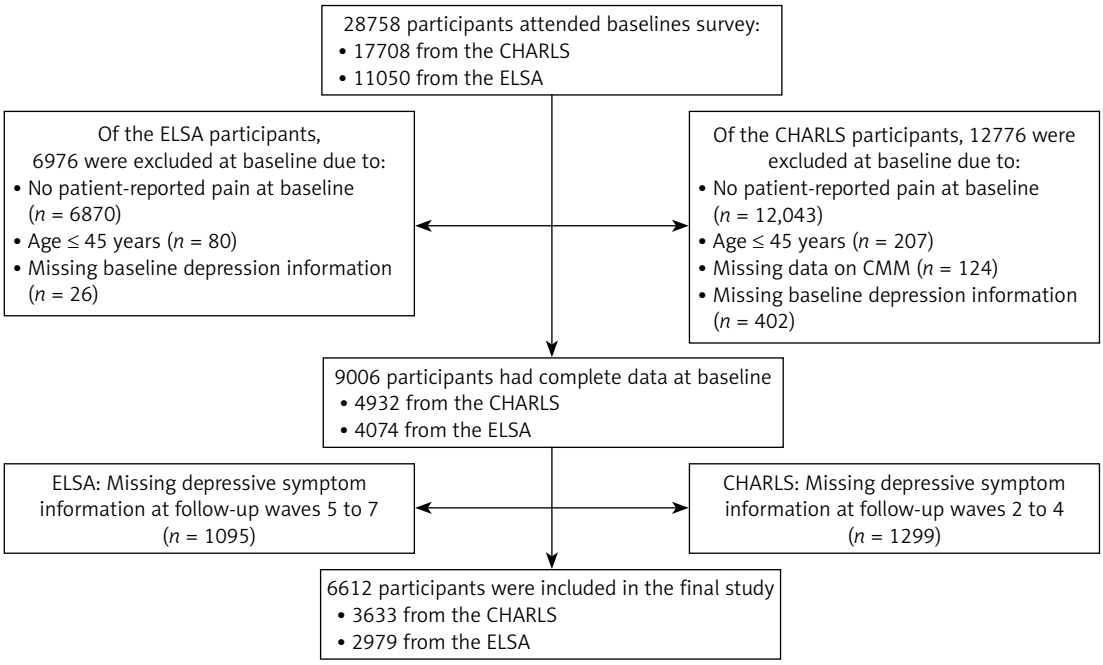


Figure 1. Flowchart of study population inclusion

Assessment of depressive symptomatology

Depressive symptomatology was quantified using cohort-appropriate versions of the Center for Epidemiologic Studies Depression Scale (CES-D). The ELSA cohort employed an eight-item version (score range: 0–8), with a validated cutoff of ≥ 4 indicating clinically relevant depressive symptomatology [20]. In CHARLS, a ten-item version was used, with items scored on a 0–3 scale and total scores ranging from 0 to 30; a threshold of ≥ 12 indicated the presence of depressive symptomatology [21]. Although the two versions differ in item count, their constituent items show substantial overlap, and both have been extensively validated for use in older adult populations with demonstrated reliability and validity. Importantly, prior multi-cohort studies employing both CHARLS and ELSA have similarly utilized the CES-D 10-item and CES-D 8-item versions in their respective cohorts, a practice consistent with established conventions in this field [22, 23]. As the present study did not perform direct quantitative comparisons of depressive symptom scores across cohorts, but instead fitted independent trajectory models within each cohort and presented findings as parallel evidence, potential comparability concerns arising from instrument differences are considered minimal.

Cardiometabolic multimorbidity

CMM was operationalized as the co-occurrence of two or more of the following conditions: cerebrovascular accident, heart disease, diabetes mellitus, hypertension, and dyslipidemia. Ascertainment combined self-reported physician diagnosis, current treatment receipt, and objective biomarker-based criteria. Hypertension was identified by systolic/diastolic blood pressure ≥ 140/90 mm Hg or self-report. Diabetes mellitus was defined by fasting plasma glucose ≥ 126 mg/dl, random glucose ≥ 200 mg/dl, or HbA1c ≥ 6.5% [24]. Dyslipidemia was defined as total cholesterol ≥ 240 mg/dl, low-density lipoprotein cholesterol (LDL-C) ≥ 160 mg/dl, high-density lipoprotein cholesterol (HDL-C) < 40 mg/dl, or serum triglycerides ≥ 200 mg/dl [25]. Consistent with the chronic nature of these conditions, diagnoses established at any assessment wave were carried forward throughout the follow-up period [26]. To address potential heterogeneity within the CMM construct, a sensitivity analysis was conducted stratifying participants by comorbidity burden (< 2 vs. ≥ 2 cardiometabolic conditions). Multinomial logistic regression was performed to examine the association between CMM status and depressive symptom trajectory membership (low trajectory as reference), adjusting for the same covariates as the primary analyses.

Covariates

The following covariates were included on the basis of their established associations with depressive disorders and cardiometabolic disease: age, sex, educational attainment, smoking status, alcohol consumption, and marital status. Educational attainment was dichotomized as high school or below versus above high school level.

Smoking status and alcohol consumption were each classified as never versus ever or current use. Marital status was categorized as married or non-married.

Statistical analysis

Baseline characteristics were reported as means ± standard deviations or frequencies (percentages), stratified by trajectory group. GBTM was used to derive latent depressive symptom trajectories, with models ranging from two to five trajectory groups evaluated. Trajectory shape was determined by testing linear, quadratic, and cubic polynomial terms for CES-D scores over time. Optimal model selection was based on the following criteria: first, the Bayesian information criterion (BIC), with lower values indicating superior model fit [27]; second, average posterior probabilities (AvePP) of ≥ 0.70 per group, reflecting the probability of correct individual assignment to the respective trajectory group [28]; third, a minimum trajectory group size of ≥ 5% of the total sample, to avoid statistically unstable groups with insufficient membership [29]; and fourth, clinical interpretability of the resulting trajectory solution. On the basis of these criteria, a three-trajectory solution was identified as optimal in both cohorts, consistent with prior longitudinal studies of depressive symptom trajectories in middle-aged and older adults with chronic disease. Between-group differences in baseline characteristics were assessed using χ^2 tests and one-way analysis of variance (ANOVA). Multinomial logistic regression was then applied to quantify associations between CMM and trajectory membership, yielding odds ratios (ORs) with 95% confidence intervals (CIs), adjusted for all covariates. Subgroup analyses stratified by age (< 65 vs. ≥ 65 years), sex, marital status, smoking, and alcohol consumption were performed, with interaction terms formally tested. To quantitatively assess the potential impact of residual confounding, E-value analyses were performed for all statistically significant associations. The E-value represents the minimum strength of association that an unmeasured confounder would need to have with both the exposure and the outcome to fully explain away the observed association. All analyses were conducted in R Studio (version 4.5.2); two-sided *p*-values < 0.05 were deemed statistically significant.

Results

Trajectories of depressive symptoms

To identify longitudinal patterns of depressive symptomatology among individuals with chronic pain, group-based trajectory modeling was applied separately to the CHARLS and ELSA datasets. Model fit was evaluated using the Akaike information criterion (AIC), Bayesian information criterion (BIC), and average posterior probabilities (APP); goodness-of-fit statistics are presented in Tables I and II. Comparison across models of varying group numbers indicated that a three-trajectory solution provided optimal fit in both cohorts. Three stable depressive symptom trajectories were consistently identified: a persistently low-symptom group (CHARLS: 42.6%; ELSA: 38.1%), a persistently moderate-symptom group (CHARLS: 43.4%; ELSA: 49.0%), and a persistently high-symptom group (CHARLS: 14.0%; ELSA: 12.9%). All three trajectories remained stable throughout the observation period, with no discernible temporal trend (Figure 2). These findings indicate marked popula-

Table I. Goodness-of-fit statistics of group-based trajectory analysis (CHARLS)

Number of groups	Trajectory shape	BIC for total number of observations	Group proportion (%)	Average posterior probabilities
2	3 3	–44588.27	66.91/33.10	0.94/0.90
3	3 3 3	–44333.11	42.57/43.42/14.01	0.87/0.82/0.87
4	3 3 3 3	–44295.60	43.60/22.25/20.84/13.30	0.87/0.66/0.67/0.84
3	2 3 3	–44329.42	42.35/43.57/14.08	0.87/0.82/0.87

Notes: Trajectory shape (0 = z ero order, 1 = linear, 2 = quadratic, 3 = cubic).

Table II. Goodness-of-fit statistics of group-based trajectory analysis (ELSA)

Number of groups	Trajectory shape	BIC for total number of observations	Group proportion (%)	Average posterior probabilities
2	3 3	–21217.63	66.67/33.33	0.94/0.92
3	3 3 3	–20822.40	38.05/49.03/12.93	0.88/0.88/0.88
4	3 3 3 3	–20720.75	23.13/48.76/23.23/4.88	0.84/0.84/0.82/0.87
3	3 0 2	–20809.32	38.19/48.91/12.89	0.88/0.87/0.88

Notes: Trajectory shape (0 = zero order, 1 = linear, 2 = quadratic, 3 = cubic).

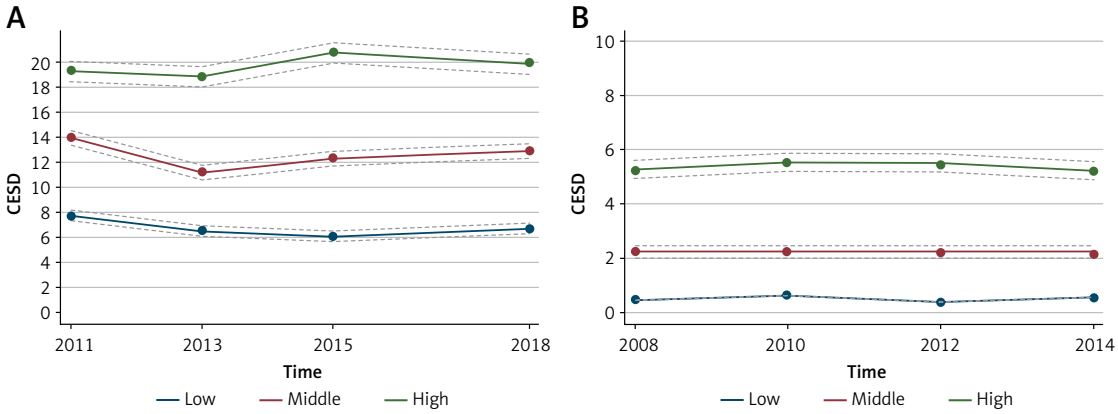


Figure 2. Depressive symptom score trajectories among individuals with chronic pain: **A** – CHARLS cohort; **B** – ELSA cohort

tion-level heterogeneity in the longitudinal course of depressive symptomatology among individuals with chronic pain, with analogous patterns observed across two cohorts of distinct cultural and epidemiological backgrounds.

Baseline characteristics of study participants

Analyses were conducted using data from the CHARLS and ELSA cohorts. The CHARLS cohort comprised 3,633 individuals with chronic pain, classified into low- (*n* = 1,549), moderate- (*n* = 1,610), and high-symptom (*n* = 474) trajectory groups (Table III). The ELSA cohort included 2,979 participants with chronic pain, similarly stratified into low- (*n* = 1,145), moderate- (*n* = 1,457), and high-symptom (*n* = 377) groups (Table IV). Statistically significant between-group differences were observed across multiple baseline characteristics in both cohorts. With respect to demographic characteristics, the mean age of CHARLS participants ranged from 58 to 59 years, whereas ELSA participants were older on average, ranging from 64 to 66 years. In both cohorts, the proportion of female participants increased progressively with greater depressive symptom severity. Regarding educational attainment, the majority of CHARLS participants had completed high school or below, while a higher proportion of ELSA participants had attained post-secondary education; nevertheless, an inverse association between educational level and depressive symptom severity was observed in both cohorts. Lifestyle characteristics differed be-

Table III. Patient demographics and baseline characteristics (CHARLS)

Characteristic	Depressive symptom trajectory group			*P*-value
	Low *N* = 1,549	Middle *N* = 1,610	High *N* = 474	
Age, mean ± SD	58 ±9	59 ±9	59 ±8	0.023
Sex, *n* (%)				< 0.001
Men	706 (45.6%)	546 (33.9%)	121 (25.5%)	
Women	843 (54.4%)	1,064 (66.1%)	353 (74.5%)	
Education, *n* (%)				0.002
High school and below	1,514 (97.7%)	1,595 (99.1%)	471 (99.4%)	
Above high school	35 (2.3%)	15 (0.9%)	3 (0.6%)	
Smoking status, *n* (%)	603 (38.9%)	517 (32.1%)	137 (28.9%)	< 0.001
Alcohol consumption, *n* (%)	599 (38.7%)	548 (34.0%)	136 (28.7%)	< 0.001
Marital status, *n* (%)				< 0.001
Married	1,394 (90.0%)	1,401 (87.0%)	386 (81.4%)	
Non-married	155 (10.0%)	209 (13.0%)	88 (18.6%)	
CMM, *n* (%)				0.056
No	1,366 (88.2%)	1,403 (87.1%)	398 (84.0%)	
Yes	183 (11.8%)	207 (12.9%)	76 (16.0%)	

Table IV. Patient demographics and baseline characteristics (ELSA)

Characteristic	Depressive symptom trajectory group			*P*-value
	Low *N* = 1,145	Middle *N* = 1,457	High *N* = 377	
Age, mean ± SD	64 ±8	66 ±9	65 ±10	< 0.001
Sex, *n* (%)				< 0.001
Men	561 (49.0%)	498 (34.2%)	120 (31.8%)	
Women	584 (51.0%)	959 (65.8%)	257 (68.2%)	
Education, *n* (%)				< 0.001
High school and below	658 (57.5%)	1,027 (70.5%)	296 (78.5%)	
Above high school	487 (42.5%)	430 (29.5%)	81 (21.5%)	
Smoking status, *n* (%)				0.016
No	450 (39.3%)	527 (36.2%)	118 (31.3%)	
Yes	695 (60.7%)	930 (63.8%)	259 (68.7%)	
Alcohol consumption, *n* (%)				< 0.001
No	93 (8.1%)	191 (13.1%)	76 (20.2%)	
Yes	1,052 (91.9%)	1,266 (86.9%)	301 (79.8%)	
Marital status, *n* (%)				< 0.001
Married	882 (77.0%)	927 (63.6%)	168 (44.6%)	
Non-married	263 (23.0%)	530 (36.4%)	209 (55.4%)	
CMM, *n* (%)				< 0.001
No	1,002 (87.5%)	1,182 (81.1%)	285 (75.6%)	
Yes	143 (12.5%)	275 (18.9%)	92 (24.4%)	

tween the two cohorts. In CHARLS, the prevalence of tobacco use and alcohol consumption declined with increasing depressive symptom severity. In ELSA, the prevalence of tobacco use increased with symptom severity, while alcohol consumption showed an inverse pattern. With regard to marital status, being married was associated with lower depressive symptom burden in both cohorts, with a more pronounced gradient observed in ELSA. Cardiometabolic multimorbidity was positively associated with depressive symptom severity in both cohorts. In CHARLS, the proportion of participants with CMM increased from 11.8% in the low-symptom group to 16.0% in the high-symptom group. A more pronounced gradient was observed in ELSA, where corresponding proportions rose from 12.5% to 24.4%. In summary, despite differences in age structure, educational background, and certain lifestyle characteristics, both cohorts consistently indicated that female sex, lower educational attainment, non-married status, and the presence of CMM were associated with more severe depressive symptom trajectories.

Association between cardiometabolic multimorbidity and depressive symptom trajectories

Multinomial logistic regression was employed to examine the association between CMM and depressive symptom trajectory group membership among individuals with chronic pain. CMM was significantly associated with trajectory classification in both cohorts, although the magnitude and pattern of associations differed across study settings. In the ELSA cohort, unadjusted analyses (Model 1) revealed that, compared with participants without CMM, those with CMM had a 1.63-fold increased odds of belonging to the moderate-symptom trajectory (OR = 1.63, 95% CI: 1.31–2.03; $p < 0.001$) and a 2.26-fold increased odds of belonging to the high-symptom trajectory (OR = 2.26, 95% CI: 1.69–3.03; $p < 0.001$). These associations remained statistically significant after adjustment for age, sex, educational attainment, tobacco use, alcohol consumption, and marital status (Model 2; Table V). In the CHARLS cohort, the pattern of association differed. In unadjusted analyses (Model 1), CMM was significantly associated only with membership in the high-symptom trajectory (OR = 1.43, 95% CI: 1.07–1.90; $p < 0.05$), with no statistically significant association observed for the moderate-symptom trajectory. This association remained significant following full covariate adjustment (Model 2; Table VI). Collectively, findings from both cohorts support a significant association between CMM and more severe longitudinal depressive symptomatology among individuals with chronic pain, particularly among those at the

Table V. Trajectories of depressive symptoms over 8 years associated with CMM status (ELSA)

Variables	Medium vs. Low	High vs. Low	Medium vs. Low	High vs. Low
	OR (95% CI) *P*-value	OR (95% CI) *P*-value	OR (95% CI) *P*-value	OR (95% CI) *P*-value
	Model 1		Model 2	
Status				
Non-CMM	Reference	Reference	Reference	Reference
CMM	1.63 (1.31, 2.03) < 0.001	2.26 (1.69, 3.03) < 0.001	1.56 (1.24, 1.96) < 0.001	2.20 (1.61, 3.02) < 0.001

Table VI. Trajectories of depressive symptoms over 8 years associated with CMM status (CHARLS)

Variables	Medium vs. Low	High vs. Low	Medium vs. Low	High vs. Low
	OR (95% CI) *p*-value	OR (95% CI) *p*-value	OR (95% CI) *p*-value	OR (95% CI) *p*-value
	Model 1		Model 2	
Status				
Non-CMM	Reference	Reference	Reference	Reference
CMM	1.10 (0.89, 1.36) 0.374	1.43 (1.07, 1.90) 0.017	1.08 (0.87, 1.33) 0.506	1.39 (1.03, 1.86) 0.030

highest risk of severe and persistent depression. The effect size differed markedly across cohorts: in ELSA, the association was broader and more pronounced, encompassing both moderate- and high-symptom trajectories, whereas in CHARLS, it was more circumscribed, confined to the most severe depressive trajectory. This cross-cohort heterogeneity may reflect differences in population characteristics, cultural context, or health system structures, underscoring the importance of considering study setting when interpreting associations between comorbidity burden and the longitudinal course of depressive disorders. E-value analyses were conducted to assess the robustness of these findings to potential residual confounding. In the ELSA cohort, the E-value for the association between CMM and the moderate-symptom trajectory was 2.49, and that for the high-symptom trajectory was 3.82. In the CHARLS cohort, the E-value for the association between CMM and the high-symptom trajectory was 2.13; the association with the moderate-symptom trajectory was an E-value of 1.37. These results suggest that a relatively strong unmeasured confounding effect would be required to fully account for the observed associations, supporting the robustness of the primary findings.

Subgroup analyses

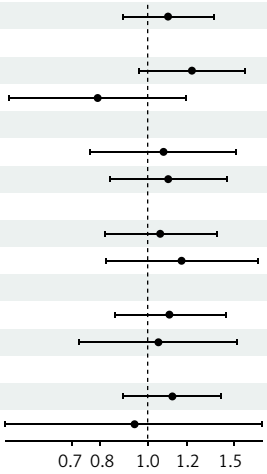
Subgroup analyses were conducted in two cohorts to explore the relationship between cardiometabolic multimorbidity (CMM) and depression trajectory scores (Figure 3). In the CHARLS cohort, CMM was not significantly associated with moderate depression (OR = 1.10, 95% CI: 0.89–1.36, $p = 0.373$), but was significantly associated with high-symptom trajectory (OR = 1.43, 95% CI: 1.07–1.90, $p = 0.017$), with a more significant association in females (OR = 1.61, 95% CI: 1.14–2.26, $p = 0.006$). In the ELSA cohort, CMM was significantly positively associated with moderate depression (OR = 1.63, 95% CI: 1.31–2.03, $p < 0.001$); its association with high-symptom trajectory was modified by age, with a stronger effect in those under 65 (OR = 3.20, 95% CI: 2.07–4.96, $p < 0.001$) and still significant in those ≥ 65 (OR = 1.67, 95% CI: 1.12–2.50, $p = 0.013$). Overall, most stratifying factors showed no significant interaction, and the association was generally robust. As shown in Table VII, sensitivity analyses stratifying CMM by comorbidity burden yielded results consistent with the primary findings. In the CHARLS cohort, hypertension and diabetes showed no statistically significant associations with depressive symptom trajectories in either model, whereas heart problem and stroke were significantly associated with membership in the high trajectory group (heart problem: Model 2 OR = 1.79, 95% CI: 1.39–2.31; stroke: Model 2 OR = 1.97, 95% CI: 1.17–3.30), with findings remaining robust after covariate adjustment. In the ELSA cohort, all four cardiometabolic components were significantly associated with both the medium and high depressive trajectory groups across both models. Cross-cohort consistency was observed specifically for heart problem and stroke, suggesting that these conditions may have cross-culturally generalizable effects on sustained elevated depressive trajectories, thereby corroborating the robustness of the primary analysis linking CMM to unfavorable depressive symptom trajectories.

Discussion

As reported in the results, CMM was significantly associated with more severe depressive symptom trajectory groups in both cohorts, though the

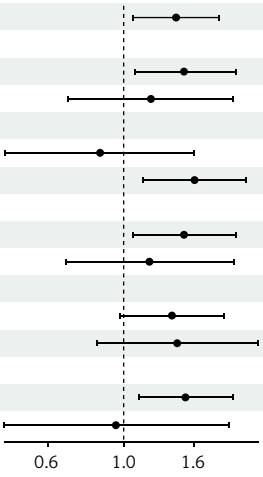
A

Subgroup	OR (95% CI)	*P*-value	*P* for interaction
Overall	1.10 (0.89, 1.36)	0.373	
Age			0.070
< 65	1.23 (0.96, 1.58)	0.096	
≥ 65	0.79 (0.52, 1.20)	0.265	
Gender			0.930
Man	1.08 (0.76, 1.52)	0.665	
Woman	1.10 (0.84, 1.45)	0.491	
Smoke			0.665
No	1.06 (0.82, 1.38)	0.657	
Yes	1.17 (0.82, 1.68)	0.389	
Drink			0.792
No	1.11 (0.86, 1.44)	0.419	
Yes	1.05 (0.72, 1.52)	0.808	
Marital status			0.579
Married	1.12 (0.89, 1.41)	0.321	
Non-married	0.94 (0.51, 1.71)	0.827	



B

Subgroup	OR (95% CI)	*P*-value	*P* for interaction
Overall	1.43 (1.07, 1.90)	0.017	
Age			0.480
< 65	1.51 (1.08, 2.13)	0.017	
≥ 65	1.20 (0.69, 2.08)	0.525	
Gender			0.084
Man	0.85 (0.45, 1.61)	0.617	
Woman	1.61 (1.14, 2.26)	0.006	
Smoke			0.485
No	1.50 (1.07, 2.12)	0.020	
Yes	1.19 (0.68, 2.08)	0.540	
Drink			0.912
No	1.39 (0.98, 1.96)	0.062	
Yes	1.44 (0.84, 2.48)	0.185	
Marital status			0.265
Married	1.52 (1.11, 2.08)	0.009	
Non-married	0.95 (0.45, 2.04)	0.904	



C

Subgroup	OR (95% CI)	*P*-value	*P* for interaction
Overall	1.63 (1.31, 2.03)	< 0.001	
Age			0.916
< 65	1.55 (1.08, 2.23)	0.018	
≥ 65	1.51 (1.14, 2.00)	0.004	
Gender			0.336
Man	1.95 (1.43, 2.67)	< 0.001	
Woman	1.57 (1.15, 2.15)	0.005	
Smoke			0.394
No	1.85 (1.26, 2.72)	0.002	
Yes	1.51 (1.16, 1.98)	0.002	
Drink			0.541
No	1.90 (1.02, 3.54)	0.044	
Yes	1.54 (1.22, 1.95)	< 0.001	
Marital status			0.482
Married	1.67 (1.28, 2.18)	< 0.001	
Non-married	1.41 (0.95, 2.10)	0.090	

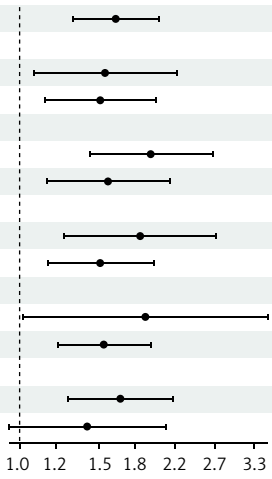


Figure 3. Subgroup analysis results: **A** – Low- versus moderate-symptom depressive trajectory groups in the CHARLS cohort. **B** – Low- versus high-symptom depressive trajectory groups in the CHARLS cohort. **C** – Low- versus moderate-symptom depressive trajectory groups in the ELSA cohort

D

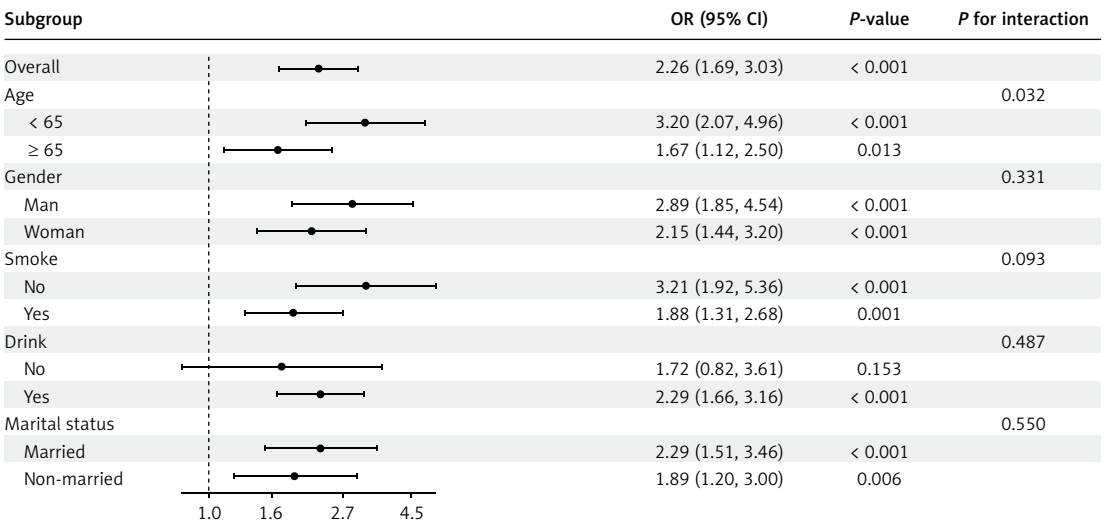


Figure 3. Cont. **D** – Low- versus high-symptom depressive trajectory groups in the ELSA cohort

Table VII. Trajectories of depressive symptoms over 8 years associated with CMM comorbidities status (CHARLS and ELSA)

Variables	Medium vs. Low	High vs. Low	Medium vs. Low	High vs. Low
	OR (95% CI) *P*-value	OR (95% CI) *P*-value	OR (95% CI) *P*-value	OR (95% CI) *P*-value
	Model 1		Model 2	
Status (CHARLS)				
Hypertension	Reference	Reference	Reference	Reference
	1.02 (0.88, 1.20) 0.778	1.06 (0.84, 1.33) 0.633	0.98 (0.84, 1.15) 0.788	1.00 (0.80, 1.27) 0.974
Diabetes	Reference	Reference	Reference	Reference
	1.06 (0.80, 1.40) 0.681	1.12 (0.75, 1.67) 0.579	1.04 (0.78, 1.37) 0.802	1.10 (0.74, 1.65) 0.643
Heart problem	Reference	Reference	Reference	Reference
	1.24 (1.02, 1.50) 0.029	1.93 (1.50, 2.48) < 0.001	1.18 (0.98, 1.44) 0.088	1.79 (1.39, 2.31) < 0.001
Stroke	Reference	Reference	Reference	Reference
	1.16 (0.78, 1.75) 0.465	1.82 (1.10, 3.03) 0.021	1.19 (0.79, 1.80) 0.398	1.97 (1.17, 3.30) 0.011
Status (ELSA)				
Hypertension	Reference	Reference	Reference	Reference
	1.37 (1.17, 1.60) < 0.001	1.77 (1.40, 2.24) < 0.001	1.25 (1.06, 1.47) 0.008	1.65 (1.28, 2.11) < 0.001
Diabetes	Reference	Reference	Reference	Reference
	1.46 (1.12, 1.92) 0.006	1.90 (1.32, 2.73) < 0.001	1.43 (1.08, 1.89) 0.013	1.74 (1.18, 2.56) 0.005
Heart problem	Reference	Reference	Reference	Reference
	1.56 (1.26, 1.93) < 0.001	1.95 (1.45, 2.61) < 0.001	1.49 (1.19, 1.86) < 0.001	1.93 (1.41, 2.64) < 0.001
Stroke	Reference	Reference	Reference	Reference
	1.79 (1.16, 2.76) 0.008	2.02 (1.14, 3.59) 0.017	1.56 (1.00, 2.44) 0.049	1.80 (0.99, 3.29) 0.055

pattern of association differed markedly between the two study settings.

This divergence likely reflects systematic differences in healthcare infrastructure, sociocultural determinants of health, and population-level disease profiles between China and the United Kingdom. Regarding healthcare access, middle-aged and older adults in rural China face more pronounced inequities in the distribution of medical resources, resulting in relatively low diagnosis rates and treatment coverage for cardiometabolic diseases [30, 31]. In terms of disease management, the National Health Service in the United Kingdom provides more standardized pathways for chronic disease management, whereas middle-aged and older adults in China exhibit substantial differences in self-management awareness and medication adherence with respect to cardiometabolic multimorbidity [32]. With regard to baseline population characteristics, the two cohorts differ systematically in age structure, educational attainment, urban-rural distribution, and prevalence of chronic pain, all of which may collectively influence the distribution of depressive symptom trajectories across cohorts. Among middle-aged and older adults in China, the cumulative burden of coexisting chronic conditions may produce a threshold effect, wherein the adverse psychological impact of CMM becomes clinically detectable only beyond a critical level of multimorbidity. These findings further suggest that the hypothesized mechanistic pathways linking cardiometabolic multimorbidity to depressive disorders may vary across sociocultural contexts, highlighting the necessity of interpreting such associations within their respective epidemiological frameworks.

Existing evidence supports an association between cardiometabolic multimorbidity and elevated risk of depressive disorders, a relationship corroborated across diverse populations. A study conducted in Germany among adults aged 80 years and older demonstrated that individuals with CMM exhibited a significantly greater depressive symptom burden [33]. Research in middle-aged and older Chinese adults further indicated that those with two or more cardiometabolic conditions, including cerebrovascular accident, heart disease, or diabetes mellitus, faced substantially higher risk of depressive disorders compared to those with only one such condition [34]. A 27-year longitudinal investigation additionally provided evidence of a sustained association between depressive symptomatology and cardiovascular disease [35]. Notably, a Swedish twin-based study suggested that genetic factors may moderate this relationship: CMM was significantly associated with increased depression risk among dizygotic twins, yet no significant effect was observed in monozygotic pairs, implying a potential role of shared genetic liability in the CMM–depression association [36]. Collectively, these findings are consistent with the present study's results, supporting the premise that CMM is associated with additional depressive risk among individuals with concurrent chronic pain.

The association between CMM and depressive symptomatology may be explained through several interrelated mechanisms.

First, the psychological burden and self-management demands imposed by chronic disease represent a putative contributing pathway [37, 38]. As the number of coexisting conditions increases, patients are required to navigate progressively complex management regimens, encompassing long-term pharmacotherapy, continuous monitoring of physiological parameters such as blood pressure and glycemia, and sustained behavioral modification. Healthcare providers further emphasize adherence to lifestyle changes, including dietary adjustment, increased physical activity, smoking cessation, and alcohol abstinence [28]. Non-adherence to these behavioral targets is associated with poorer disease progression and more severe symptomatology [39], including back pain linked to ischemic heart disease and cardiac dysfunction [40], which may in turn be associated with compromised health-related quality of life and negative affect [41].

Second, shared behavioral risk factors may underlie both conditions. CMM is frequently accompanied by obesity, tobacco use, and physical inactivity, all of which are independently recognized risk factors for depressive disorders [42].

Third, CMM and depressive disorders are hypothesized to share common biological mechanisms, including elevated inflammatory biomarkers, endothelial dysfunction, and reduced heart rate variability [43–45]. These overlapping pathophysiological pathways suggest that CMM and depressive symptomatology may mutually reinforce one another through shared neurobiological substrates, further compounding disease burden in affected individuals.

As global population aging intensifies, demographic aging has increasingly been recognized as a worldwide social and public health challenge. Population aging may in turn elevate the incidence of chronic pain arising from diverse etiologies, including injury- and disease-related causes [46]. Accumulating evidence demonstrates that chronic pain is associated with the onset of depressive disorders [13, 47, 48], with implicated mechanisms encompassing neuroinflammation and genetic predisposition [49–52].

Neuroinflammation has been identified as a contributing factor in the pathogenesis of depressive disorders [52], and both chronic pain and CMM have been independently associated

with upregulation of pro-inflammatory cytokines. Based on prior literature, an additive or synergistic effect of these two conditions may be associated with a greater depressive symptom burden, though this pathway was not directly examined in the present study. Furthermore, the interaction between chronic pain and CMM introduces considerable complexity into clinical management, potentially prolonging hospitalization, and imposing compounding economic and psychological burdens on affected patients and their caregivers.

The present study benefits from the use of two large, nationally representative cohorts with harmonized analytical approaches, ensuring cross-cohort comparability of findings. Nevertheless, several limitations warrant acknowledgement. First, as an observational study, the possibility of residual confounding cannot be fully excluded despite adjustment for established covariates. Second, the underlying biological mechanisms through which CMM influences depressive symptom trajectories were not directly examined; future investigations incorporating comprehensive biomarker data, including inflammatory markers and metabolic indices, are needed to elucidate these pathways.

In conclusion, drawing on comparative data from the CHARLS and ELSA cohorts, this study identified CMM as significantly associated with more severe depressive symptom trajectories among individuals with chronic pain. Although the pattern of association varied across distinct sociocultural and healthcare contexts, the association between CMM and poorer psychological well-being was consistent across both populations. These findings highlight the importance of considering CMM in the clinical assessment of individuals with chronic pain and underscore the potential value of integrated, multidisciplinary care strategies for this vulnerable population.

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Data availability

Publicly available datasets were analyzed in this study. These data can be found here: http://charls.pku.edu.cn/; https://beta.ukdataservice.ac.uk/datacatalogue/series/series?id=2 00011

Ethical approval

The studies involving human participants were reviewed and approved by London Multicentre Research Ethics Committee and Peking University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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