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Joint Trajectories of Pain Sleep Disturbance and Depressive Symptoms and Incident ADL Disability: A Four-Cohort Study

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Abstract

Background Pain, sleep disturbance and depressive symptoms commonly cooccur later in life and may jointly accelerate the loss of functional independence. We examined whether their longitudinal joint trajectories were associated with incident activities of daily living (ADL) disability across four national aging cohorts.

Methods We analysed data from the China Health and Retirement Longitudinal Study (CHARLS), the Health and Retirement Study (HRS), the English Longitudinal Study of Ageing (ELSA), and the Mexican Health and Ageing Study (MHAS). Cohort-specific joint latent-class trajectory models identified patterns of binary pain, sleep disturbance and depressive symptoms. Participants without ADL disability at the cohort-specific baseline were followed for incident disability. Cox models were used to estimate hazard ratios (HRs), and fully adjusted estimates for comparable trajectories were pooled via random effects meta-analysis. Sensitivity analyses included classification certainty, exclusion of the first two years, inverse probability-of-censoring weighting, and pain severity adjustment in the CHARLS.

Results The trajectory samples included 11,318 CHARLS, 12,378 HRS, 7,323 ELSA and 7,580 MHAS participants; the corresponding incident-ADL cohorts included 8,317, 9,527, 5,287 and 5,361 participants, respectively. Compared with persistently low symptoms, persistent high cooccurring symptoms were associated with greater ADL-disability hazards after full adjustment: CHARLS HR 2.23 (95% CI 1.89–2.63), HRS 3.03 (2.59–3.55), ELSA 2.67 (2.16–3.32), and MHAS 1.67 (1.47–1.89). The pooled HR was 2.33 (1.76–3.10; I^2=91.9%). The results remained positive when restricted to participants with a posterior probability ≥0.80 (pooled HR 2.70, 1.95–3.73), after excluding the first two years (2.18, 1.72–2.75), and with censoring weights (2.39, 1.77–3.21). Additional adjustment for pain severity in CHARLS patients attenuated but did not eliminate the association (HR 1.46, 1.20–1.77).

Conclusions Persistent cooccurring pain, sleep disturbance and depressive symptoms were consistently associated with increased incident ADL disability across four aging cohorts. The association remained robust across sensitivity analyses, although substantial between-cohort heterogeneity indicates that the pooled estimate should be interpreted as an average rather than a universal effect. Repeated multidomain symptom assessment may help identify adults at elevated risk of functional decline.

Keywords pain; sleep disturbance; depressive symptoms; joint trajectory; activities of daily living; disability; ageing; multicohort study; Cox regression; meta-analysis

Introduction

The aging population is increasing the number of adults who develop limitations in activities of daily living (ADL), including bathing, dressing, eating, transferring and toileting[1]. ADL disability is associated with a loss of functional independence, increased need for family and formal care, and restricted participation, falls, health-care use and mortality[2]. Recent longitudinal work in the Health and Retirement Study revealed that earlier and more severe disability onset is associated with a particularly high subsequent mortality risk[3]. In England, area-level socioeconomic disadvantage was associated with shorter disability-free life expectancy and more years lived with ADL disability[4]. Body composition, BMI and inflammatory burden have also been linked to later disability in CHARLS [5–7], whereas prospective evidence across CHARLS, ELSA and SHARE suggests that sarcopenia is associated with subsequent ADL dependency [8]. These findings underscore the multifactorial and socially patterned nature of functional decline.

Pain, sleep disturbance and depressive symptoms are common in later life and may form a mutually reinforcing symptom system. Pain can restrict mobility, physical activity and rehabilitation; disturbed sleep can increase fatigue, impair recovery and amplify pain sensitivity; and depressive symptoms can reduce motivation, social participation and adherence to health-promoting behaviours[9–11]. The clinical relevance of multidomain burden is supported by evidence that higher intrinsic capacity scores and their psychological, sensory and locomotor components are associated with a lower risk of functional decline[12], whereas sensory impairment, multimorbidity and depressive symptoms may jointly influence independence in daily living (ADL) and social participation[13,14]. Multimorbidity patterns are also associated with increased BADL and IADL disability [15], and recent longitudinal work indicates reciprocal associations between multimorbidity, depressive symptoms and functional dependence

[9]. These findings suggest that symptom persistence and co-occurrence may be more informative than any single symptom measured at one time point.

Most previous studies assess pain, sleep or depressive symptoms separately or classify exposure using a single baseline measurement[16–18]. Such approaches may miss persistence, remission, accumulation and clinically meaningful symptom combinations. Trajectory methods provide a person-centred way to summarise repeated observations while preserving temporal information. Recent studies have demonstrated that persistent possible sarcopenia trajectories predict adverse outcomes [19], that joint ADL-cognition-depression trajectories identify groups with different fall risks [1], and that trajectories of chronic disease burden, depressive symptoms and functional limitations are informative for later adverse health outcomes [2]. Evidence from the ELSA further suggests that the initial level of physical health affects the evolution of ADL disability [20]. However, few studies have jointly modelled pain, sleep disturbance and depressive symptoms before incident ADL disability, and evidence across different national aging contexts remains limited.

We therefore examined the joint trajectories of pain, sleep disturbance and depressive symptoms in four national aging cohorts and evaluated their associations with new-onset ADL disability. We used cohort-specific Cox regression, random effects meta-analysis, classification-certainty and censoring sensitivity analyses, and prespecified subgroup and interaction analyses. We hypothesised that persistent high rates of cooccurring symptoms would identify the subgroup at greatest risk of subsequent ADL disability.

Methods

Data availability

All original data used in the study from the CHARLS[21], HRS[22], MHAS[23], and ELSA[24] can be freely downloaded from their official websites, which can be obtained from the Gateway to Global Aging Data (https://g2aging.org/home).

Study Design and Participants

We conducted a harmonised longitudinal cohort study using four population-based aging surveys: the China Health and Retirement Longitudinal Study (CHARLS), the Health and Retirement Study (HRS), the Mexican Health and Aging Study (MHAS), and the English Longitudinal Study of Ageing (ELSA). Joint symptom trajectories were established from 2011–2015 in CHARLS, 2002–2006 in HRS, 2001–2012 in MHAS, and 2002–2006 in ELSA.

Participants were eligible for the incident ADL analysis if they had a valid trajectory classification, available baseline ADL information, no ADL disability at the baseline assessment, and at least one valid postbaseline ADL observation. The baseline years were 2015 for CHARLS, 2006 for HRS, 2012 for MHAS, and 2006 for ELSA; follow-up began in 2018, 2008, 2015, and 2008, respectively.

The original cleaned datasets included 25,873 CHARLS, 45,232 HRS, 26,839 MHAS, and 21,679 ELSA participants. After requiring adequate information for trajectory classification and applying baseline eligibility criteria, 8,317 CHARLS, 9,527 HRS, 5,361 MHAS, and 5,287 ELSA participants were included in the final incident-ADL cohorts. Participants with prevalent baseline ADL disability or without valid postbaseline ADL measurements were excluded. During follow-up, 1,981, 3,856, 1,370, and 1,666 incident ADL events were observed in the CHARLS, HRS, MHAS, and ELSA, respectively. Participants who did not develop ADL disability were censored at their last available ADL assessment (Figure 1 Participant selection flowchart for the four longitudinal cohorts).

We used deidentified, publicly available data from 4 public databases. Ethical approval was approved by the original surveys, and no additional ethical approval was required for the present study. All participants provided written informed consent. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Joint Trajectory Modelling

Pain, sleep disturbance and depressive symptoms were used as binary indicators. A joint latent-class trajectory model was fitted within each cohort, with a shared latent class and class-specific linear logit time trends for the three symptom series[25]. The candidate solutions included two to six classes in CHARLS and HRS and two to five classes in ELSA and MHAS. The selection used the BIC, entropy, average posterior probability and minimum class size. The selected solution was the lowest-BIC model satisfying an entropy ≥0.70, minimum average posterior probability ≥0.70 and minimum class proportion ≥5% when available. The participants were assigned to their highest posterior probability class[25–27]. The selected models contained six classes in CHARLS, five in HRS, five in ELSA and two in MHAS. The class labels were descriptive rather than diagnostic.

Measurement of ADLs

The total score of the ADL score ranged from 0–6[28]. The harmonised disability indicator was defined as an ADL total score >0. Values outside the valid 0–6 range were set to missing values[29]. Baseline ADL status was assessed at the cohort-specific outcome baseline. Participants with positive baseline disability were excluded so that the outcome represented incident rather than prevalent disability.

Outcome assessment

The primary outcome was incident ADL disability. Follow-up began in 2018 for CHARLS, 2008 for HRS and ELSA, and 2015 for MHAS. The event year was the first observed follow-up year with ADL disability. Participants remaining disability-free were censored at their last year with a valid ADL assessment. Survival time was recorded as an event or censoring year minus the outcome baseline year and was stored as time. The follow-up windows were 2018–2020, 2008–2020, 2008–2018 and 2015–2018.

Covariates

Covariates were selected a priori via a study-specific directed acyclic graph informed by previous longitudinal evidence on pain, sleep disturbance, depressive symptoms, and functional disability rather than on statistical significance in the present data[11,30–33]. Demographic, socioeconomic, lifestyle, and baseline chronic disease factors are considered potential common causes of joint symptom trajectories and incident ADL disability[34]. Variables considered likely mediators were not included in the primary adjustment set.

Statistical analysis

Cohort-specific Cox proportional hazards models estimated HRs and 95% CIs for each trajectory class versus persistently low symptoms (class 0)[35]. Model 1 included trajectory class only; Model 2 included age, sex and BMI; and Model 3 additionally included marital status, education, wealth, retirement, smoking, alcohol use, hypertension, diabetes and multimorbidity count. Complete cases were used for each model, and N and event counts were reported separately. Fully adjusted cohort estimates for comparable trajectory contrasts were combined via a DerSimonian–Laird inverse-variance random-effects model on the log-HR scale[36]. Standard errors were derived from 95% CIs. Heterogeneity was summarised by Cochran's Q, heterogeneity P, I^2 and τ^2. The primary meta-analysis compared persistent high cooccurring symptoms with persistently low symptoms; secondary analyses examined persistent pain-dominant and sleep-disturbance-dominant classes where comparable classes were

available. Sensitivity analyses restricted participants to posterior probabilities ≥0.80, excluded participants with events or censoring within two years of the outcome baseline, and applied marginal inverse probability-of-censoring weights estimated from the empirical censoring survival function. The CHARLS additionally included a maximum trajectory-period pain severity indicator (ordinal score ≥3) as a covariate. Subgroup models were fitted by sex, age (<65 vs ≥65 years), arthritis status and baseline multimorbidity (0–1 vs ≥2); corresponding interaction models included trajectory-by-subgroup terms. The interaction *P* values were Wald tests and were interpreted as exploratory without multiplicity correction. Sleep duration, death competing-risk and country-income stratification could not be analysed because the required variables were absent from the supplied extracts. Two-sided $P<0.05$ was considered statistically significant. The analyses used Python with the bundled lifeline implementation.

Results

Study population selection

The supplied extracts contained 96,628 CHARLS, 253,998 HRS, 180,095 ELSA and 103,665 MHAS records, corresponding to 25,873, 45,232, 21,679 and 26,839 unique participants, respectively, after cohort-specific cleaning. Complete symptom observations yielded 11,318, 12,378, 7,323 and 7,580 trajectory participants, respectively. After the exclusion of prevalent baseline ADL disability data and participants without valid postbaseline ADL data, the final incident-ADL cohort comprised 8,317 CHARLS, 9,527 HRS, 5,287 ELSA and 5,361 MHAS participants. The number of incident ADL events was 1,981, 3,856, 1,666 and 1,370, respectively. Censoring at the last valid ADL observation affected 6,336, 5,671, 3,621 and 3,991 participants, respectively (Figure 1).

Baseline characteristics

The cohort-level baseline summary revealed different age, socioeconomic and health profiles. The HRS and MHAS participants were the oldest, whereas the CHARLS participants had the lowest mean BMI. Women accounted for 52.2% of the CHARLS, 60.9% of the HRS, 62.2% of the MHAS and 56.7% of the ELSA. Married or partnered participants were most common in the CHARLS, retirement was most common in the HRS and ELSA, smoking was most common in the CHARLS and alcohol use was most common in the ELSA. Hypertension and arthritis were common, depression prevalence was highest in MHAS, and multimorbidity was most common in MHAS. Patients with baseline ADL disability were excluded by design (Table 1).

Joint trajectory classes

The selected solutions contained six classes in CHARLS, five in the HRS, five in the ELSA and two in MHAS. All classes met the prespecified average posterior probability criterion; the minimum class-specific values ranged from 0.701 in the ELSA to 0.913 in the MHAS. Persistently low symptoms were the most common class in the CHARLS (41.6%), HRS (49.9%), ELSA (39.5%) and MHAS (56.4%) groups. Persistent high cooccurring symptoms accounted for 17.2%, 5.4%, 11.2% and 43.6%, respectively, and were present in all four cohorts. Pain-dominant classes appeared in the CHARLS, HRS and ELSA; persistent sleep-disturbance-dominant classes appeared in the HRS and ELSA. CHARLS additionally identified mixed and changing patterns (Table 2).

Cox regression

In Model 1, all reported trajectory contrasts had HRs above one. In the fully adjusted Model 3, persistent high cooccurring symptoms remained the highest-risk class in every cohort: CHARLS HR 2.23 (95% CI 1.89–2.63), HRS HR 3.03 (2.59–3.55), ELSA HR 2.67 (2.16–3.32) and MHAS HR 1.67 (1.47–1.89). Adjustment attenuated most estimates but did not change their direction. The persistent pain-dominant class remained associated with disability in the HRS and ELSA, whereas the ELSA sleep disturbance-dominant class was associated with disability in 1.15 patients (0.99–1.34; P=0.059) after full adjustment (Table 3).

Meta-analysis

The primary random effects meta-analysis revealed a greater hazard of incident ADL disability for persistent high cooccurring symptoms than for persistently low symptoms (pooled HR 2.33, 95% CI 1.76–3.10; I^2=91.9%; P for heterogeneity<0.001). The pooled HR for persistent pain-dominant symptoms was 1.85 (1.70–2.01; I^2=0.0%; P=0.396), whereas the pooled HR for persistent sleep-disturbance-dominant symptoms was 1.32 (1.03–1.69; I^2=87.9%; P=0.004). These secondary analyses included only two cohorts (Table 4 and Figure 2).

Sensitivity analyses

The primary association persisted across the completed sensitivity analyses. Restricting the analysis to participants with a posterior probability ≥0.80 produced a pooled HR of 2.70 (95% CI 1.95–3.73; I^2=87.3%). Excluding participants whose first event or censoring occurred within two years of the outcome baseline yielded a pooled HR of 2.18 (1.72–2.75; I^2=79.1%). Marginal inverse-probability-of-censoring weighting produced a pooled HR of 2.39 (1.77–3.21; I^2=88.1%). In the CHARLS, adding a trajectory-period maximum pain severity indicator (ordinal score

≥3) attenuated the persistent high cooccurring contrast, but the association remained statistically significant (HR 1.46, 1.20–1.77). Sleep duration and competing-risk analyses could not be performed because no sleep-hours or mortality variables were present in the supplied files (Table S1).

Subgroup and interaction analyses

The persistent high cooccurring trajectory remained associated with incident ADL disability in both sex strata, in participants aged below and at least 65 years, among those with and without arthritis, and in participants with 0–1 or at least 2 baseline chronic conditions in the cohort-specific models. Interaction tests were generally nonsignificant, although isolated nominal interactions were observed for selected trajectory classes and age or arthritis in the CHARLS, HRS and ELSA. These isolated findings were not corrected for multiple comparisons and were not pooled across cohorts. No country-income subgroup analysis was estimable because each database represented a single national aging survey (Table S2).

Discussion

Pain, sleep disturbance and depressive symptoms are each plausible precursors of functional decline. Pain may limit mobility, physical activity and participation in rehabilitation, whereas persistent pain is associated with the subsequent onset of disability in community-dwelling older adults [37,38]. Sleep problems may contribute through fatigue, impaired recovery, daytime sleepiness and reduced physical performance; prospective studies have similarly linked sleep complaints and self-reported sleep problems to incident disability [26,29]. Depressive symptoms may increase disability risk through reduced motivation, social withdrawal, lower adherence to health-promoting behaviours and impaired engagement in everyday activities; conversely, emerging functional dependence may further worsen mood [9,25].

These symptoms should not be viewed as isolated exposures. Pain and poor sleep can reinforce one another through sleep fragmentation, heightened pain sensitivity and impaired overnight recovery [11], and sleep disturbance and depression show a bidirectional relationship over time [10]. Pain-related activity restriction and sleep-related fatigue may also amplify depressive symptoms, whereas depression can reduce coping capacity and self-management[39,40]. The resulting cycle may progressively erode physical and psychological reserves, making a cooccurring, persistent symptom pattern more informative for future ADL disability than any single symptom measured at one time point.

In this four-cohort longitudinal study, joint trajectories of pain, sleep disturbance and depressive symptoms were associated with subsequent incident ADL disability. Persistent high cooccurring symptoms showed the most consistent and largest association after adjustment in every cohort, with a pooled hazard ratio (HR) of 2.33. The association remained positive in high-certainty, early-event exclusion and censoring-weighted analyses. Persistent pain-dominant trajectories were also associated with disability in the cohorts contributing to the secondary analysis, whereas sleep-dominant associations were positive but more heterogeneous.

The findings are biologically and clinically plausible. Pain may restrict mobility and physical activity; disturbed sleep may increase fatigue and pain sensitivity; and depressive symptoms may reduce motivation, social participation and adherence to health-promoting behaviours. These pathways may reinforce one another and lead to the loss of functional reserves. The persistent high cooccurring class may therefore identify a multidomain vulnerability state rather than an isolated symptom. The persistence of the association after adjustment for demographic, socioeconomic, lifestyle and chronic-condition variables suggests that longitudinal symptom burden provides information beyond measured conventional risk factors. However, the observational design does not establish causality, and residual confounding and reverse causation remain possible.

The present study extends research that has examined individual symptoms or single baseline measurements by identifying longitudinal combinations and changing symptom patterns[41]. It complements evidence linking multimorbidity patterns to ADL disability, depressive symptoms to functional dependence, and intrinsic-capacity domains to functional decline[9,12,15]. It also aligns with recent trajectory studies showing that persistent sarcopenia or combined ADL-cognitive-depression decline is associated with adverse outcomes [1,19]. Our results support a person-centered view of functional vulnerability while focusing on pain, sleep and depressive symptoms before new-onset ADL disability. The findings should be interpreted as prognostic associations rather than evidence that trajectory membership itself causes disability.

The primary meta-analysis revealed substantial heterogeneity, and heterogeneity remained high in the sensitivity meta-analyses. Differences in age structure, healthcare system, socioeconomic context, chronic disease incidence, follow-up duration, symptom instruments and trajectory class composition may explain part of this variation. The number and composition of trajectory classes differed, particularly because MHAS identified two broad classes, whereas the other cohorts identified dominant or changing patterns. The pooled estimate therefore summarises related but not identical constructs. The pain-dominant secondary analysis was more homogeneous, whereas the

sleep-dominant analysis remained heterogeneous and included only two cohorts. These differences support the interpretation of the pooled estimate as an average association rather than a universal effect size.

Repeated assessment of pain, sleep and depressive symptoms may help identify adults at increased risk of losing independence in ADL. The findings support integrated assessment rather than evaluation of one symptom in isolation. Potential prevention strategies could combine pain management, sleep care, depression treatment, exercise or rehabilitation and chronic disease management. Trajectory modelling should complement, rather than replace, individual clinical assessment.

Repeated assessment of pain, sleep and depressive symptoms may help identify adults at increased risk of losing independence in ADL. The findings support integrated assessment rather than evaluation of one symptom in isolation. Potential prevention strategies could combine pain management, sleep care, depression treatment, exercise or rehabilitation and chronic disease management. The subgroup analyses did not provide consistent evidence that sex, age, arthritis or baseline multimorbidity universally changed the association, but the nominal age and arthritis interactions suggest that effect modification deserves prospective testing. Trajectory modelling should complement, rather than replace, individual clinical assessment.

The strengths of this study include four population-based longitudinal cohorts, exposure trajectories established before outcome follow-up, the exclusion of baseline ADL disability, harmonised sequential Cox models, classification-certainty and censoring sensitivity analyses, prespecified subgroup analyses and random effects meta-analyses. Limitations include the reduction of heterogeneous measures to binary indicators, uncertainty from most-likely class assignment, complete-case analysis, intermittently observed event time, possible selection and healthy-participant bias, and substantial between-cohort heterogeneity. Pain severity was available only in the CHARLS and was added as a covariate rather than used to refit trajectories. Sleep duration and mortality variables were absent, preventing the requested sleep duration and competing-risk analyses. Country–income stratification was not estimable within single-country cohorts. Interaction analyses were exploratory, class-specific and not corrected for multiple comparisons. These constraints should be considered when interpreting the robustness and transportability of the pooled association.

Future studies should harmonise continuous pain and sleep measures, propagate class-member uncertainty, address missingness and informative censoring, model competing mortality risk and test prespecified effect modifications with adequate power. Cross-national pooled individual–participant analyses can be used to evaluate country-level

socioeconomic context and measurement invariance. Intervention studies are needed to determine whether reducing persistent multidomain symptom burden preserves independence in ADL.

5. Conclusions

Across the CHARLS, HRS, ELSA and MHAS, persistent cooccurring pain, sleep disturbance and depressive symptoms were associated with a greater hazard of incident ADL disability than persistently low symptoms were. The direction and magnitude of the associations remained positive after classification-certainty restrictions, early-event exclusion and marginal censoring weighting. Integrated repeated assessment may improve the identification of adults at risk of functional loss, although causal and intervention-specific conclusions require further research.

Abbreviations

ADL	activities of daily living
BADL	basic activities of daily living
BIC	Bayesian information criterion
BMI	body mass index
CHARLS	China Health and Retirement Longitudinal Study
CI	confidence interval
ELSA	English Longitudinal Study of Ageing
HR	hazard ratio
HRS	Health and Retirement Study
IADL	instrumental activities of daily living
IPCW	inverse probability of censoring weighting
MHAS	Mexican Health and Aging Study
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

Supplementary Information

Acknowledgements

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Author contributions

ZC conceived and designed the study, curated the data, performed the formal analyses, interpreted the findings, prepared the figures and tables, and drafted the original manuscript. JH and ZH contributed to the study methodology, data validation, formal analyses, and critical revision of the manuscript. ML, YJM, QZ, XZ, YFM, and HL contributed to data curation, investigation, interpretation of the findings, and critical revision of the manuscript. YL and PH conceived and supervised the study, secured funding, administered the project, interpreted the findings, and critically revised the manuscript. YL and PH are cocorresponding authors. All the authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

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Data availability

All original data used in the study from the CHARLS, HRS, MHAS, and ELSA can be freely downloaded from their official websites, which can be obtained from the Gateway to Global Aging Data (https://g2aging.org/home)

Figure legends

Figure 1. Flow diagram of participant selection across the four cohorts.

The diagram presents participant selection in the China Health and Retirement Longitudinal Study (CHARLS), Health and Retirement Study (HRS), English Longitudinal Study of Ageing (ELSA), and Mexican Health and Aging Study (MHAS), including exclusions for incomplete symptom or trajectory data, missing baseline ADL information, prevalent ADL disability, and absence of valid post-baseline ADL assessments. ADL, activities of daily living.

Figure 2. Associations of joint symptom trajectories with incident ADL disability across the participating cohorts.

Forest plots show cohort-specific and random-effects pooled hazard ratios with 95% confidence intervals for persistent high co-occurring symptoms, persistent pain-dominant symptoms, and persistent sleep-disturbance-dominant symptoms, compared with persistent low symptoms. Cohort-specific estimates were obtained from fully adjusted Cox proportional hazards models. Squares represent cohort-specific hazard ratios, horizontal lines represent 95% confidence intervals, and diamonds represent pooled random-effects estimates. The vertical reference line indicates a hazard ratio of 1. ADL, activities of daily living; CI, confidence interval; HR, hazard ratio.

Declarations

Ethics approval and consent to participate

This study was a secondary analysis of publicly available, deidentified data from the China Health and Retirement Longitudinal Study (CHARLS), the Health and Retirement Study (HRS), the English Longitudinal Study of Ageing (ELSA), and the Mexican Health and Ageing Study (MHAS). Ethical approval was obtained from each original cohort, and all participants provided written informed consent. No additional ethical approval was required for this secondary analysis.

Consent for publication

All the authors provided consent for publication.

Competing interests

The authors declare that they have no competing interests.

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References

1. Lv Q, Chen D, Zhu H, Li Z, Qin Y, Zheng C, Cui J, Yu H. Multi-trajectory patterns of ADL, cognition, and depression with fall risk: evidence from a longitudinal study in China. BMC Geriatr England; 2026 Jun 27;26(1). PMID:42365258

2. Wang M, Cui Y, Duan L, Qin X. Trajectories of chronic disease burden, depressive symptoms, and functional limitations related to falls in middle-aged and older adults: a matched longitudinal study. Front Aging Neurosci Switzerland; 2026;18:1896362. PMID:42682760

3. Bai A, Liu C, Jiang Y, Xu W, Cao J. Association Between Age and Severity at Disability Onset and All-Cause Mortality: Longitudinal Observational Study From the Health and Retirement Study. JMIR Aging Canada; 2025 Oct 3;8:e73254. PMID:41043133

4. Davies LE, Sinclair DR, Todd C, Hanratty B, Matthews FE, Kingston A. Area-level socioeconomic inequalities in activities of daily living disability-free life expectancy in England: a modelling study. Lancet Healthy Longev England; 2025 Apr;6(4):100700. PMID:40120596

5. Guo R, Zhang S, Fu T, Guan Y, Luo Y, Wu Y. Association between body mass index and disability among older population in China: analysis of 2011-2020 data from the China Health and Retirement Longitudinal Study. J Glob Health Scotland; 2025 Dec 5;15:04277. PMID:41346246

6. Lai S-M, Kuang L, Tang X-L, Qiu C-S, Huang H-X, Liao D-Q, Li H-M, Du L-Y, Xiong Z-Y, Zhang B-Y, Chen H-J, Li Z-H. The Role of High-Sensitivity C-Reactive Protein in Activities of Daily Living Among Middle-Aged and Older Adults: A Prospective Cohort Study. Nutrients Switzerland; 2025 May 20;17(10). PMID:40431471

7. Du Y, Zhang W, Chen Z, Zhu X, Lyu M, Wei Y, Hu Y. Associations of a body shape index, weight-adjusted waist index with the activities of daily living impairment in the middle-aged and elderly population: results from the China Health and Retirement Longitudinal Study. Front Med (Lausanne) Switzerland; 2025;12:1519362. PMID:40400640

8. Fang Y, Xu W, Li X, Wu G, Cai Y. Association between sarcopenia and daily living dependency among middle-aged and older adults: findings from three prospective cohort studies. Exp Gerontol England; 2026 Sep;222:113209. PMID:42323963

9. She R, Luo H, Chen S, Xiong F, Liu KPY, Pang MYC. The interplay of multimorbidity and depressive symptoms: mediation role of functional dependence. Epidemiol Psychiatr Sci England; 2026 Apr 7;35:e21. PMID:41943950

10. Alvaro PK, Roberts RM, Harris JK. A Systematic Review Assessing Bidirectionality between Sleep Disturbances, Anxiety, and Depression. Sleep United States; 2013 Jul 1;36(7):1059–1068. PMID:23814343

11. Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. J Pain United States; 2013 Dec;14(12):1539–1552. PMID:24290442

12. Gou X, Li M, Lu N, Yang T, Li W, Yan L, Yang L, Li Y, Leng M. Intrinsic capacity and the risk of adverse health outcomes in older adults: a population-based study. BMC Geriatr England; 2026 May 19;26(1). PMID:42157111

13. Liu L, Cao Z, Ma Q, Liao Z. The association between dual sensory impairment and social participation among older adults in China: a moderated mediation model of activities of daily living and depressive symptoms. BMC Geriatr England; 2025 Jul 14;25(1):526. PMID:40660134

14. Huang C, He S. Sensory impairment, activities of daily living, and multimorbidity in middle-aged and older adults: evidence from the China health and retirement longitudinal study. BMC Public Health England; 2026 Jul 15;26(1). PMID:42458365

15. Li R, Che B, Xiao W, Shu J, Ma X, Wang Y, Nie P, Wang Y, Sun X. Association between multimorbidity patterns and activities of daily living function among older adults in China: a longitudinal population-based cohort study. BMC Geriatr England; 2025 Nov 10;25(1):885. PMID:41214545

16. Cheng F, Wang Z, Li Y, Wang P, Wang C. Longitudinal associations of chronic pain severity trajectories and number of pain site trajectories with risk of limitations in ability in daily activities: Evidence from two 10-year prospective cohort studies. J Nutr Health Aging France; 2026 Mar;30(3):100781. PMID:41544571

17. Zhou L, Wang W, Ma X. The bidirectional association between the disability in activities of daily living and depression: a longitudinal study in Chinese middle-aged and older adults. BMC Public Health England; 2024 Jul 15;24(1):1884. PMID:39010036

18. Yang S, Wang S, Liu G, Li R, Li X, Chen S, Zhao Y, Liu M, Liu Y, He Y. The relationship between sleep status and activity of daily living: based on China Hainan centenarians cohort study. BMC Geriatr England; 2023 Dec 4;23(1):796. PMID:38049752

19. Jiang D, Li J, Liang T. Dynamic trajectories of possible sarcopenia under the AWGS 2025 criteria and long-term prognosis: A national landmark cohort study. Exp Gerontol England; 2026 Oct 1;223:113271. PMID:42570738

20. Wu J, Grundy EM. Housing adaptations and older adults' health trajectories by level of initial health: evidence from the English Longitudinal Study of Ageing. Age Ageing England; 2025 Feb 2;54(2). PMID:39957554

21. Zhao Y, Hu Y, Smith JP, Strauss J, Yang G. Cohort profile: the China Health and Retirement Longitudinal Study (CHARLS). Int J Epidemiol England; 2014 Feb;43(1):61–68. PMID:23243115

22. Sonnega A, Faul JD, Ofstedal MB, Langa KM, Phillips JWR, Weir DR. Cohort Profile: the Health and Retirement Study (HRS). Int J Epidemiol England; 2014 Apr;43(2):576–585. PMID:24671021

23. Wong R, Michaels-Obregon A, Palloni A. Cohort Profile: The Mexican Health and Aging Study (MHAS). Int J Epidemiol England; 2017 Apr 1;46(2):e2. PMID:25626437

24. Steptoe A, Breeze E, Banks J, Nazroo J. Cohort profile: the English longitudinal study of ageing. Int J Epidemiol England; 2013 Dec;42(6):1640–1648. PMID:23143611

25. Nagin DS, Jones BL, Elmer J. Recent Advances in Group-Based Trajectory Modeling for Clinical Research. Annu Rev Clin Psychol United States; 2024 Jul;20(1):285–305. PMID:38382118

26. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. Annu Rev Clin Psychol United States; 2010;6:109–138. PMID:20192788

27. Nagin DS, Jones BL, Passos VL, Tremblay RE. Group-based multi-trajectory modeling. Stat Methods Med Res England; 2018 Jul;27(7):2015–2023. PMID:29846144

28. Yan Y, Du Y, Li X, Ping W, Chang Y. Physical function, ADL, and depressive symptoms in Chinese elderly: Evidence from the CHARLS. Front Public Health Switzerland; 2023;11:1017689. PMID:36923048

29. Min S, Park CG, Shim M-S. Network-based identification of central ADL and IADL items in older adults living alone. BMC Geriatr England; 2026 May 12;26(1). PMID:42121067

30. Friedman EM. Self-Reported Sleep Problems Prospectively Increase Risk of Disability: Findings from the Survey of Midlife Development in the United States. J Am Geriatr Soc United States; 2016 Nov;64(11):2235–2241. PMID:27626617

31. Eggermont LHP, Leveille SG, Shi L, Kiely DK, Shmerling RH, Jones RN, Guralnik JM, Bean JF. Pain characteristics associated with the onset of disability in older adults: the maintenance of balance, independent living, intellect, and zest in the Elderly Boston Study. J Am Geriatr Soc United States; 2014 Jun;62(6):1007–1016. PMID:24823985

32. Buchman AS, Shah RC, Leurgans SE, Boyle PA, Wilson RS, Bennett DA. Musculoskeletal pain and incident disability in community-dwelling older adults. Arthritis Care Res (Hoboken) United States; 2010 Sep;62(9):1287–1293. PMID:20853470

33. Park M, Buchman AS, Lim ASP, Leurgans SE, Bennett DA. Sleep complaints and incident disability in a community-based cohort study of older persons. Am J Geriatr Psychiatry England; 2014 Jul;22(7):718–726. PMID:23567404

34. Chen P, Xu W. Activity of Daily Living and Depressive Symptoms in Chinese Older Adults: A Latent Profile and Mediation Analysis. Int J Public Health Switzerland; 2025;70:1608149. PMID:40519229

35. Yao X, Liu L, Zhao L, Zhang N. Association between the single-point insulin sensitivity estimator and cardiovascular disease incidence: A prospective nationwide cohort study involving two cohorts. Atherosclerosis Ireland; 2026 Jan;412:120591. PMID:41275597

36. Fatemeh G, Sajjad M, Niloufar R, Neda S, Leila S, Khadijeh M. Effect of melatonin supplementation on sleep quality: a systematic review and meta-analysis of randomized controlled trials. J Neurol Germany; 2022 Jan;269(1):205–216. PMID:33417003

37. Ren X-Q, Zhao G-M, Fang S-W, Xu L-F, Wang L-D, Zhao L-H, Lu M-M. Mediating roles of activities of daily living and depression on the relationship between sleep quality and health-related quality of life. Sci Rep England; 2024 Jun 18;14(1):14057. PMID:38890451

38. Wang J, Luo N, Sun Y, Bai R, Li X, Liu L, Wu H, Liu L. Exploring the reciprocal relationship between activities of daily living disability and depressive symptoms among middle-aged and older Chinese people: a four-wave, cross-lagged model. BMC Public Health England; 2023 Jun 20;23(1):1180. PMID:37337186

39. Nakamura Y, Shibata M, Morisaki Y, Hirabayashi N, Higashioka M, Hata J, Hosoi M, Sudo N, Yamaura K, Ninomiya T. Autonomic nervous system function assessed by heart rate variability and the presence of symptoms affecting activities of daily living in community-dwelling residents with chronic pain: The Hisayama Study. Eur J Pain England; 2024 May;28(5):831–844. PMID:38102889

40. Li J, Yang L, Lv R, Kuang J, Zhou K, Xu M. Mediating effect of post-stroke depression between activities of daily living and health-related quality of life: meta-analytic structural equation modeling. Qual Life Res Netherlands; 2023 Feb;32(2):331–338. PMID:35972616

41. Li J, Lin S, Yan X, Pei L, Wang Z. Adverse Childhood Experiences and Trajectories of ADL Disability among Middle-Aged and Older Adults in China: Findings from the CHARLS Cohort Study. J Nutr Health Aging France; 2022;26(12):1034–1041. PMID:36519765

CHARLS

Original participants
N = 25,873

Complete symptom / trajectory data
n = 11,318

Excluded before trajectory missing / incomplete baseline data
n = 14,555

Baseline ADL-free with trajectory
n = 8,816

Excluded at baseline ADL missing: 64 prevalent ADL disability: 2,438

At least one valid post-baseline ADL observation
n = 8,317

Excluded: no valid follow-up ADL
n = 499

Final incident-ADL cohort
n = 8,317

Incident ADL events: 1,981
Censored: 6,336

HRS

Original participants
N = 45,232

Complete symptom / trajectory data
n = 12,378

Excluded before trajectory missing / incomplete baseline data
n = 32,854

Baseline ADL-free with trajectory
n = 10,068

Excluded at baseline ADL missing: 0 prevalent ADL disability: 2,310

At least one valid post-baseline ADL observation
n = 9,527

Excluded: no valid follow-up ADL
n = 541

Final incident-ADL cohort
n = 9,527

Incident ADL events: 3,856
Censored: 5,671

MHAS

Original participants
N = 26,839

Complete symptom / trajectory data
n = 7,580

Excluded before trajectory missing / incomplete baseline data
n = 19,259

Baseline ADL-free with trajectory
n = 6,023

Excluded at baseline ADL missing: 1 prevalent ADL disability: 1,556

At least one valid post-baseline ADL observation
n = 5,361

Excluded: no valid follow-up ADL
n = 662

Final incident-ADL cohort
n = 5,361

Incident ADL events: 1,370
Censored: 3,991

ELSA

Original participants
N = 21,679

Complete symptom / trajectory data
n = 7,323

Excluded before trajectory missing / incomplete baseline data
n = 14,356

Baseline ADL-free with trajectory
n = 5,894

Excluded at baseline ADL missing: 0 prevalent ADL disability: 1,429

At least one valid post-baseline ADL observation
n = 5,287

Excluded: no valid follow-up ADL
n = 607

Final incident-ADL cohort
n = 5,287

Incident ADL events: 1,666
Censored: 3,621

Joint symptom trajectories and incident ADL disability

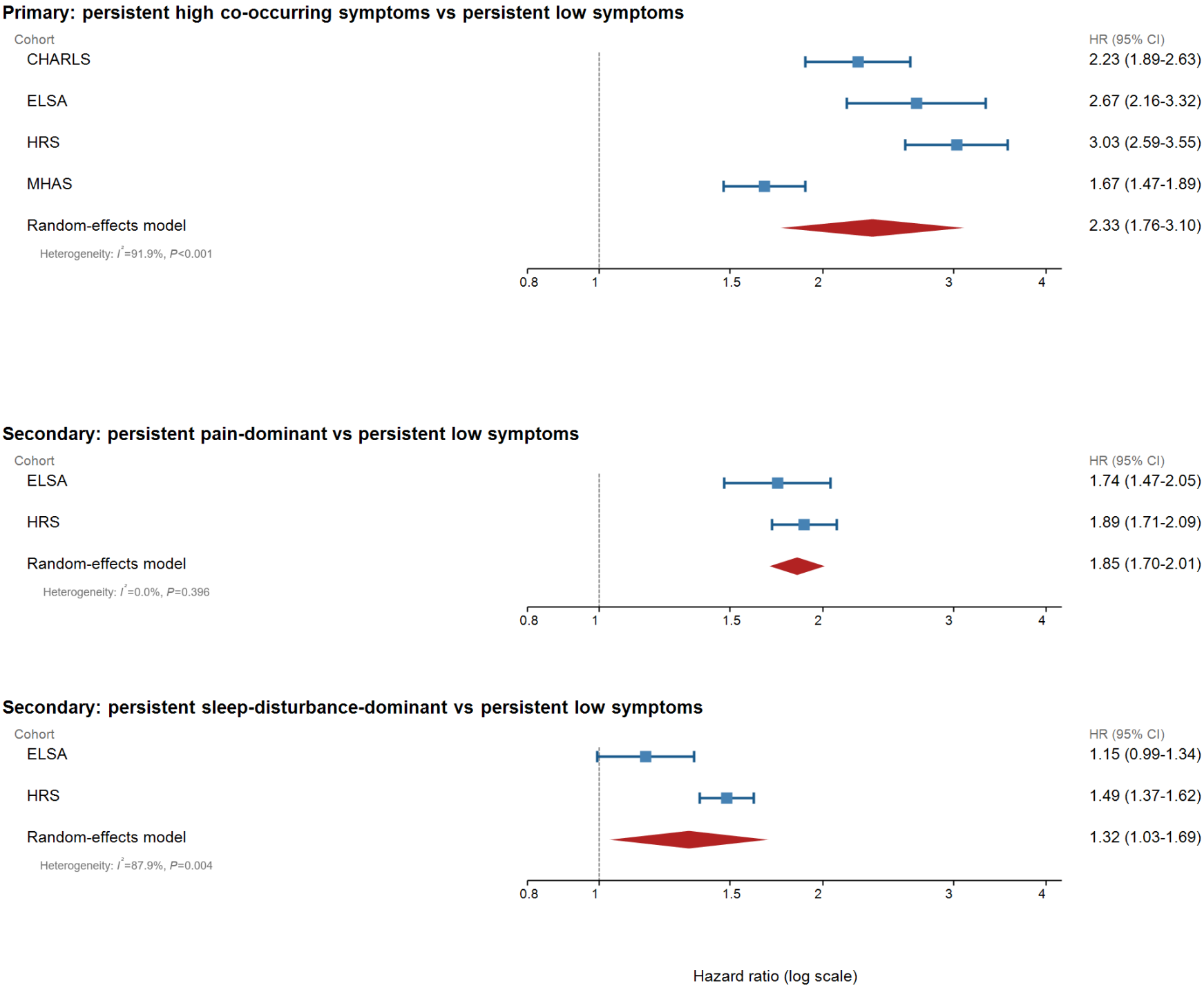


Table 1. Baseline characteristics of participants in four cohorts

Characteristic	CHARLS (n=8,317)	HRS (n=9,527)	MHAS (n=5,361)	ELSA (n=5,287)
Age, y, median (IQR)	60.0 (54.0-67.0)	69.0 (64.0-75.0)	67.0 (63.0-73.0)	64.0 (58.0-72.0)
Sex, n (%)				
Female	4,339 (52.2)	5,802 (60.9)	3,334 (62.2)	3,000 (56.7)
BMI, mean ± SD	23.9 ± 4.0	27.5 ± 5.2	27.4 ± 4.7	27.6 ± 4.8
Education, n (%)				
Below high school	7,324 (88.1)	1,760 (18.5)	4,795 (89.5)	1,603 (33.0)
High school	871 (10.5)	5,669 (59.5)	133 (2.5)	2,410 (49.6)
College or above	122 (1.5)	2,098 (22.0)	430 (8.0)	841 (17.3)
Marital status, n (%)				
Married and partnered	7,344 (88.3)	6,131 (64.4)	3,258 (60.8)	3,659 (69.2)
Unmarried and others	973 (11.7)	3,396 (35.6)	2,103 (39.2)	1,628 (30.8)
Retirement status, n (%)				
Not retired	7,086 (85.9)	3,032 (31.9)	4,436 (85.0)	2,456 (46.5)
Retired	1,160 (14.1)	6,485 (68.1)	781 (15.0)	2,830 (53.5)
Wealth, n (%)				
Low	2,229 (33.3)	3,176 (33.3)	1,787 (33.3)	1,729 (33.3)
Middle	2,228 (33.3)	3,175 (33.3)	1,787 (33.3)	1,728 (33.3)
High	2,228 (33.3)	3,176 (33.3)	1,787 (33.3)	1,729 (33.3)
Current smoking, n (%)				
No	5,977 (71.9)	8,387 (88.7)	4,795 (89.5)	4,605 (87.1)
Yes	2,336 (28.1)	1,067 (11.3)	565 (10.5)	681 (12.9)
Alcohol use, n (%)				
No	5,405 (65.0)	4,512 (47.4)	4,612 (86.3)	1,359 (29.5)
Yes	2,907 (35.0)	5,015 (52.6)	731 (13.7)	3,249 (70.5)
Hypertension, n (%)	2,578 (31.5)	5,180 (54.4)	3,131 (58.5)	2,157 (40.8)
Diabetes, n (%)	707 (8.7)	1,641 (17.2)	1,295 (24.2)	393 (7.4)

Characteristic	CHARLS (n=8,317)	HRS (n=9,527)	MHAS (n=5,361)	ELSA (n=5,287)
Lung/respiratory disease, n (%)	1,048 (12.7)	666 (7.0)	510 (9.5)	227 (4.3)
Cancer, n (%)	110 (1.3)	1,395 (14.6)	167 (3.1)	386 (7.3)
Stroke, n (%)	208 (2.5)	584 (6.1)	136 (2.5)	153 (2.9)
Arthritis, n (%)	3,360 (40.9)	5,493 (57.7)	1,512 (28.2)	1,580 (29.9)
Depression, n (%)	2,352 (28.3)	1,493 (15.7)	2,034 (37.9)	811 (15.3)
Multimorbidity (>=2), n (%)	2,082 (25.0)	2,194 (23.0)	2,051 (38.4)	1,271 (24.0)

Values are presented as median (interquartile range), mean ± standard deviation, or number (percentage), as appropriate. The analytical samples included participants who had valid joint symptom trajectory assignments, were free of ADL disability at the cohort-specific outcome baseline, and had at least one valid post-baseline ADL assessment. BMI indicates body mass index; CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Ageing; HRS, Health and Retirement Study; IQR, interquartile range; MHAS, Mexican Health and Aging Study; SD, standard deviation. Percentages may not sum to 100% because of rounding.

Table 2. Characteristics and classification quality of joint symptom trajectory models across four cohorts

Cohort	Trajectory years	Class	Joint trajectory pattern	Participants, *n*	Proportion, %	Average posterior probability
CHARLS	**2011, 2013, 2015**	**0**	**Persistently low symptoms**	4713	41.6416	0.875095
		1	Pain-depression mixed	1330	11.7512	0.71159
		2	Multi-symptom remitting	1118	9.87807	0.760999
		3	Multi-symptom increasing	1139	10.0636	0.785656
		4	Sleep-disturbance remitting	1068	9.4363	0.768915
		5	Persistently high co-occurring symptoms	1950	17.2292	0.847271
ELSA	**2002, 2004, 2006**	**0**	**Persistently low symptoms**	2896	39.5466	0.898561
		1	Persistent sleep-disturbance-dominant	1771	24.1841	0.794903
		2	Persistent pain-dominant	1132	15.4581	0.783183
		3	Increasing pain-dominant	706	9.64086	0.700616
		4	Persistently high co-occurring symptoms	818	11.1703	0.866375
HRS	**2002, 2004, 2006**	**0**	**Persistently low symptoms**	6173	49.8707	0.887335
		1	Single-symptom pain-dominant	1436	11.6012	0.803274
		2	Persistent sleep-disturbance-dominant	2427	19.6074	0.866465
		3	Pain-dominant with co-occurring symptoms	1676	13.5402	0.792125
		4	Persistently high co-occurring symptoms	666	5.38051	0.840589
MHAS	**2001, 2003, 2012**	**0**	**Persistently low symptoms**	4274	56.3852	0.924579

Cohort	Trajectory years	Class	Joint trajectory pattern	Participants, *n*	Proportion, %	Average posterior probability
		1	Persistently high co-occurring symptoms	3306	43.6148	0.912862

AvePP, average posterior probability. AvePP ≥0.70 was considered to indicate acceptable classification quality. Percentages may not total exactly 100.0 because of rounding.

Table 3 Associations of joint symptom trajectories with incident ADL disability

Cohort / joint trajectory	Events/*n*	Model 1 HR (95% CI)	*P* value 1	Model 2 HR (95% CI)	*P* value 2	Model 3 HR (95% CI)	*P* value 3
CHARLS							
Persistently low symptoms	628/4039	Reference		Reference		Reference	
Pain-dominant	286/893	2.16 (1.88-2.49)	<0.001	2.17 (1.87-2.52)	<0.001	1.95 (1.65-2.31)	<0.001
Moderate symptom-increasing	237/834	1.89 (1.63-2.20)	<0.001	1.82 (1.55-2.14)	<0.001	1.53 (1.27-1.85)	<0.001
Sleep-disturbance-dominant	220/770	1.91 (1.64-2.22)	<0.001	1.88 (1.59-2.21)	<0.001	1.69 (1.39-2.04)	<0.001
High-symptom-increasing	200/826	1.58 (1.35-1.86)	<0.001	1.49 (1.25-1.77)	<0.001	1.41 (1.16-1.72)	<0.001
Persistent high multimorbidity	410/955	3.06 (2.71-3.47)	<0.001	2.85 (2.49-3.27)	<0.001	2.23 (1.89-2.63)	<0.001
HRS							
Persistently low symptoms	1752/5420	Reference		Reference		Reference	
Pain-dominant single-symptom	520/1037	1.81 (1.64-2.00)	<0.001	1.94 (1.76-2.15)	<0.001	1.89 (1.71-2.09)	<0.001
Sleep-disturbance-dominant persistent	861/1875	1.61 (1.48-1.74)	<0.001	1.61 (1.48-1.75)	<0.001	1.49 (1.37-1.62)	<0.001
Pain-dominant multisymptom worsening	545/928	2.43 (2.21-2.67)	<0.001	2.62 (2.37-2.89)	<0.001	2.38 (2.15-2.63)	<0.001
Persistent high multimorbidity	178/267	3.19 (2.74-3.73)	<0.001	3.47 (2.96-4.06)	<0.001	3.03 (2.59-3.55)	<0.001
MHAS							
Persistently low symptoms	656/3341	Reference		Reference		Reference	
Persistent high multimorbidity	714/2020	2.00 (1.80-2.22)	<0.001	1.95 (1.73-2.19)	<0.001	1.67 (1.47-1.89)	<0.001
ELSA							
Persistently low symptoms	587/2468	Reference		Reference		Reference	
Sleep-disturbance-dominant persistent	385/1384	1.21 (1.07-1.38)	0.003	1.27 (1.12-1.45)	<0.001	1.15 (0.99-1.34)	0.059
Pain-dominant persistent	308/714	2.17 (1.89-2.49)	<0.001	2.00 (1.74-2.31)	<0.001	1.74 (1.47-2.05)	<0.001
Pain-dominant symptom-increasing	192/396	2.56 (2.18-3.02)	<0.001	2.49 (2.09-2.96)	<0.001	2.05 (1.67-2.51)	<0.001

Cohort / joint trajectory	Events/*n*	Model 1 HR (95% CI)	*P* value 1	Model 2 HR (95% CI)	*P* value 2	Model 3 HR (95% CI)	*P* value 3
Persistent high multimorbidity	194/325	3.76 (3.18-4.44)	<0.001	3.78 (3.17-4.50)	<0.001	2.67 (2.16-3.32)	<0.001

Events/n indicates the number of events and participants in the full cohort-specific analysis dataset; model-specific numbers of participants and events are reported separately. Model 1, unadjusted. Model 2, adjusted for age, sex, and body mass index (BMI). Model 3, further adjusted for marital status, education, wealth, retirement status, smoking, alcohol consumption, hypertension, diabetes, and multimorbidity. BMI indicates body mass index; CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Ageing; HRS, Health and Retirement Study; MHAS, Mexican Health and Aging Study; and HR, hazard ratio.

Table 4. Random-effects meta-analysis of joint symptom trajectories and incident ADL disability

Comparison	Cohort	Trajectory definition	Cohort-specific HR (95% CI)	Pooled HR (95% CI)	Heterogeneity
Primary: persistent high multimorbidity	CHARLS	Class 5: persistent high multimorbidity	2.23 (1.89–2.63)		
	ELSA	Class 4: persistent high multimorbidity	2.67 (2.16–3.32)		
	HRS	Class 4: persistent high multimorbidity	3.03 (2.59–3.55)		
	MHAS	Class 1: persistent high multimorbidity	1.67 (1.47–1.89)		
Random-effects pooled estimate	**4 cohorts**	**DerSimonian–Laird model**		**2.33 (1.76–3.10)**	**I^2=91.9%; P<0.001**
Secondary: persistent pain-dominant	ELSA	Class 2: persistent pain-dominant	1.74 (1.47–2.05)		
	HRS	Class 1: single-symptom pain-dominant	1.89 (1.71–2.09)		
Random-effects pooled estimate	**2 cohorts**	**DerSimonian–Laird model**		**1.85 (1.70–2.01)**	**I^2=0.0%; P=0.396**
Secondary: persistent sleep-disturbance-dominant	ELSA	Class 1: persistent sleep-disturbance-dominant	1.15 (0.99–1.34)		
	HRS	Class 2: persistent sleep-disturbance-dominant	1.49 (1.37–1.62)		
Random-effects pooled estimate	**2 cohorts**	**DerSimonian–Laird model**		**1.32 (1.03–1.69)**	**I^2=87.9%; P=0.004**

HR, hazard ratio; CI, confidence interval; ADL, activities of daily living. Random-effects models were fitted on log HRs. Secondary analyses included only clinically comparable persistent symptom-dominant trajectories.

Supplementary Files

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

- TableS1Sensitivityanalyses.docx
- TableS2subgroupandinteractionresults.docx