

Latent multimorbidity patterns and their longitudinal associations with depressive symptom trajectories and ADL limitations among middle-aged and older adults in China: a longitudinal analysis of the CHARLS

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Abstract

Background

Multimorbidity is heterogeneous, but longitudinal evidence from China on how specific disease patterns relate to changes in depressive symptoms and functional limitations remains limited. This study aimed to identify baseline multimorbidity patterns and examine their longitudinal associations with trajectories of depressive symptoms and activities of daily living (ADL) limitations in a nationally representative cohort.

Methods

Data were drawn from the China Health and Retirement Longitudinal Study (CHARLS), 2011–2018. Latent class analysis (LCA) was used to identify baseline (2011) multimorbidity patterns based on 12 chronic conditions. Linear and generalized linear mixed-effects models were applied to assess the associations between baseline patterns and changes in depressive symptoms and the risk of ADL limitation from 2013 to 2018. Exploratory mediation analysis examined whether pain statistically mediated the association between multimorbidity patterns and subsequent depressive symptoms.

Results

Four multimorbidity patterns were identified: cardiometabolic (Class 1), respiratory-dominant (Class 2), musculoskeletal–digestive (Class 3), and relatively healthy (Class 4). Compared with Class 4, Class 3 showed a steeper increase in depressive symptom scores over time ($\beta = 0.099$, $P = 0.020$). Findings were directionally consistent in sensitivity analyses, including the random-slope model ($\beta = 0.096$) and the high-classification-certainty subsample ($\beta = 0.102$). In exploratory mediation analyses, pain indicators measured in 2013 were associated with higher subsequent depressive scores, but no clear statistically indirect effect was observed for Class 3. The risk of ADL limitation increased over time ($P < 0.001$), but no significant differences in the rate of change were found across patterns (all class-by-time interaction terms $P > 0.05$).

Conclusions

Distinct multimorbidity patterns were differentially associated with depressive symptom trajectories among middle-aged and older adults in China. The musculoskeletal–digestive pattern was associated with a faster increase in depressive symptoms over time. Pain may reflect an important symptom-burden correlate of this pattern, but no clear mediation evidence was observed under the current model specification. These findings suggest that mental health screening and symptom-oriented assessment may be particularly relevant for high-symptom-burden multimorbidity patterns in primary care.

1. Introduction

Population aging is accelerating worldwide, alongside a growing burden of chronic disease among middle-aged and older adults. Multimorbidity has become an increasing challenge for healthcare systems, particularly for care coordination, long-term care planning, and resource allocation[1, 2]. In addition to disease accumulation, multimorbidity is often accompanied by greater symptom burden, polypharmacy, and a higher risk of drug–drug interactions, and has been associated with increased healthcare use, functional decline, and poorer health-related quality of life[2]. In healthy aging and chronic disease management, identifying high-risk groups and understanding how psychological and functional outcomes change over time may help improve risk stratification, intervention planning, and resource allocation[3].

Multimorbidity is not a homogeneous construct. In epidemiological research, it is commonly defined using a threshold approach (e.g., ≥ 2 chronic conditions) or simple disease counts. Although these approaches are useful for quantifying burden, they may overlook differences in how chronic conditions cluster and in the clinical implications of specific combinations[4–6]. Evidence suggests that chronic conditions tend to cluster into relatively stable patterns, such as cardiometabolic or respiratory–musculoskeletal groupings[7]. These patterns may reflect different underlying mechanisms and risk profiles and may therefore be associated with different trajectories of mental and functional outcomes. From a public health perspective, examining specific multimorbidity patterns may be more informative than relying on disease counts alone when assessing patient-centered outcomes.

Latent class analysis (LCA) is a data-driven method for identifying such patterns. By modelling multiple binary disease indicators simultaneously, LCA classifies individuals into latent subgroups with similar co-occurrence structures and provides probabilistic class assignments, allowing the identification of interpretable multimorbidity patterns[8]. Although the use of LCA in multimorbidity research has increased in recent years, most studies remain cross-sectional. In longitudinal research, analyses often focus on a single outcome or a single time point, and less is known about whether baseline multimorbidity patterns are associated with different changes in psychological and functional outcomes over time[3]. Evidence linking baseline multimorbidity patterns to subsequent outcome trajectories therefore remains limited.

This question is particularly relevant in China, where population aging is occurring rapidly. National surveys indicate that multimorbidity among adults aged 60 years and older is common, with reported prevalence estimates of approximately 46–57%, and the burden continues to increase[9, 10]. These patterns reflect not only the epidemiological transition but also persistent urban–rural disparities and inequalities in healthcare access. Despite the scale of the burden, longitudinal evidence on how distinct multimorbidity patterns relate to mental and functional outcomes in the Chinese population remains limited [11].

Depressive symptoms and limitations in activities of daily living (ADL) are two indicators of aging-related vulnerability. Depressive symptoms are commonly measured using standardized instruments and are associated with healthcare use and mortality risk. ADL limitation reflects impairment in basic self-care

and is a predictor of disability progression and long-term care needs[12]. Previous longitudinal studies suggest that psychological distress and functional decline may influence one another over time, but it remains unclear whether different multimorbidity structures are associated with different trajectories of these outcomes in the Chinese context[12, 13].

Using nationally representative data from the China Health and Retirement Longitudinal Study (CHARLS), this study aimed to identify latent multimorbidity patterns at baseline (2011) and examine their longitudinal associations with subsequent changes in depressive symptoms and ADL limitation from 2013 to 2018. Specifically, we aimed to: (1) use LCA to identify latent classes based on baseline chronic disease indicators; (2) assess differences in depressive symptom levels and the risk of ADL limitation across classes during follow-up; and (3) examine whether rates of change in these outcomes differed across classes through class-by-time interaction terms.

2. Methods

2.1 Study design and sample

This prospective observational study examined whether baseline multimorbidity patterns were associated with subsequent longitudinal outcomes. Data came from the China Health and Retirement Longitudinal Study (CHARLS), a nationally representative panel survey of Chinese adults aged 45 years and older conducted by the National School of Development at Peking University[14]. Across repeated survey waves, CHARLS collects information on demographic characteristics, socioeconomic status, health conditions, and functional status. For the present analysis, the 2011 wave served as baseline, and follow-up information was taken from the 2013, 2015, and 2018 waves. The dataset is publicly available upon approved application.

At baseline, CHARLS included 17,708 respondents. Because latent class membership could not be estimated for participants with missing data on all 12 chronic disease indicators, these individuals were excluded. This left 17,091 participants with non-missing most-likely latent class assignments for the latent class analysis (LCA) (Table 3). We further excluded respondents with implausible baseline age values and those who had no valid outcome observations during follow-up from 2013 to 2018. After these exclusions, the final longitudinal cohort comprised 15,879 individuals. Among them, 14,725 contributed to the depressive symptom models and 13,673 to the ADL limitation models. The difference in analytic sample size mainly reflected outcome-specific missingness and attrition across waves.

Table 3
Estimated and Most Likely Latent Class Proportions (N = 17,091)

Latent Class	Model-estimated Proportion	Most-likely Class Proportion	Clinical Interpretation
Class 4	69.11%	77.10%	Relatively healthy
Class 1	13.82%	10.58%	Cardiometabolic
Class 3	14.12%	10.01%	Musculoskeletal–digestive
Class 2	2.95%	2.32%	Respiratory-dominant
Note: N denotes the number of participants with non-missing most-likely class assignments obtained from the baseline latent class analysis (LCA). Model parameters in the LCA were estimated using full information maximum likelihood (FIML) to account for partial missing data in the chronic disease indicators.			

2.2 Variable measurement and definitions

2.2.1 Exposure: Chronic disease assessment and latent class identification

Baseline multimorbidity was defined using 12 chronic conditions assessed in 2011 on the basis of self-reported physician diagnoses or medical history. The conditions were hypertension, dyslipidemia, diabetes, malignant tumour, chronic lung disease, liver disease, heart disease, stroke, kidney disease, digestive disease, arthritis, and asthma. In large epidemiological surveys, self-reported physician diagnoses are commonly used. Studies based on CHARLS have shown moderate agreement and high specificity when these reports are compared with objective biomedical measurements, supporting their use in population-based research [15, 16].

To identify multimorbidity patterns, we conducted LCA in Mplus version 8.3 using the 12 binary chronic disease indicators. Models with two to six classes were estimated. Selection of the final model considered several criteria: the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), sample-size adjusted BIC (aBIC), entropy, the Lo–Mendell–Rubin adjusted likelihood ratio test (LMR), the bootstrap likelihood ratio test (BLRT), class size, and clinical interpretability. Within the LCA framework, missing data on individual disease indicators were handled using full information maximum likelihood (FIML), so all available responses could contribute to estimation. Participants with missing values on all 12 indicators were excluded because class membership could not be estimated.

Once the final model had been selected, participants were assigned to latent classes using the most-likely class approach based on maximum posterior probability (MaxPP). Class membership was then entered into subsequent regression analyses as a categorical exposure variable, with the relatively healthy class as the reference group. Posterior probabilities were retained to evaluate classification quality. To assess the possible influence of classification uncertainty, we repeated key analyses in

subsamples restricted to participants with higher assignment certainty according to prespecified MaxPP thresholds.

2.2.2 Outcomes

Depressive symptoms were measured with the 10-item Center for Epidemiologic Studies Depression Scale (CES-D-10). This instrument has been validated in Chinese populations and has shown acceptable reliability and construct validity[17]. Scores range from 0 to 30, with higher values indicating more severe depressive symptoms. Before summation, the two positively worded items were reverse-coded.

For the primary longitudinal analyses, CES-D-10 total score was modelled as a continuous outcome. A conventional cut-off of ≥ 10 was used for descriptive purposes to indicate elevated depressive symptoms, but it was not adopted in the primary modelling strategy unless otherwise specified.

ADL limitation was defined as reporting difficulty or requiring assistance in at least one basic activity of daily living, namely dressing, bathing, eating, getting in or out of bed, toileting, and continence. At each follow-up wave, this information was used to construct a binary variable (any limitation vs. none). This variable was then used to examine change in the risk of ADL limitation over time.

2.2.3 Covariates

All covariates were measured at baseline in 2011 and treated as time-invariant in the longitudinal analyses. They included age, sex, educational attainment, marital status, urban–rural residence, body mass index (BMI), and smoking status.

Because baseline levels of the outcomes may influence subsequent change, the models also adjusted for the corresponding baseline outcome measure. Specifically, the depressive symptom models included the 2011 CES-D score, whereas the ADL models included baseline ADL limitation status. This adjustment was intended to reduce confounding by initial health status.

2.3 Statistical analysis

To analyse the longitudinal associations between baseline multimorbidity patterns and subsequent outcomes, we constructed a person-wave dataset in long format and fitted mixed-effects models. Depressive symptoms (CES-D-10 total score) were analysed using linear mixed-effects models (LMMs), whereas ADL limitation was analysed using logistic generalized linear mixed-effects models (GLMMs). In all models, a random intercept was included to account for between-individual differences in baseline outcome levels. The main parameter of interest was the interaction between latent class membership and time, which tested whether rates of change in the outcomes differed across multimorbidity patterns.

Time was parameterized as years since the first post-baseline follow-up wave (2013) and coded 0, 2, and 5 for the 2013, 2015, and 2018 waves, respectively. Exposure, covariates, and baseline outcome levels were all defined from the 2011 wave, which was therefore not included in the trajectory models. Model

adjustment covered baseline demographic characteristics, socioeconomic factors, health behaviours, and the corresponding baseline outcome measure.

Missing baseline covariate data were addressed using multiple imputation by chained equations (MICE; $m = 20$), after which estimates were pooled according to Rubin's rules [18, 19]. The LCA was performed before imputation based on the baseline chronic disease indicators, and missingness in those indicators was handled in Mplus using FIML. For that reason, the LCA indicators themselves were not imputed. Missing follow-up outcome data were handled under the maximum likelihood framework of the mixed-effects models, assuming missing at random (MAR). Sensitivity analyses considered alternative parameterizations of time, random-slope models, and analyses restricted to outcome-free subsamples at baseline. In addition, exploratory mediation analysis was conducted within a counterfactual framework to estimate the statistical indirect effect of pain on subsequent depressive symptoms.

2.4 Robustness and classification certainty analyses

Several sensitivity analyses were performed to examine whether the primary findings were robust to alternative model specifications and sample restrictions.

We first considered alternative ways of modelling time. To allow for potential non-linear trends, the continuous time variable was replaced with categorical wave indicators, using 2013 as the reference. In the depressive symptom models, we also fitted random-slope models for time to account for between-individual variation in rates of change.

We next repeated the primary analyses in restricted subsamples to reduce the possibility that baseline outcome status influenced subsequent associations. For depressive symptoms, analyses were limited to participants without elevated depressive symptoms at baseline ($\text{CES-D} < 10$). For ADL limitation, analyses were restricted to those without baseline ADL limitation. These models were used to examine whether the observed associations were similar among participants free of the corresponding outcome at study entry.

Classification certainty was examined in a further set of analyses. The primary models were based on most-likely class assignment. To assess whether classification uncertainty materially affected the estimates, we re-estimated the models after restricting the sample to participants with higher assignment certainty, defined by maximum posterior probability (MaxPP) thresholds of ≥ 0.70 and ≥ 0.80 .

2.5 Mechanistic exploration: mediation analysis

To explore a possible pathway underlying the association between the musculoskeletal–digestive pattern (Class 3) and subsequent depressive symptoms, we conducted an exploratory mediation analysis within a counterfactual framework following Imai et al[20, 21]. Latent class membership in 2011 was treated as the exposure, pain indicators measured in 2013 as the mediator, and depressive symptom scores measured in 2015 and 2018 as the outcome. Pain was examined in three forms: any

pain, pain severity, and number of pain sites. The primary comparison was between Class 3 and the relatively healthy class (Class 4).

Mediator models were specified according to the type of mediator, using logistic regression for binary pain indicators and linear regression for continuous or count-based pain indicators. Outcome models were estimated using linear regression adjusted for baseline depressive symptoms, baseline demographic and health-behaviour covariates, and survey wave. The average causal mediation effect (ACME) and average direct effect (ADE) were estimated.

For the multiply imputed datasets (MICE, $m = 20$), mediation analyses were conducted separately within each imputed dataset and pooled according to Rubin’s rules. Given the observational design and the assumptions required for mediation analysis, these results were interpreted as exploratory evidence relevant to potential mechanisms rather than as confirmation of a causal pathway.

3. Results

3.1 Identification of latent classes

Using the 12 binary chronic disease indicators measured at baseline in 2011, we fitted latent class models with two to six classes and compared their fit (Table 1). Model selection considered statistical fit indices, likelihood ratio tests, entropy, class size, and clinical interpretability. On balance, the four-class model was selected for the primary analyses.

Table 1
Model Fit Indices for Latent Class Analysis (K = 2–6)

Classes (K)	LL	AIC	BIC	aBIC	Entropy	LMR P-value	BLRT P-value
2 Classes	-60820.794	121,691.59	121,885.25	121,805.80	0.543	< 0.001	< 0.001
3 Classes	-60113.081	120,302.16	120,596.52	120,475.76	0.636	< 0.001	< 0.001
4 Classes	-59816.962	119,735.93	120,130.99	119,968.91	0.702	0.001	< 0.001
5 Classes	-59660.225	119,448.45	119,944.21	119,740.83	0.63	< 0.001	< 0.001
6 Classes	-59619.025	119,392.05	119,988.52	119,743.82	0.647	0.046	< 0.001

Note: LL = log-likelihood; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; aBIC = sample-size adjusted BIC. The four-class solution was selected as the final latent class model.

The four-class model had an entropy of 0.702, higher than that of the three-class model (0.636) and the five-class model (0.630) (Table 1). Although the five-class model showed a slightly lower BIC than the four-class model, the BIC increased again in the six-class model. In addition, models with more classes tended to yield smaller class sizes and lower classification quality. Taken together, these results supported the four-class solution as the most interpretable and parsimonious model. The LMR and BLRT also indicated improved fit up to the four-class model (Table 1).

Conditional probabilities from the four-class model suggested four distinct multimorbidity patterns (Table 2 and Fig. 1). Class 1 was labelled cardiometabolic, characterized by higher probabilities of hypertension, dyslipidemia, and diabetes. Class 2 was labelled respiratory-dominant, with chronic lung disease and asthma as the main conditions. Class 3 was labelled musculoskeletal–digestive, marked by arthritis and stomach or digestive disease. Class 4 was labelled relatively healthy, with low probabilities across all conditions. In the five- and six-class models, additional classes mainly reflected further subdivision of these patterns or smaller subgroups with limited added clinical interpretability.

Table 2
Item-Response Probabilities for the Four-Class Model

Chronic Conditions	Cardiometabolic	Respiratory-dominant	Musculoskeletal–digestive	Relatively healthy
hypertension	0.784	0.277	0.288	0.133
dyslipidemia	0.411	0.103	0.111	0.027
diabetes mellitus	0.261	0.067	0.055	0.018
heart disease	0.363	0.294	0.284	0.033
stroke	0.109	0.034	0.026	0.006
chronic lung disease	0.071	1	0.233	0.045
asthma	0.023	0.702	0.05	0.009
arthritis	0.313	0.443	0.798	0.237
stomach or digestive disease	0.148	0.293	0.62	0.154
kidney disease	0.078	0.101	0.221	0.028
liver disease	0.045	0.056	0.133	0.018
cancer	0.017	0	0.016	0.008
Note: Values represent the item–response (conditional) probabilities estimated from the four-class latent class model. Probabilities indicate the likelihood of reporting the presence of each chronic condition (coded as 1) given membership in a specific latent class. Higher values indicate greater concentration of the condition within that class. These probabilities are model estimates and do not represent crude prevalence in the overall sample.				

As shown in Table 3, the model-estimated class proportions and the most-likely class assignments were broadly similar. Because some degree of classification uncertainty remained, we conducted additional analyses using maximum posterior probability (MaxPP) thresholds of ≥ 0.70 and ≥ 0.80 . Key class-by-time interaction terms were then re-estimated in subsamples with higher assignment certainty to examine whether the direction and magnitude of the estimates changed materially.

3.2 Baseline characteristics across multimorbidity patterns

Among the 15,879 participants included in the longitudinal cohort, several baseline characteristics differed across the four latent classes (Table 4). Age, sex, and marital status did not differ significantly across classes (all $P > 0.05$). In contrast, educational attainment, urban–rural residence, and BMI showed significant between-class differences (all $P < 0.01$). Participants in the cardiometabolic class (Class 1) had the highest mean BMI.

Table 4
Baseline characteristics across latent multimorbidity classes among participants included in the longitudinal cohort (N = 15,879)

Characteristic	Relatively healthy (n = 12,249)	Cardiometabolic (n = 1,669)	Respiratory-dominant (n = 362)	Musculoskeletal-digestive (n = 1,599)	P value
Age (mean (SD))	58.82 (9.66)	58.49 (9.20)	58.73 (9.16)	58.94 (9.73)	0.554
Female, n (%)	6315 (51.6)	865 (51.8)	172 (47.5)	816 (51.1)	0.467
Education level, %					0.006
No formal education	3346 (27.4)	418 (25.1)	104 (28.7)	450 (28.2)	
Primary school	4868 (39.8)	625 (37.5)	131 (36.2)	664 (41.6)	
Middle school	2496 (20.4)	391 (23.5)	83 (22.9)	311 (19.5)	
High school and above	1524 (12.5)	232 (13.9)	44 (12.2)	173 (10.8)	
Residence (Urban), %	5641 (46.1)	809 (48.5)	172 (47.5)	734 (46.0)	< 0.001
Marital status (Married), %	10717 (87.5)	1484 (88.9)	317 (87.6)	1388 (86.8)	0.301
Current smoking, %	3494 (29.6)	464 (28.7)	108 (30.9)	445 (28.7)	0.698
BMI (mean (SD))	23.48 (3.93)	24.21 (4.37)	23.35 (3.61)	23.45 (3.91)	< 0.001
Baseline CES-D-10 score, mean (SD)	8.45 (6.34)	8.17 (6.53)	8.46 (6.55)	8.75 (6.22)	0.106
No ADL limitation, %	6408 (76.2)	894 (77.7)	202 (78.0)	886 (75.0)	0.4

Note: Continuous variables are presented as mean (standard deviation, SD), and categorical variables as number (percentage, %). Baseline depressive symptoms were assessed using the CES-D-10 scale (range: 0–30), with higher scores indicating more severe symptoms. Limitation in activities of daily living (ADL) was defined as dependence on or need for assistance with at least one basic ADL task. P-values for continuous variables were derived from one-way analysis of variance (ANOVA), and P-values for categorical variables from chi-square tests. The total sample entering the longitudinal analyses was N = 15,879. Sample sizes varied slightly across outcome models due to missing data; details are provided in the Methods section.

The crude distribution of individual chronic conditions across classes was generally consistent with the conditional probabilities estimated from the LCA model (Table 4). Baseline CES-D-10 scores and the prevalence of ADL limitation were similar across classes, with no statistically significant differences observed (both $P > 0.05$). These baseline characteristics provide context for the subsequent longitudinal analyses, in which all models were adjusted for baseline covariates and the corresponding baseline outcome measure.

3.3 Longitudinal associations between multimorbidity patterns and depressive symptom trajectories

In linear mixed-effects models pooled across 20 imputed datasets, CES-D-10 scores increased over follow-up from 2013 to 2018 ($\beta = 0.200$ per year, 95% CI: 0.171–0.229; $P < 0.001$) (Table 5). Adjusted predicted trajectories are shown in Fig. 2. Compared with the relatively healthy class (Class 4), the musculoskeletal–digestive class (Class 3) was the only class with a significant class-by-time interaction ($\beta = 0.099$, 95% CI: 0.016–0.183; $P = 0.020$), corresponding to a steeper increase in depressive symptom scores over time. Baseline depressive symptom scores did not differ significantly between Class 3 and Class 4 ($P = 0.538$). For the cardiometabolic class (Class 1), the class-by-time interaction was positive but did not reach statistical significance ($P = 0.083$).

Table 5
Longitudinal Associations Between Multimorbidity Patterns and Depressive Symptom Trajectories (CES-D Scores) Among Middle-Aged and Older Adults, 2013–2018

Variable	β (95% CI)	P value
Baseline level, vs. Class 4 (Relatively healthy)		
Cardiometabolic (Class 1)	-0.142 (-0.459, 0.176)	0.382
Respiratory-dominant (Class 2)	0.128 (-0.499, 0.754)	0.689
Musculoskeletal–digestive (Class 3)	0.101 (-0.221, 0.423)	0.538
Time effect (per year)	0.200 (0.171, 0.229)	< 0.001
Interaction terms: differences in rate of change		
Cardiometabolic $\times$ Time	0.074 (-0.010, 0.157)	0.083
Respiratory-dominant $\times$ Time	0.037 (-0.127, 0.201)	0.658
Musculoskeletal–digestive $\times$ Time	0.099 (0.016, 0.183)	0.020
Note: CES-D = Center for Epidemiologic Studies Depression Scale; CI = confidence interval. All estimates were obtained from linear mixed-effects models (LMMs) and pooled across 20 multiply imputed datasets using Rubin’s rules. Interaction terms represent the estimated differences in the rate of change in depressive symptoms over time for each multimorbidity pattern relative to the reference group. Statistical significance was defined as $P < 0.05$.		

3.4 Longitudinal associations between multimorbidity patterns and risk of ADL limitation

In logistic generalized linear mixed-effects models pooled across 20 imputed datasets, the odds of ADL limitation increased over time (OR = 1.083 per year, 95% CI: 1.064–1.103; P < 0.001) (Table 6). After adjustment for baseline ADL limitation status and covariates, the musculoskeletal–digestive class (Class 3: OR = 1.141, 95% CI: 0.959–1.358; P = 0.138) and the cardiometabolic class (Class 1: OR = 1.136, 95% CI: 0.950–1.359; P = 0.162) showed higher point estimates than the relatively healthy class, although these differences were not statistically significant.

Table 6
Longitudinal Associations Between Multimorbidity Patterns and Risk of ADL Limitation Among Middle-Aged and Older Adults, 2013–2018

Variable	OR (95% CI)	P value
Baseline level, vs. Class 4 (Relatively healthy)		
Cardiometabolic (Class 1)	1.136 (0.950, 1.359)	0.162
Respiratory-dominant (Class 2)	0.949 (0.659, 1.367)	0.780
Musculoskeletal–digestive (Class 3)	1.141 (0.959, 1.357)	0.138
Time effect (per year)	1.083 (1.064, 1.103)	< 0.001
Interaction terms: differences in rate of change		
Cardiometabolic × Time	1.029 (0.978, 1.082)	0.268
Respiratory-dominant × Time	1.029 (0.930, 1.140)	0.576
Musculoskeletal–digestive × Time	0.984 (0.936, 1.033)	0.515
Note: ADL = activities of daily living; OR = odds ratio; CI = confidence interval. Estimates were derived from generalized linear mixed-effects models (GLMMs) and pooled across 20 multiply imputed datasets using Rubin’s rules. Class 4 (relatively healthy) served as the reference group. Interaction terms represent differences in the rate of change in ADL limitation risk over time between each multimorbidity pattern and the reference group. Statistical significance was defined as P < 0.05.		

No class-by-time interaction terms reached statistical significance (all P > 0.05), suggesting that the rate of change in ADL limitation risk did not differ across multimorbidity classes under the specified model.

3.5 Robustness and sensitivity analyses

Sensitivity analyses were conducted to examine the robustness of the primary findings under alternative model specifications and sample restrictions (Table 7). Among participants without elevated depressive symptoms at baseline, the class-by-time interaction for the musculoskeletal–digestive class (Class 3) was similar in magnitude to that in the primary analysis (β = 0.095 vs. 0.099), although the estimate was less precise in the smaller sample (P = 0.059). In random-slope models that allowed individual-specific

rates of change, the Class 3 interaction remained similar to the primary estimate ($\beta = 0.096$; $P = 0.028$). When time was parameterized using wave indicators, depressive symptoms increased across follow-up waves, and the difference between Class 3 and the relatively healthy class was larger at the 2018 wave (β for Class 3 vs. Class 4 at 2018 relative to 2013 = 0.496; $P = 0.020$), consistent with the positive class-by-time interaction observed in the primary model.

Table 7
Summary of Robustness Analyses for the Association Between the Musculoskeletal–Digestive Multimorbidity Pattern and Health Outcomes

Robustness analysis model	Depressive symptoms (DEP) β (95% CI)	P value	ADL limitation OR (95% CI)	P value
Primary analysis model	0.099 (0.016, 0.183)	0.020	0.984 (0.936, 1.033)	0.515
Nonlinear time specification	0.496 (0.077, 0.915)	0.020	0.933 (0.725, 1.200)	0.589
Random-slope model	0.096 (0.010, 0.182)	0.028	0.984 (0.937, 1.034)	0.519
Baseline outcome exclusion	0.095 (-0.004, 0.193)	0.059	0.983 (0.925, 1.043)	0.564
High classification certainty sample	0.102 (-0.030, 0.234)	0.131	0.994 (0.921, 1.072)	0.874
Note: DEP = depressive symptoms; ADL = activities of daily living. This table summarizes the interaction coefficients between the musculoskeletal–digestive multimorbidity pattern (Class 3) and time (or survey wave) across multiple robustness analyses. All models were adjusted for the same covariates as in the primary analysis. For ADL outcomes, the reported odds ratios correspond to the Class 3 $\times$ Time interaction term, representing differences in the rate of change in ADL limitation risk over the follow-up period rather than baseline group differences.				

In analyses restricted to participants with higher classification certainty, the Class 3 interaction estimates in the depressive symptom models were broadly similar to those in the primary analysis (e.g., $\beta = 0.102$), although confidence intervals widened in some specifications because of smaller sample size. In the ADL limitation models, point estimates for some classes increased as the maximum posterior probability (MaxPP) threshold was raised (e.g., OR ≈ 1.26), but the confidence intervals continued to include the null.

Overall, the direction of the estimates was generally consistent across sensitivity analyses. Although statistical significance varied across some specifications, the results did not materially differ from the primary findings.

3.6 Exploratory analysis of pain distribution and mediation

Because the musculoskeletal–digestive class (Class 3) showed a steeper increase in depressive symptoms over follow-up, we further examined pain characteristics measured in 2013 and their potential relevance to later depressive symptoms.

As shown in Table 8, overall pain prevalence, pain severity, and number of pain sites differed across classes. Class 3 had the highest overall pain prevalence (40.2%). It also showed a heavier overall pain burden in terms of pain severity and number of pain sites (both $P < 0.05$). By contrast, no significant between-class differences were observed for single-site pain indicators, including stomach, waist, and knee pain. Although the overall distributions of pain severity and number of pain sites differed across classes, their medians and interquartile ranges were the same, suggesting that the differences were more apparent in the distribution as a whole than in central tendency.

Table 8
Pain characteristics in 2013 across latent multimorbidity classes (N = 12,585)

Pain indicators	Class 4 (Relatively healthy) (n = 9,698)	Class 1 (Cardiometabolic) (n = 1,303)	Class 2 (Respiratory) (n = 302)	Class 3 (Musculoskeletal–digestive) (n = 1,282)	P value
Overall pain prevalence (%)	36.7	34.5	34.8	40.2	0.017
Site-specific pain prevalence (%)					
Stomach	4.1	3.9	3.0	5.3	0.127
Lower back	15.9	14.7	14.2	18.0	0.094
Knees	9.6	8.5	8.6	10.5	0.369
Number of pain sites, median [IQR]	0 [0,1]	0 [0,1]	0 [0,1]	0 [0,1]	0.017
Pain severity (Median [IQR])	0 [0,1]	0 [0,1]	0 [0,1]	0 [0,1]	0.001
Note: Categorical variables are presented as percentages, and ordinal or count variables as median [IQR]. Between-class differences were assessed using chi-square tests for categorical variables and Kruskal–Wallis tests for pain severity and number of pain sites. The total sample (N = 12,585) included participants in the longitudinal cohort who had at least one depressive outcome record in 2015 or 2018 and had available pain measures in 2013. Although the median and IQR were identical across classes, the Kruskal–Wallis test indicated differences in the overall distributions.					

We then examined whether pain indicators measured in 2013 statistically mediated the association between baseline multimorbidity class and depressive symptom scores in 2015 and 2018. Across all three pain measures—any pain, pain severity, and number of pain sites—pain in 2013 was associated with higher subsequent depressive scores. However, the association between Class 3 and these pain

indicators was modest, and no indirect effect reached statistical significance. For example, when number of pain sites was used as the mediator, the average causal mediation effect (ACME) was 0.032 (95% CI: -0.012 to 0.081; $P = 0.190$).

Overall, these findings suggest that pain may reflect a higher symptom burden in the musculoskeletal–digestive class and may be related to subsequent depressive symptoms. Under the current model specification, however, no clear statistical mediation effect was observed.

4. Discussion

Multimorbidity is increasingly recognized as a heterogeneous construct rather than a simple accumulation of chronic conditions[7, 22]. Much of the existing literature has relied on disease counts or cross-sectional clustering, with less attention to how baseline multimorbidity patterns relate to subsequent psychological and functional outcomes over time[23]. In China, associations between multimorbidity patterns and depression or functional impairment have been reported, but longitudinal evidence remains limited[24]. Using a nationally representative cohort, we identified four clinically interpretable multimorbidity patterns and found that depressive symptom trajectories differed across classes, whereas the rate of change in ADL limitation did not. These findings support a structure-oriented perspective on multimorbidity and suggest that psychological and functional outcomes may not evolve in the same way across multimorbidity patterns[25, 26].

The main finding of this study was that the musculoskeletal–digestive pattern (Class 3) was associated with a steeper increase in depressive symptoms over time, and this pattern was generally consistent across sensitivity analyses. Baseline depressive symptom levels did not differ significantly between Class 3 and the relatively healthy class, but their trajectories diverged during follow-up. This suggests that multimorbidity structure may be relevant not only to baseline burden, but also to subsequent change in mental health[27]. The finding is also consistent with previous studies showing that specific multimorbidity patterns are associated with later-life depression and poorer mental health outcomes[28].

One possible explanation is symptom burden. Persistent pain, gastrointestinal discomfort, and related symptoms may affect mood through daily disruption, reduced activity, and lower social participation[29–33]. By contrast, cardiometabolic conditions may be less symptomatically salient at earlier stages and may be managed through more standardized care pathways, which could partly attenuate their psychological impact[5, 28]. Previous studies have linked musculoskeletal disease and chronic pain to depression[34], and musculoskeletal-dominant multimorbidity patterns have also been associated with poorer quality of life and mental health[28, 32]. Our findings extend this literature by suggesting that the difference may lie in the trajectory of depressive symptoms over time rather than in baseline depressive levels alone[27, 35]. More broadly, they are consistent with the view that different combinations of chronic conditions may reflect different levels of physiological burden, symptom experience, and care needs, which may in turn shape subsequent psychological outcomes[6, 24, 36].

The exploratory mediation analysis showed that pain was associated with higher subsequent depressive symptom scores, but no clear statistical indirect effect was observed for the musculoskeletal–digestive pattern under the current model specification. Pain therefore appears more consistent with a symptom-burden correlate than with a confirmed mediator in this analysis.

Even so, pain may still be relevant to the association between this pattern and later depressive symptoms. Within a biopsychosocial framework, pain may influence mood through disrupted sleep and a possible pain–insomnia–depression cycle[33, 37], reduced activity and social participation accompanied by greater isolation or perceived loss[27], and increased bodily vigilance related to gastrointestinal symptoms[31]. These possibilities are broadly consistent with the higher overall pain burden observed in the musculoskeletal–digestive class.

Other mechanisms, including systemic inflammation and gut–brain pathways, have also been proposed in the literature, but they were not measured in the present study and therefore remain speculative[23]. Further studies incorporating inflammatory markers, sleep measures, medication use, and repeated pain assessments may help clarify the behavioural and biological pathways involved.

Unlike the findings for depressive symptoms, we did not observe significant between-class differences in the rate of change in ADL limitation, although some point estimates were higher in the musculoskeletal–digestive and cardiometabolic classes. Several explanations are possible. First, change in basic ADL may emerge more slowly or nonlinearly than change in depressive symptoms, and the follow-up period may not have been long enough to detect differences in slopes[23, 38]. Earlier or subtler functional changes may also be better captured by more sensitive measures such as instrumental activities of daily living (IADL)[38]. Second, attrition due to loss to follow-up or mortality may have attenuated associations, particularly if participants with poorer health were less likely to remain under observation. Classification uncertainty may also have reduced the contrast between classes, although point estimates tended to increase in some higher-certainty analyses[38–40]. Third, in community-dwelling populations, compensatory strategies may allow individuals to maintain basic ADL despite declines in intrinsic capacity[41].

Taken together, these findings suggest that multimorbidity structure may be more informative for depressive symptom trajectories than for short- to mid-term change in basic ADL. Within the present follow-up period, the increase in ADL limitation appeared to reflect a more general age-related pattern across classes.

We also observed opposite directional associations of BMI with depressive symptom change and ADL limitation risk. This pattern is broadly consistent with discussions of an “obesity paradox” in older adults, whereby higher BMI may reflect greater nutritional reserve and lower wasting risk, while also increasing the risk of functional limitation through mechanical and cardiopulmonary burden[38, 41, 42]. At the same time, BMI is an imperfect marker in older populations because it does not distinguish fat mass from lean mass and may be influenced by illness-related weight loss or reverse causation. This finding should

therefore be interpreted cautiously. Future studies incorporating body composition, sarcopenia, and physical performance measures may provide a clearer picture.

From a public health and primary care perspective, these findings suggest that multimorbidity management may benefit from moving beyond simple disease counts. Stratification based only on the number of conditions may overlook clinically relevant heterogeneity. In particular, patterns characterized by higher symptom burden, such as the musculoskeletal–digestive class, may warrant closer attention to mental health risk and symptom management[43, 44].

Several practical implications follow. First, mental health screening could be more explicitly incorporated into routine chronic disease management, particularly for individuals with chronic musculoskeletal pain and gastrointestinal conditions[28]. Second, care models that integrate symptom control and psychological support may be useful, especially where pain management, primary care, and mental health services are delivered separately[24]. Third, the absence of clear between-class differences in ADL slope, alongside the earlier divergence in depressive symptoms, may indicate a window for earlier intervention before functional decline becomes more apparent. In resource-limited settings, simple rule-based identification strategies and longitudinal follow-up within primary care or electronic health record systems may help target support more efficiently[23, 43–45].

Limitations

Several limitations should be considered when interpreting these findings. First, classification quality in the latent class model was moderate (entropy = 0.702), indicating some uncertainty in individual class assignment. Although sensitivity analyses using MaxPP thresholds showed generally similar results, the latent classes are better interpreted as population-level multimorbidity structures than as fixed labels at the individual level. Second, ADL limitation was self-reported and may have been less sensitive to early or subtle functional change. In addition, the respiratory-dominant class was relatively small, which reduced the precision of estimates for this pattern. Third, attrition due to loss to follow-up or mortality may have introduced selection bias if it was related to health status. Although missing data were handled using multiple imputation and maximum likelihood under a missing at random (MAR) assumption, missing not at random (MNAR) mechanisms cannot be ruled out. Finally, the exploratory mechanistic analyses were based on an observational design and remained subject to unmeasured confounding and other assumptions required for mediation analysis. These results should therefore be interpreted as exploratory evidence on possible pathways rather than confirmation of a causal mechanism. Future studies with longer follow-up, repeated symptom assessments, and more detailed behavioural and biological measures may help clarify these pathways.

Conclusion

Using nationally representative longitudinal data, this study identified four clinically interpretable multimorbidity patterns and showed that different multimorbidity structures were associated with different longitudinal patterns of depressive symptoms and ADL limitation. The musculoskeletal–

digestive pattern was the only class associated with a faster increase in depressive symptoms over time. By contrast, although the risk of ADL limitation increased across all classes, no clear between-class differences in the rate of change were observed under the current analytical framework.

Exploratory analyses further suggested that pain may reflect a higher symptom burden in the musculoskeletal–digestive pattern and may be related to subsequent depressive symptoms, although no clear mediation effect was observed. Overall, these findings support the value of considering multimorbidity structure alongside disease counts in risk assessment. In public health and primary care settings, identifying patterns with higher symptom burden may help inform mental health screening and follow-up among middle-aged and older adults.

Abbreviations

ADL

Activities of daily living

BMI

Body mass index

BLRT

Bootstrap likelihood ratio test

CES-D-10

10-item Center for Epidemiologic Studies Depression Scale

CHARLS

China Health and Retirement Longitudinal Study

CI

Confidence interval

FIML

Full information maximum likelihood

GLMM

Generalized linear mixed-effects model

IADL

Instrumental activities of daily living

LCA

Latent class analysis

LMM

Linear mixed-effects model

LMR

Lo–Mendell–Rubin adjusted likelihood ratio test

MAR

Missing at random

MaxPP

Maximum posterior probability

MICE
Multiple imputation by chained equations
MNAR
Missing not at random
OR
Odds ratio
PHQ
Patient Health Questionnaire
SD
Standard deviation

Declarations

Ethics approval and consent to participate

The CHARLS study was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015). The study was conducted in accordance with relevant institutional and national regulations. All participants provided written informed consent prior to participation. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Clinical trial number

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

Kaige Gao, Yanjie Zhao, Xuehong Zhang, Kanbao Su, Jia Jia and Yuezhen Xu wrote the main manuscript text and prepared figures and tables. All authors reviewed the manuscript.

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Data Availability

The datasets analyzed in this study are available in the China Health and Retirement Longitudinal Study (CHARLS) repository. Access to the data requires online registration and approval through the official CHARLS website.

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Figures



Figure 1

Conditional probabilities of chronic conditions by latent class (K = 4)

Note: Darker shading indicates a higher model-estimated conditional probability of the corresponding chronic condition within each latent class.

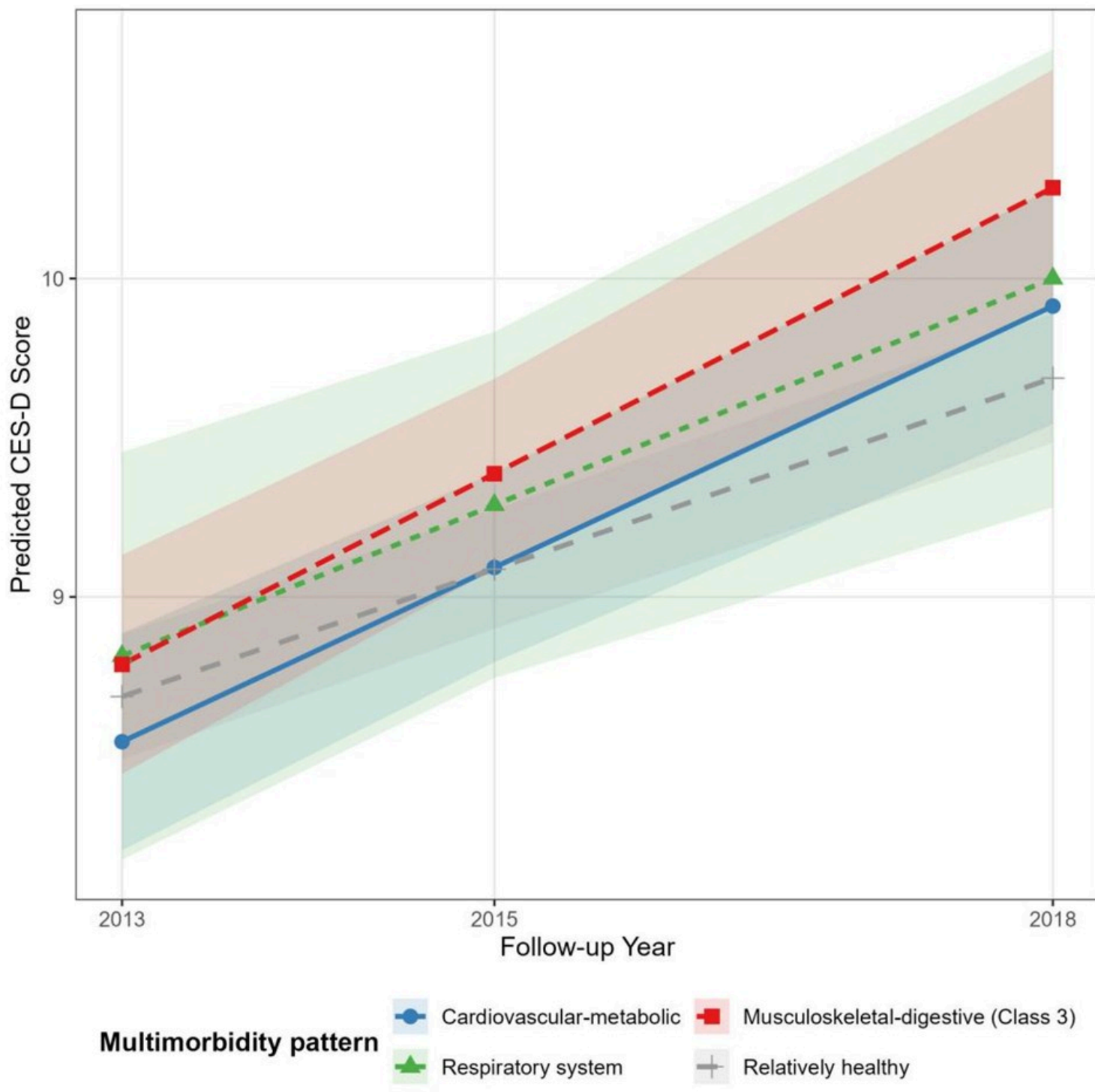


Figure 2

Predicted trajectories of depressive symptoms (CES-D scores) across multimorbidity patterns among middle-aged and older adults, 2013–2018

Note: Figure 2 illustrates the longitudinal trajectories of CES-D scores across the four multimorbidity patterns from 2013 to 2018. Scores were estimated using linear mixed-effects models (LMMs) with 20 multiple imputations. Lines represent predicted means; shaded areas indicate 95% CIs pooled via

Rubin's rules. The model adjusted for all baseline (2011) covariates, including baseline CES-D, demographics, and health behaviours. Follow-up year 0 corresponds to 2013.