

Trajectories of Cardiopulmonary-Depressive Symptom Comorbidity Burden and Subsequent Activities of Daily Living Disability and Cognitive Function among Middle-Aged and Older Chinese Adults: A Nationally Representative Longitudinal Cohort Study

Fei Cao#

Baotou Central Hospital, Inner Mongolia Autonomous Region

Yunhao Jiang#

Daqing People's Hospital

Chen Chen

1019182985@qq.com

Daqing People's Hospital

Article

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Abstract

Background

With population aging, the coexistence of cardiopulmonary diseases and psychological distress has evolved into a severe symptom cluster. Traditional static disease count fails to capture the dynamic accumulation of chronic conditions. This study aimed to identify the long-term trajectories of comorbidity burden characterized by cardiopulmonary diseases and depressive symptoms, and to explore their predictive effects on activities of daily living (ADL) disability and cognitive function among middle-aged and older adults in China.

Methods

Data were derived from four waves of the China Health and Retirement Longitudinal Study (CHARLS) conducted between 2011 and 2018, and a total of 13,008 participants were included. A comorbidity score (range: 0–3) was constructed based on depressive symptoms, chronic respiratory diseases and cardiovascular diseases. Growth mixture modeling (GMM) was used to identify comorbidity trajectories. Multivariate logistic regression and linear regression analyses were applied to examine the associations between trajectories and incident ADL disability as well as memory scores in 2018.

Results

Three distinct trajectories were identified: stable low burden group (81.2%), persistent high burden group (12.6%), and rapidly increasing burden group (6.2%). In the fully adjusted model, compared with the stable low burden group, the persistent high burden group (OR = 1.75, 95% CI: 1.38–2.22) and rapidly increasing burden group (OR = 1.88, 95% CI: 1.37–2.54) were strong predictors of incident ADL disability. Regarding cognitive function, only the rapidly increasing burden group was significantly associated with lower memory scores in 2018 ($\beta = -0.368$, 95% CI: -0.661 to -0.075 , $P = 0.014$), while no significant independent association was observed in the persistent high burden group ($P = 0.084$).

Conclusions

Both persistently high burden and rapid growth of cardiopulmonary-depressive comorbidity significantly elevate the risk of functional disability. Rapid accumulation of comorbidity is a key risk factor for impaired memory function in later life. Clinical assessment should shift from static disease evaluation to dynamic trajectory monitoring, with targeted attention to older adults experiencing accelerated comorbidity progression.

1. Introduction

The clinical landscape of aging is increasingly characterized by the coexistence of multiple chronic conditions—a phenomenon termed multimorbidity—which poses a substantial threat to functional independence and cognitive health^{1–3}. While previous epidemiological studies have linked individual conditions (e.g., cardiovascular diseases, chronic respiratory disorders, and depression) to these adverse geriatric outcomes, these conditions frequently cluster and interact synergistically. Specifically, the cardiopulmonary-depressive symptom cluster represents a highly prevalent and debilitating phenotype. The cumulative burden of this specific cluster may compromise physiological reserve and daily independence far more than the mere summation of individual diseases. Despite its clinical significance, the prognostic value of cumulative comorbidity trajectories remains poorly characterized due to methodological constraints. The vast majority of existing literature relies on static, cross-sectional designs or single baseline measurements of disease counts. Such approaches fundamentally overlook the dynamic, life-course nature of disease accumulation. Over time, older adults exhibit highly heterogeneous health trajectories: some maintain stable profiles, while others experience persistently high burdens or periods of rapid, accelerated health deterioration. Consequently, treating comorbidity as a static baseline predictor may mask the prognostic impact of the pace of disease accumulation^{4,5}. Growth mixture modeling (GMM) addresses this critical gap by identifying distinct, latent longitudinal patterns of disease progression within a population. Shifting from static counts to trajectory-based assessments enables the identification of individuals undergoing active, rapid health decline, facilitating precise and timely interventions.

To this end, leveraging a nationally representative cohort from the China Health and Retirement Longitudinal Study (CHARLS) spanning a seven-year period (2011–2018), this study aimed to characterize the longitudinal trajectories of a highly relevant comorbidity cluster—encompassing cardiovascular disease, chronic respiratory disease, and depressive symptoms—among middle-aged and older Chinese adults. We prospectively examined the associations of these identified trajectories with subsequent incident ADL disability and late-life cognitive function. We hypothesized that adverse longitudinal patterns, particularly persistently high or rapidly escalating comorbidity burdens, would independently predict a higher risk of functional disability and poorer cognitive outcomes compared to a low-stable trajectory, even after accounting for baseline health status.

2. Methods

2.1 Study Population

This longitudinal cohort study utilized data from the China Health and Retirement Longitudinal Study (CHARLS), a nationally representative survey of community-dwelling adults aged 45 and older in China⁶. The study employs a stratified, multi-stage probability sampling design. The CHARLS protocol was approved by the Biomedical Ethics Review Committee of Peking University, and all participants provided written informed consent. For the present analysis, we extracted data from the 2011 baseline survey and three subsequent follow-up waves (2013, 2015, and 2018). Of the 14,628 participants assessed at

baseline, we restricted our primary analytical sample to 13,008 individuals who possessed at least two valid waves of comorbidity data, a prerequisite for robust longitudinal trajectory modeling. For subsequent outcome-specific regression analyses, we utilized complete-case samples, excluding participants with missing covariate data or pre-existing conditions related to the specific outcome (yielding 4,823 participants for the incident ADL analysis and 4,974 participants for the late-life cognitive evaluation).

2.2 Assessment of comorbidity burden

To capture the dynamic burden of the cardiopulmonary-psychological symptom cluster over time, we constructed a targeted comorbidity score based on three high-impact conditions: depressive symptoms, chronic respiratory disease, and cardiovascular disease. Depressive symptoms were ascertained using the 10-item Center for Epidemiologic Studies Depression Scale (CES-D 10), dichotomized at a well-validated cutoff score of ≥ 10 . Chronic respiratory disease (chronic lung disease or asthma) and cardiovascular disease (heart disease or stroke) were defined based on self-reported physician diagnoses. For each survey wave, the number of these conditions was summed to yield a specific comorbidity score ranging from 0 to 3. Growth mixture modeling (GMM) was then employed across the four survey waves to identify distinct latent longitudinal patterns (trajectories) of this comorbidity burden. Model selection was based on the Bayesian Information Criterion (BIC), distinctiveness of trajectory shapes, and ensuring an adequate proportion of the sample in each classified group.

2.3 Assessment of activities of daily living disability and cognitive function

The primary functional outcome was incident activities of daily living (ADL) disability during follow-up. ADL was evaluated based on the self-reported ability to perform six basic tasks: dressing, bathing, eating, transferring, toileting, and continence. ADL disability was defined as experiencing difficulty (a score of ≥ 3) in at least one of these domains. To strictly evaluate incident disability, participants with ADL disability at the 2011 baseline were excluded from this specific analysis. The secondary outcome, global cognitive function, was assessed in the 2018 wave using a composite score derived from three domains: immediate word recall (10 items), delayed word recall (10 items), and intact mental status/numeracy (serial subtraction of 7 from 100, up to five times). The scores were summed to create a global cognitive score ranging from 0 to 25, with higher values indicating superior cognitive performance.

2.4 Covariates

Covariates were selected based on previous literature and their potential confounding effects on the association between multimorbidity trajectories and aging-related outcomes. The adjusted models incorporated sociodemographic characteristics, health behaviors and other health-related factors, including age, sex, educational level, marital status, smoking status, alcohol consumption and body mass index (BMI). BMI was calculated as body weight divided by the square of height. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or a physician-

diagnosed self-reported history. hyperlipidemia was defined as total cholesterol ≥ 238.93 mg/dL or triglycerides ≥ 200.90 mg/dL. Diabetes mellitus was defined as glycated hemoglobin (HbA1c) $\geq 6.5\%$ or self-reported physician diagnosis.

2.5 Statistical Analysis

Baseline demographic and clinical characteristics of the study population were summarized according to the identified comorbidity trajectory groups. Continuous variables are expressed as mean $\pm$ standard deviation (SD) and compared across groups using one-way analysis of variance (ANOVA). Categorical variables are presented as frequencies and percentages and compared using chi-square tests. Growth mixture modeling (GMM) was applied to classify participants by longitudinal patterns of cumulative comorbidity burden across four survey waves (2011–2018). Models with 1 to 4 trajectory groups were tested to select the optimal solution. Analyses were performed using latent class linear mixed models (LCLMM), a generalized form of growth mixture models (GMM), with random intercepts and slopes to account for individual deviations from group-averaged trends^{7,8}. To evaluate the prospective associations of comorbidity trajectories with subsequent incident ADL disability and global cognitive scores in 2018, we constructed three progressive regression models, using the "Low-stable" trajectory group as the reference category. For the binary outcome of incident ADL disability, we utilized multivariable logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs), excluding participants with pre-existing ADL disability at the 2011 baseline to establish a robust temporal sequence. For the continuous outcome of 2018 global cognitive scores, we applied ordinary least squares (OLS) linear regression models to estimate β coefficients and 95% CIs. Model 1 was unadjusted. Model 2 adjusted for key sociodemographic characteristics, including age, sex, educational attainment, and marital status. Model 3 (the fully adjusted model) further controlled for body mass index (BMI), smoking status, drinking status, health insurance, hypertension, diabetes, hyperlipidemia, arthritis, and baseline ADL or cognitive scores to minimize potential confounding and reverse causality.

Finally, to test the robustness of our primary functional findings, we conducted a sensitivity analysis using 2018 ADL disability status as an alternative outcome definition. In this analysis, participants with baseline ADL disability were retained rather than excluded, and their baseline ADL status was adjusted for as a covariate in the fully adjusted model to confirm whether adverse comorbidity trajectories remained independent predictors of subsequent functional decline in a broader cohort. All statistical tests were two-sided, with significance set at $P < 0.05$. All analyses were performed using R software (version 4.5.2).

2.6 Ethical Considerations

The Institutional Review Board of Peking University approved all CHARLS survey protocols. All participants provided written informed consent. This study used publicly available, de-identified CHARLS data, which exempted it from further ethical review.

3. Results

3.1 Baseline characteristics of participants

The exclusion process was illustrated in Fig. 1. Following the application of inclusion and exclusion criteria, a total of 13,008 participants were retained for the longitudinal trajectory analysis. Among these, the cohort was classified into three distinct comorbidity trajectory groups: low-stable ($n = 10,566$; 81.2%), high-persistent ($n = 1,640$; 12.6%), and rapid-increasing ($n = 802$; 6.2%). Outcome-specific analytical samples comprised 4,823 participants for incident ADL disability and 4,974 for cognitive evaluation, after excluding cases with missing data or pre-existing target conditions. Baseline characteristics, detailed in Table 1, revealed distinct demographic and clinical profiles across the three groups. Participants in the high-persistent group were notably older (mean age: 61.25 years), predominantly female, and possessed lower educational attainment compared to the low-stable and rapid-increasing cohorts. Crucially, the high-persistent group exhibited a profoundly heavier baseline disease burden extending beyond the three targeted conditions. For instance, the prevalence of hypertension (38.6%) and arthritis (54.9%) was markedly elevated in this group relative to the low-stable reference. Expectedly, baseline functional and cognitive metrics were most compromised in the high-persistent trajectory, which registered the highest baseline ADL disability rate (10.6%) and the lowest mean cognitive score (9.42).

Table 1
Basic characteristics of the study population in Charl

Characteristics	Low-stable	High-persistent	Rapid-increasing	P-value
n	10566	1640	802	
Age,years	58.08(8.96)	61.25(9.21)	58.48(8.03)	< 0.001
Gender,n(%)				< 0.001
Male	52.21(49.4)	666(40.6)	377(47.0)	
Female	53.36(50.5)	974(59.4)	424(52.9)	
Marital Status,n(%)				< 0.001
Married	9464(89.6)	1368(83.4)	719(89.7)	
Never marride	1102(10.4)	272(16.6)	83(10.3)	
Education,n(%)				0.029
Junior high school and below	10028(94.9)	1586(96.7)	772(96.3)	
Senior high school and vocational high school	450(4.3)	45(2.9)	28(3.5)	
University and above	84(0.8)	9(0.5)	2(0.2)	
Smoke,n(%)				0.026
Yes	3344(31.6)	455(27.7)	83(10.3)	
No	7220(68.3)	1185(72.3)	561(70.0)	
Alcohol,n(%)				< 0.001
Yes	2855(27.0)	290(17.7)	197(24.6)	
No	7711(73.0)	1350(82.3)	605(75.4)	
BMI				< 0.001
< 20	1479(14.0)	279(17.0)	93(11.6)	
20–25	4785(45.3)	628(38.3)	360(44.9)	
25–30	2381(22.5)	380(23.2)	184(22.9)	
>=30	418(4.0)	74(4.5)	53(6.6)	

Characteristics	Low-stable	High-persistent	Rapid-increasing	P-value
Hypertension,n(%)				< 0.001
Yes	2215(21.0)	633(38.6)	252(31.4)	
No	8308(78.6)	1000(61.0)	549(68.5)	
Diabetes,n(%)				< 0.001
Yes	488(4.6)	177(10.8)	49(6.1)	
No	10007(94.7)	1453(88.6)	751(93.6)	
Hyperlipidemia,n(%)				< 0.001
Yes	836(7.9)	275(16.8)	94(11.7)	
No	9577(90.6)	1332(81.2)	701(87.4)	
Arthritis,n(%)				< 0.001
Yes	3157(29.9)	901(54.9)	316(39.4)	
No	7400(70.0)	738(45.0)	486(60.6)	
Insurance,n(%)				0.890
Yes	9909(93.8)	1528(93.2)	753(93.9)	
No	625(5.9)	106(6.5)	46(5.7)	
Comorbidity_score,(n%)	0.38(0.50)	2.04(0.48)	0.65(0.48)	< 0.001
Adl_disability,(n%)				< 0.001
Yes	293(2.8)	174(10.6)	38(4.7)	
No	6043(57.2)	1311(79.9)	229(28.6)	
Adl_score,(n%)	6.47(1.43)	7.07(2.07)	6.61(1.78)	< 0.001
Cog_total,(n%)	10.64(4.50)	9.42(4.44)	10.16(4.41)	< 0.001

3.2 Comorbidity trajectory groups

Group-based trajectory modelling identified three distinct longitudinal patterns of cumulative comorbidity burden from 2011 to 2018. The largest group was the low-stable trajectory, which included

10,566 participants. This group was characterized by a consistently low mean comorbidity score throughout follow-up. The mean score remained below 0.5 across all survey waves, indicating a persistently low comorbidity burden. The high-persistent trajectory included 1,640 participants. This group had the highest comorbidity burden at baseline and remained at a high level throughout follow-up. The trajectory showed a mean comorbidity score of approximately 2.0 in 2011, followed by a slight decrease in 2013 and 2015, and a subsequent increase by 2018. Overall, this trajectory represented a group with sustained high comorbidity burden. The rapid-increasing trajectory included 802 participants. This group started with a moderate comorbidity burden in 2011 and 2013, increased by 2015, and then showed a sharp increase by 2018. By the end of follow-up, the mean comorbidity score in this group exceeded that of the high-persistent group. This pattern suggests that a subset of participants experienced accelerated accumulation of comorbidity burden over time.

The morphology of these trajectories is shown in Fig. 2. The three patterns indicate substantial heterogeneity in the longitudinal development of comorbidity burden among middle-aged and older Chinese adults.

3.3 Association between comorbidity trajectories and incident ADL disability

The associations between comorbidity trajectory groups and incident ADL disability are shown in Table 2 and Fig. 3. The low-stable trajectory group was used as the reference group. In the unadjusted model, both the high-persistent and rapid-increasing trajectory groups had higher odds of incident ADL disability. The unadjusted odds ratio was 2.11 for the high-persistent group and 1.86 for the rapid-increasing group. After adjustment for age, sex, education, and marital status, the associations remained statistically significant. In Model 2, the odds ratio was 1.98 for the high-persistent group and 1.96 for the rapid-increasing group. Further adjustment for BMI, smoking, drinking, health insurance, hypertension, diabetes, hyperlipidemia, arthritis, and baseline ADL score slightly attenuated the association for the high-persistent group but did not materially change the overall pattern. In the fully adjusted model, participants in the high-persistent group had 75% higher odds of developing ADL disability than those in the low-stable group, with an OR of 1.75 and a 95% CI of 1.38 to 2.22. Participants in the rapid-increasing group had 88% higher odds of incident ADL disability, with an OR of 1.88 and a 95% CI of 1.37 to 2.54. Both associations were statistically significant, with $P < 0.001$. These findings indicate that both persistently high and rapidly increasing comorbidity burden were associated with an increased likelihood of subsequent ADL disability. The magnitude of association was slightly stronger for the rapid-increasing trajectory in the fully adjusted model.

Table 2
Associations between comorbidity trajectory groups and incident ADL disability

	Model1		Model2		Model3	
	OR(95%CI)	P-value	OR(95%CI)	P-value	OR(95%CI)	P-value
Low-stable	Ref		Ref		Ref	
High-persistent	2.11 (1.68, 2.64)	< 0.001	1.98 (1.58, 2.49)	< 0.001	1.75 (1.38, 2.22)	< 0.001
Rapid-increasing	1.86 (1.36, 2.49)	< 0.001	1.96 (1.44, 2.65)	< 0.001	1.88 (1.37, 2.54)	< 0.001

Reference group: Low-stable trajectory group. Model 1 was unadjusted. Model2 adjusted for age, sex, education, and marital status. Model 3 further adjusted for BMI, smoking, drinking, health insurance, hypertension, diabetes, Hyperlipidemia, arthritis, and baseline ADL score.

3.4 Association between comorbidity trajectories and episodic memory outcomes

The associations between comorbidity trajectory groups and episodic memory outcomes are shown in Table 3 and Fig. 4s. The low-stable trajectory group was used as the reference group. For memory performance in 2018, both adverse trajectory groups showed lower memory scores than the low-stable group in the unadjusted model. The high-persistent trajectory was associated with a 1.207-point lower memory score ($\beta = -1.207$, 95% CI: -1.486 -0.928, $P < 0.001$), while the rapid-increasing trajectory was associated with a 0.694-point lower memory score ($\beta = -0.694$, 95% CI: -1.033 -0.355, $P < 0.001$). After adjustment for age, sex, education, and marital status, the associations were attenuated but remained statistically significant for both the high-persistent trajectory ($\beta = -0.324$, 95% CI: -0.557 -0.091, $P = 0.006$) and the rapid-increasing trajectory ($\beta = -0.324$, 95% CI: -0.604 -0.044, $P = 0.023$). In the fully adjusted model, which further included BMI, smoking status, drinking status, health insurance, hypertension, diabetes, hyperlipidemia, arthritis, and baseline memory score, the rapid-increasing trajectory remained significantly associated with poorer memory performance in 2018 ($\beta = -0.368$, 95% CI: -0.661 to -0.075, $P = 0.014$). The high-persistent trajectory showed a similar negative direction, although the association did not reach statistical significance ($\beta = -0.221$, 95% CI: -0.473 to 0.030, $P = 0.084$).

We further examined memory change from 2011 to 2018 as a longitudinal cognitive outcome. In the unadjusted model, neither the high-persistent trajectory ($\beta = -0.204$, 95% CI: -0.496 0.088, $P = 0.170$) nor the rapid-increasing trajectory ($\beta = -0.092$, 95% CI: -0.447 0.263, $P = 0.611$) was significantly associated with memory change. After adjustment for sociodemographic characteristics, the high-persistent trajectory showed a positive but non-significant association with memory change ($\beta = 0.257$, 95% CI: -0.028 0.542, $P = 0.077$), while the rapid-increasing trajectory remained non-significant ($\beta = 0.102$, 95% CI: -0.241 0.445, $P = 0.560$). In the fully adjusted model, neither the high-persistent trajectory ($\beta = 0.171$, 95% CI: -0.144 0.487, $P = 0.287$) nor the rapid-increasing trajectory ($\beta = -0.035$, 95% CI: -0.403 0.333, $P =$

0.852) was significantly associated with memory change from 2011 to 2018. Taken together, these findings indicate that rapidly increasing comorbidity burden was independently associated with poorer follow-up episodic memory performance, whereas no significant association was observed between comorbidity trajectories and memory change over the study period.

Table 3

Association between comorbidity trajectories and episodic memory outcomes A. Memory score in 2018

	Model1		Model2		Model3	
	β (95%CI)	P-value	β (95%CI)	P-value	β (95%CI)	P-value
Low-stable	Ref		Ref		Ref	
High-persistent	-1.207 (-1.486, -0.928)	< 0.001	-0.324 (-0.557, -0.091)	0.006	-0.221 (-0.473, 0.030)	0.084
Rapid-increasing	-0.694 (-1.033, -0.355)	< 0.001	-0.324 (-0.604, -0.044)	0.023	-0.368 (-0.661, -0.075)	0.014

B. Memory change from 2011 to 2018

	Model1		Model2		Model3	
	β (95%CI)	P-value	β (95%CI)	P-value	β (95%CI)	P-value
Low-stable	Ref		Ref		Ref	
High-persistent	-0.204 (-0.496, 0.088)	0.170	0.257 (-0.028, 0.54)	0.077	0.171 (-0.144, 0.487)	0.287
Rapid-increasing	-0.092 (-0.447, 0.263)	0.61	0.102 (-0.241, 0.445)	0.560	-0.035 (-0.403, 0.300)	0.852

Model 1 was unadjusted. Model 2 adjusted for age, sex, education, and marital status. Model 3 further adjusted for BMI, smoking status, drinking status, health insurance, hypertension, diabetes, Hyperlipidemia, arthritis, and baseline memory score for the 2018 memory-score model. For the memory-change model, Model 3 adjusted for the same covariates except baseline memory score. β values represent mean differences compared with the low-stable trajectory group.

3.5 Sensitivity analysis using ADL disability status

A sensitivity analysis was conducted using ADL disability status as an alternative outcome definition to assess the robustness of the association between comorbidity trajectories and functional disability. This analysis included 5,108 participants, as shown in the participant flow diagram. The sensitivity analysis produced results consistent with the primary incident ADL disability analysis. In the fully adjusted model, the high-persistent trajectory remained associated with higher odds of ADL disability status, with an OR

of 1.59 and a 95% CI of 1.27 to 1.97. The rapid-increasing trajectory was also associated with higher odds of ADL disability status, with an OR of 1.71 and a 95% CI of 1.27 to 2.27. Both associations were statistically significant. Taken together, the primary and sensitivity analyses consistently suggested that adverse comorbidity trajectories were associated with functional disability (TS2).

TS2:Supplementary Table 2:Sensitivity analysis for ADL disability status in 2018

This sensitivity analysis retained participants with baseline ADL disability and adjusted for baseline ADL disability status.

4. Discussion

In this nationally representative longitudinal study of middle-aged and older Chinese adults, we identified three distinct trajectories of cardiopulmonary-depressive comorbidity burden: low-stable, high-persistent, and rapid-increasing. Our principal finding is that both sustained high and rapidly increasing comorbidity burdens are strong independent predictors of subsequent ADL disability^{9,10}. Crucially, regarding cognitive outcomes, we found that only the rapid-increasing trajectory was significantly associated with poorer late-life episodic memory scores, while the high-persistent trajectory showed a negative but non-significant trend. These findings highlight that the **pace** of comorbidity accumulation may be as important as, if not more important than, the absolute burden in predicting geriatric syndromes.

The robust association between adverse comorbidity trajectories and incident ADL disability aligns with the "synergistic effect" hypothesis of multimorbidity. The coexistence of cardiovascular diseases, chronic respiratory conditions, and depressive symptoms creates a bio-behavioral vicious cycle that severely depletes physiological reserve. Pathophysiologically, persistent cardiopulmonary insufficiency induces chronic tissue hypoxia and systemic inflammation, directly compromising peripheral perfusion and skeletal muscle metabolism^{11–13}. This physical decline is further exacerbated by depressive symptoms, which are often associated with hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis and elevated levels of pro-inflammatory cytokines (e.g., IL-6 and TNF- α). These mechanisms collectively accelerate the progression of sarcopenia and frailty, ultimately manifesting as a loss of independence in activities of daily living.

A key highlight of this study is the nuanced association between comorbidity trajectories and cognitive function. Unlike previous studies that treated multimorbidity as a static count, our dynamic approach revealed that the rapid-increasing trajectory—representing a sharp uptick in health deterioration—was independently linked to lower memory scores in 2018 ($\beta = -0.368, P = 0.014$). Interestingly, the high-persistent group, despite having a high cumulative burden, did not reach statistical significance ($P = 0.084$). This suggests that the acute stress and rapid physiological transition associated with escalating disease burdens may overwhelm the brain's compensatory mechanisms more effectively than a chronic, stable high-burden state^{14,15}. The "rapid-increasing" group may experience a burst of neuroinflammation and vascular damage that acutely impairs hippocampal function and episodic memory.

Furthermore, we observed that while trajectories predicted late-life memory scores, they were not significantly associated with the change in memory scores from 2011 to 2018. This discrepancy may suggest that the cognitive impact of comorbidity trajectories is a cumulative "end-state" effect that is best captured by cross-sectional evaluation after the trajectory has stabilized^{16,17}. Alternatively, the 7-year follow-up period might be sufficient to observe differences in cognitive status but not long enough to capture the full slope of cognitive decline, or the baseline differences in cognitive reserve might have already been established prior to the study period.

Clinically, these findings emphasize a paradigm shift from static disease counting to dynamic risk monitoring. The rapid-increasing trajectory serves as a critical "early warning sign." Healthcare providers should be particularly vigilant when older adults exhibit a sudden increase in the co-occurrence of cardiopulmonary and psychological symptoms. Integrated care models that simultaneously address mental and physical health—rather than fragmented, disease-specific management—are essential to mitigate the risk of functional and cognitive loss^{18,19}.

Several limitations warrant consideration. First, the comorbidity score was operationalized using only three high-impact conditions, which may underestimate the total burden of multimorbidity. Second, the reliance on self-reported physician diagnoses may introduce recall bias. Third, the high rate of attrition in the outcome-specific analytical samples might introduce a "healthy survivor" bias, potentially leading to an underestimation of the true associations²⁰. Finally, despite adjusting for a comprehensive set of sociodemographic and clinical confounders, residual confounding cannot be entirely ruled out in this observational study.

5. Conclusion

This study confirmed that the trajectories of cumulative cardiopulmonary-depressive comorbidity, particularly the persistently high and rapidly increasing patterns, are independent drivers of functional disability among middle-aged and older adults in China. More importantly, rapid accumulation of comorbidity burden, rather than merely a high baseline burden, is closely linked to accelerated memory decline. These findings highlight the necessity of dynamically monitoring the progression rate of multimorbidity. To preserve older adults' ability to live independently and maintain cognitive health, healthcare models should shift from single-disease management to comprehensive early interventions targeting individuals at high risk of adverse cardiopulmonary-psychological comorbidity trajectories.

Declarations

Ethics approval and consent to participate

This research was conducted in compliance with the tenets of the Helsinki Declaration. The study protocol received approval from the Ethics Review Board of the National Center for Health Statistics, and written informed consent was secured from all participants.

Consent for publication

Participants signed informed consent upon enrolling in the study. The secondary analysis did not require additional Institutional Review Board approval.

Data Availability Statement: The datasets generated and analysed during the current study are available in CHARLS repositories:CHARLS, <https://charls.pku.edu.cn/en/>.

Clinical trial number

Not applicable.

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