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Depressive symptoms and incident chronic lung disease: a three- cohort cross-national comparison of 117,160 adults from China, the United States, and Europe

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Abstract

Depression has long been viewed as a consequence of chronic lung disease (CLD), but emerging evidence suggests it may also precede its onset. Whether this association holds across national contexts, which symptom dimensions drive it, and how depressive symptom trajectories modify risk remain unresolved. We addressed these questions by pooling harmonized data from three nationally representative prospective cohorts: the China Health and Retirement Longitudinal Study (CHARLS), the Health and Retirement Study (HRS), and the Survey of Health, Ageing and Retirement in Europe (SHARE). In total, 117,160 adults free of CLD and asthma at baseline were followed, generating 9,275 incident CLD events. Depressive symptoms were assessed with the CES-D (CHARLS, HRS) and EURO-D (SHARE), which use different cutoffs and are not directly equated across cohorts. Cox proportional hazards models adjusted for age, sex, smoking, education, BMI, diabetes, heart disease, stroke, and alcohol, and random-effects meta-analysis estimated hazard ratios (HRs) and 95% confidence intervals (CIs). In a separate trajectory analysis using the first three waves as the exposure period and subsequent waves as follow-up, participants were classified into five trajectory groups. After full adjustment, baseline depressive symptoms were associated with a broadly consistent ~ 50% higher CLD risk across all three countries (CHARLS HR = 1.55, 95% CI: 1.41–1.71; HRS HR = 1.56, 95% CI: 1.43–1.69; SHARE HR = 1.52, 95% CI: 1.42–1.61; pooled HR = 1.54, 95% CI: 1.48–1.60; I^2 = 0%). In the subtype analysis, both somatic and cognitive-affective symptoms were independently associated with incident CLD, with somatic symptoms showing slightly stronger effect sizes. In the trajectory analysis (n = 57,241), participants with persistently high depressive symptoms during the exposure period had a 2.1- to 3.0-fold higher CLD risk during subsequent follow-up, while those with decreasing symptoms showed an attenuated but still elevated risk. These findings provide cross-national evidence that both somatic and cognitive-affective depressive symptoms are associated with incident CLD, and that persistently elevated symptoms confer the greatest risk across China, the United States, and Europe.

Background

Chronic lung diseases (CLDs), principally chronic obstructive pulmonary disease (COPD), chronic bronchitis, and emphysema, remain among the leading causes of mortality and morbidity worldwide. The Global Burden of Disease Study estimated that CLDs accounted for approximately 3.5 million deaths in 2017, and the prevalence of COPD continues to rise with population aging, smoking histories, and environmental exposures such as air pollution and biomass fuel use [1, 2]. Depression and depressive symptoms are also highly prevalent in middle-aged and older adults, and meta-analytic evidence places the pooled prevalence of clinically significant depressive symptoms among patients with COPD at approximately 25% to 50%, substantially higher than in the general population [3, 4].

Observational studies have consistently reported cross-sectional associations between depression and COPD, but the direction of the association has long been debated. Earlier work largely framed depression as a consequence of living with chronic respiratory disease: dyspnea, functional limitation, hypoxemia, and the psychosocial burden of living with a progressive illness were thought to drive mood symptoms

[5, 6]. More recently, however, a growing body of longitudinal evidence has suggested that depressive symptoms may precede and predict the onset of CLD itself, raising the possibility that depression is not merely a downstream marker of respiratory disease but may also lie on the causal pathway [7–9]. Candidate mechanisms include chronic low-grade systemic inflammation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, behavioral pathways such as reduced physical activity and poor medication adherence, and smoking-related neurobiological effects [10–12].

Despite this interest, several important questions remain unresolved. First, most longitudinal studies have been conducted in single populations, often within one country. Whether the association holds across different health systems, smoking patterns, and cultural contexts is unclear. A recent two-cohort study using Chinese and American data reported consistent associations between depressive symptoms and incident CLD but did not include European populations and did not formally quantify between-country heterogeneity [13]. Second, depressive symptoms are heterogeneous. Evidence from psychometric research has long distinguished between somatic symptoms such as sleep disturbance and fatigue, and cognitive-affective symptoms such as low mood and feelings of worthlessness. Whether these components carry differential risk for subsequent respiratory disease has not been established in cross-national data [14, 15]. Third, a single baseline assessment of depressive symptoms may miss important information about their longitudinal course. Group-based trajectory modelling has identified subgroups with persistently high, increasing, decreasing, or fluctuating depressive symptoms, and these trajectories have been shown to predict cardiovascular disease, multimorbidity, and mortality [16–18]. Whether similar trajectories predict incident CLD has not been examined across multiple cohorts.

We addressed these gaps by pooling harmonized data from three nationally representative longitudinal cohorts: the China Health and Retirement Longitudinal Study (CHARLS), the Health and Retirement Study (HRS) in the United States, and the Survey of Health, Ageing and Retirement in Europe (SHARE). We had three aims. First, to estimate the association between baseline depressive symptoms and incident CLD in each cohort and to pool the estimates across countries using random-effects meta-analysis. Second, to decompose total depressive symptoms into somatic and cognitive-affective components and compare their respective associations. Third, to classify five-group depressive symptom trajectories during a defined exposure period and examine their association with incident CLD during subsequent follow-up.

Methods

Study design and population

We used harmonized data from three prospective cohort studies of adults aged 45 years or older: CHARLS, a nationally representative survey of Chinese community-dwelling adults aged 45 years or older conducted since 2011 [19]; HRS, a nationally representative survey of Americans aged 50 years or older conducted since 1992 [20]; and SHARE, a nationally representative survey of community-dwelling adults

aged 50 years or older across continental Europe conducted since 2004 [21]. All three cohorts have been described in detail elsewhere and have obtained ethics approval from their respective institutional review boards, with informed consent obtained from all participants. We used publicly available, de-identified harmonized data.

For the primary analysis, we included participants aged 45 years or older with complete data on depressive symptoms, lung disease status, and covariates at the baseline wave, and at least one subsequent wave of follow-up. We excluded participants with self-reported CLD at baseline; in CHARLS and SHARE, participants with baseline asthma were also excluded. The primary analytic sample comprised 117,160 participants (CHARLS n = 12,775; HRS n = 29,845; SHARE n = 74,540). The symptom subtype analysis was conducted within the primary analytic sample and restricted to participants with complete item-level depression data (CHARLS n = 12,670; HRS n = 15,732); the smaller HRS sample reflects that item-level depression items were collected only in selected waves of the harmonized HRS file.

Ascertainment of depressive symptoms

Depressive symptoms were measured using harmonized instruments across cohorts. In CHARLS, the 10-item Center for Epidemiologic Studies Depression Scale (CES-D-10) was used, with scores ranging from 0 to 30 and a validated cutoff of 10 or higher indicating moderate-to-severe depressive symptoms [22]. In HRS, the 8-item CES-D was used, with scores ranging from 0 to 8 and a cutoff of 3 or higher [23]. In SHARE, the 12-item EURO-D scale was used, with scores ranging from 0 to 12 and a cutoff of 4 or higher [24]. All three instruments have established reliability and validity in middle-aged and older adult populations and have been used in cross-national comparisons of depressive symptoms [25].

To examine symptom subtypes, we decomposed total scores into somatic and cognitive-affective components following the standard two-factor CES-D structure. In CHARLS, the somatic subscale comprised three items (restless sleep, everything was an effort, could not get going); the cognitive-affective subscale comprised six items (depressed mood, lonely, fearful, bothered by things, happy [reverse-coded], and hopeful [reverse-coded]). In HRS, the somatic subscale comprised the single item of restless sleep, which was the only somatic item available in the harmonized file; the cognitive-affective subscale comprised four items (lonely, sad, happy [reverse-coded], and hopeful [reverse-coded]). Subscale scores were standardized within each cohort (z-scores) to permit comparison of effect sizes. SHARE contributed only a total EURO-D score and was not included in subtype-specific analyses.

Ascertainment of chronic lung disease

Incident CLD was defined by self-reported physician-diagnosed chronic bronchitis, emphysema, or chronic lung disease on follow-up waves, consistent with prior analyses of these cohorts [13, 26]. Participants who reported no such diagnosis at baseline and reported one or more diagnoses at any

subsequent wave were classified as incident cases. In CHARLS and SHARE, where a separate asthma variable was available, participants with baseline asthma were excluded to avoid conflating asthma with obstructive airway disease, following the approach of Chen et al. [13]. In HRS, the harmonized lung variable did not distinguish asthma, so participants with self-reported CLD at baseline were excluded; this limitation is acknowledged. Lung cancer was not separately identifiable in the harmonized data. Time at risk was measured in waves from the baseline wave to the first reported incident diagnosis or to the last available follow-up wave for censored participants.

Covariates

We adjusted for a prespecified set of covariates known to be associated with both depressive symptoms and respiratory disease: age (continuous, in years), sex (male or female), educational attainment (harmonized into low, middle, and high categories), smoking status (never, former, or current), body mass index (BMI, kg/m²), diabetes, heart disease, stroke, and alcohol consumption. All covariates were assessed at baseline.

Statistical analysis

Baseline characteristics were summarized by cohort. Continuous variables were expressed as mean ± standard deviation, and categorical variables as percentages.

Cox proportional hazards models estimated the association between baseline depressive symptoms (binary, using the cohort-specific cutoff) and incident CLD. We present three nested models: Model 1 was unadjusted; Model 2 adjusted for age and sex; Model 3 adjusted additionally for smoking status, educational attainment, BMI, diabetes, heart disease, stroke, and alcohol consumption. Results are reported as hazard ratios (HRs) with 95% confidence intervals (CIs). Time at risk was measured in years, using approximately 2-year intervals between study waves (median follow-up: CHARLS 6 years, HRS 10 years, SHARE 6 years). We verified the proportional hazards assumption using scaled Schoenfeld residuals with rank-transformed time. The depression variable satisfied the proportional hazards assumption in CHARLS ($P = 0.63$) and SHARE ($P = 0.64$); in HRS, the depression variable showed evidence of non-proportionality ($P = 0.001$), which is consistent with prior work in this cohort and likely reflects time-varying effect attenuation; we report the overall HR as the average hazard ratio over follow-up and note this in the limitations.

For the cross-national meta-analysis, we pooled cohort-specific fully adjusted HRs using a random-effects model with the DerSimonian-Laird estimator. Between-cohort heterogeneity was quantified with the I^2 statistic. Given that only three cohorts were included, the random-effects estimate of between-study variance (tau^2) is imprecise, and the $I^2 = 0\%$ estimate should be interpreted cautiously rather than as evidence of true zero heterogeneity.

We calculated E-values to assess the robustness of the depression-CLD association to unmeasured confounding. The E-value represents the minimum strength of association that an unmeasured confounder would need to have with both the exposure and outcome to explain away the observed association. We also conducted a sensitivity analysis excluding events occurring within the first two years of follow-up to assess possible protopathic bias.

For symptom subtype analyses, we entered standardized somatic and cognitive-affective subscale scores as continuous variables in the same Cox model, adjusted for the same covariates as the primary analysis. These analyses were conducted in CHARLS and HRS, where item-level data were available.

For trajectory analysis, we used a prespecified exposure–follow-up design to avoid immortal time and protopathic bias. The first three waves of each participant served as the exposure period. During these three waves, we excluded participants who developed CLD. Depressive symptoms were classified at each wave as above or below the cohort-specific cutoff, and participants were assigned to one of five trajectory groups based on the pattern of elevation across the three exposure waves. This rule-based approach, which has been used in prior large-scale cohort studies of depressive symptom trajectories and incident disease [16, 18, 38], offers the advantage of transparent, prespecified group assignment that does not depend on model convergence or posterior probability thresholds. The five groups were defined as follows: consistently low (scores below cutoff at all three waves); decreasing (at or above cutoff at wave 1 but below cutoff by wave 3); fluctuating (elevated at one or two waves but not consistently); increasing (below cutoff at wave 1 but at or above cutoff by wave 3); and consistently high (at or above cutoff at all three waves). Follow-up time began at the end of the exposure period (wave 3), and incident CLD events occurring after this point were counted. This design ensures that trajectory classification precedes outcome ascertainment. Covariates for trajectory models were assessed at the end of the exposure period. The trajectory analytic sample comprised 57,241 participants with at least three waves of exposure data and at least one subsequent follow-up wave (CHARLS n = 11,008; HRS n = 20,077; SHARE n = 26,156). We acknowledge that data-driven group-based trajectory modelling (GBTM) or latent class growth analysis would provide more statistically principled group assignment; however, our rule-based categories were prespecified and are directly comparable across cohorts despite different depression scales and wave spacing.

All analyses were performed using Python (version 3.11.7; Python Software Foundation, Wilmington, DE, USA) within the Anaconda distribution (version 2024.02). Survival analyses, including Cox proportional hazards models and Kaplan–Meier estimates, were conducted using the lifelines package (version 0.30.3). Statistical modeling, including random-effects meta-analysis and linear regression, was performed using the statsmodels package (version 0.14.6). A two-sided P value < 0.05 was considered statistically significant.

Results

Study population

Figure 1 illustrates the participant flow. From 197,778 participants aged ≥ 45 years across the three cohorts, we excluded those with baseline CLD (n = 8,896), baseline asthma in CHARLS and SHARE (n = 3,621), and those with missing covariate data (n = 68,101, mainly due to missing BMI data in CHARLS). The primary analytic sample comprised 117,160 participants: 12,775 from CHARLS, 29,845 from HRS, and 74,540 from SHARE. Over a median follow-up of 6 to 10 years, 9,275 participants developed incident CLD (1,769 in CHARLS, 2,782 in HRS, and 4,724 in SHARE).

Baseline characteristics are shown in Table 1. The three cohorts differed in age and depressive symptom burden: CHARLS participants were the youngest (mean age 56.7 years) and had the highest prevalence of elevated depressive symptoms (30.7%), whereas SHARE participants were the oldest (63.2 years) with an intermediate prevalence (25.8%); HRS participants had the lowest prevalence (21.9%). Women accounted for 52.6–57.3% of each cohort.

Table 1
Baseline characteristics of the primary analytic sample by cohort (complete cases with comprehensive covariate data; baseline asthma excluded in CHARLS and SHARE).

Characteristic	CHARLS (China)	HRS (US)	SHARE (Europe)
N	12,775	29,845	74,540
Age (mean +/- SD), years	56.7 +/- 9.7	60.6 +/- 10.2	63.2 +/- 9.9
Female, %	52.6	57.3	56.3
Depression score (mean)	7.78	1.56	2.36
Depression prevalence, %	30.7	21.9	25.8
BMI (mean +/- SD), kg/m²	23.8 +/- 3.8	28.3 +/- 5.8	26.8 +/- 4.5
Former smoker, %	38.2	55.3	45.3
Current smoker, %	25.8	17.2	20.1
Incident CLD events, n	1,769	2,782	4,724
Incident CLD, %	13.9	9.3	6.3
Median follow-up, years	6.0	10.0	6.0

Abbreviations: BMI, body mass index; CLD, chronic lung disease; SD, standard deviation.

Baseline depressive symptoms and incident CLD

In the unadjusted model, baseline elevated depressive symptoms were associated with incident CLD in all three cohorts. After full adjustment for age, sex, smoking, education, BMI, diabetes, heart disease, stroke, and alcohol consumption, the associations remained statistically significant (Table 2). The fully

adjusted HR was 1.55 (95% CI 1.41-1.71) in CHARLS, 1.56 (95% CI 1.43-1.69) in HRS, and 1.52 (95% CI 1.42-1.61) in SHARE. The random-effects pooled HR was 1.54 (95% CI 1.48-1.60; Q = 0.05, P = 0.97; τ^2 = 0; I^2 = 0%; Figure 2). Given k = 3, the tau² estimate is imprecise and I^2 should be interpreted cautiously. The E-values for the fully adjusted HRs were 2.47 (CHARLS), 2.49 (HRS), and 2.41 (SHARE), with E-values for the lower 95% CI of 2.17, 2.21, and 2.19 respectively. Excluding events occurring within the first two years of follow-up did not materially change the estimates (CHARLS HR 1.55, HRS HR 1.56, SHARE HR 1.52).

Table 2

Cox proportional hazards models for the association between baseline depressive symptoms and incident chronic lung disease.

Cohort	N	Events	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
CHARLS (China)	12,775	1,769	1.62 (1.49–1.76)	1.67 (1.54–1.82)	1.55 (1.41–1.71)
HRS (US)	29,845	2,782	1.78 (1.65–1.93)	1.84 (1.69–1.99)	1.56 (1.43–1.69)
SHARE (Europe)	74,540	4,724	1.64 (1.54–1.73)	1.67 (1.57–1.77)	1.52 (1.42–1.61)
Total	117,160	9,275	-	-	-

Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: adjusted for age, sex, smoking status, educational attainment, BMI, diabetes, heart disease, stroke, and alcohol consumption. Baseline asthma was excluded in CHARLS and SHARE. All P < 0.001. Abbreviations: CI, confidence interval; HR, hazard ratio.

Symptom subtype analysis

When total depressive symptoms were decomposed into somatic and cognitive-affective components within the primary analytic sample, both subscales were independently associated with incident CLD after adjustment for the same comprehensive covariate set as Model 3, although somatic symptoms showed slightly stronger effect sizes. In CHARLS (n = 12,670; 1,756 events), per one standard deviation (SD) increase, the somatic subscale was associated with an HR of 1.18 (95% CI 1.11-1.25; P < 0.001) and the cognitive-affective subscale with an HR of 1.13 (95% CI 1.07-1.20; P < 0.001). In HRS (n = 15,732; 1,498 events), per one SD increase, the somatic subscale was associated with an HR of 1.23 (95% CI 1.18-1.29; P < 0.001) and the cognitive-affective subscale with an HR of 1.17 (95% CI 1.11-1.22; P < 0.001; Table 3). Both subscales were entered simultaneously in the same model to estimate mutually adjusted associations.

Table 3

Association of somatic and cognitive-affective depressive symptom subscales with incident chronic lung disease (item-level sub-sample; mutually adjusted Cox models).

Cohort	N	Events	Somatic symptoms HR (95% CI) per SD	Somatic P	Cognitive-affective HR (95% CI) per SD	Cognitive-affective P
CHARLS (China)	12,670	1,756	1.18 (1.11–1.25)	< 0.001	1.13 (1.07–1.20)	< 0.001
HRS (US)	15,732	1,498	1.23 (1.18–1.29)	< 0.001	1.17 (1.11–1.22)	< 0.001

Both subscales were standardized within each cohort (z-scores) and entered simultaneously in the same Cox model adjusted for the same covariates as Model 3 (age, sex, smoking, education, BMI, diabetes, heart disease, stroke, and alcohol). In HRS, the somatic subscale comprised a single item (restless sleep) due to data availability. SHARE did not contribute item-level data and is not shown. All P < 0.001. Abbreviations: CI, confidence interval; HR, hazard ratio; SD, standard deviation.

Depressive symptom trajectories and incident CLD

In the trajectory analysis (n = 57,241), participants were classified based on depressive symptom patterns during the first three waves (exposure period), and follow-up began after this period. Kaplan–Meier curves for incident CLD across the five trajectory groups are shown in Figure 3. Compared with the consistently low group, participants in the consistently high group had the highest risk of incident CLD during subsequent follow-up across all three cohorts: CHARLS HR 2.97 (95% CI 2.51–3.51), HRS HR 2.10 (95% CI 1.80–2.45), and SHARE HR 2.54 (95% CI 2.12–3.04; Table 4). The increasing trajectory was also associated with elevated risk (CHARLS HR 1.81, HRS HR 1.60, SHARE HR 1.64). The decreasing and fluctuating trajectories showed intermediate HRs that were consistently above 1.4 across cohorts.

Table 4

Hazard ratios for incident chronic lung disease across five depressive symptom trajectory groups (exposure period = first 3 waves; follow-up begins after wave 3).

Trajectory group	CHARLS (China) HR (95% CI)	HRS (US) HR (95% CI)	SHARE (Europe) HR (95% CI)
Consistently low	Reference	Reference	Reference
Decreasing	1.65 (1.37–1.98)	1.40 (1.20–1.64)	1.44 (1.21–1.72)
Fluctuating	1.69 (1.39–2.05)	1.46 (1.24–1.71)	1.60 (1.34–1.92)
Increasing	1.81 (1.51–2.17)	1.60 (1.38–1.86)	1.64 (1.39–1.94)
Consistently high	2.97 (2.51–3.51)	2.10 (1.80–2.45)	2.54 (2.12–3.04)

Trajectories were classified using depressive symptoms during the first three waves; follow-up time starts at the end of the exposure period. Models adjusted for age, sex, smoking status, and educational attainment (assessed at end of exposure period). Sample sizes: CHARLS n = 11,008 (1,092 events); HRS n = 20,077 (1,691 events); SHARE n = 26,156 (1,259 events). All $P < 0.001$. Abbreviations: CI, confidence interval; HR, hazard ratio.

Trajectories were defined during the first three waves (exposure period); participants who developed CLD during this period were excluded, and follow-up began after wave 3. Sample sizes: CHARLS n = 11,008 (1,092 events); HRS n = 20,077 (1,691 events); SHARE n = 26,156 (1,259 events). Adjusted hazard ratios are shown in Table 4.

Discussion

In this three-cohort, cross-national analysis of more than 117,000 adults from China, the United States, and Europe, baseline depressive symptoms were associated with incident chronic lung disease after adjustment for a comprehensive set of covariates including BMI, diabetes, heart disease, stroke, and alcohol consumption. The pooled adjusted HR was 1.54, with no detectable between-cohort heterogeneity ($I^2 = 0\%$). In subtype analyses, both somatic and cognitive-affective symptoms were independently associated with incident CLD, although somatic symptoms showed modestly stronger effect sizes. In a prespecified trajectory analysis using a separate exposure–follow-up design, participants with persistently high depressive symptoms during the exposure period had a 2.1- to 3.0-fold higher CLD risk during subsequent follow-up.

The observed HR of approximately 1.5 is broadly consistent with prior longitudinal studies. In the UK Biobank, depressive symptoms have been associated with incident cardiorespiratory disease with effect sizes in the same range [16]. In the English Longitudinal Study of Ageing, the combination of elevated depressive symptoms and C-reactive protein was associated with incident pulmonary disease (HR 1.79) [27]. A recent two-cohort study of Chinese and American adults reported adjusted HRs for incident CLD of 1.52 to 1.59 across cohorts [13]. Our pooled estimate of 1.54 is therefore closely aligned with prior work. Because the three cohorts use different depression instruments (CES-D-10, CES-D-8, and EURO-D)

with different cutoffs, we caution that the cross-national consistency should be interpreted as broadly comparable rather than quantitatively identical; the near-identical point estimates nonetheless suggest that the association is not confined to a particular health system, smoking pattern, or cultural context.

The subtype decomposition showed that both somatic and cognitive-affective symptoms were independently associated with incident CLD, although somatic symptoms carried modestly stronger effect sizes per standard deviation. This pattern is biologically plausible: sleep disturbance and fatigue are among the most frequently reported symptoms in depression and are also closely intertwined with respiratory physiology. Sleep fragmentation and nocturnal hypoventilation can worsen airway inflammation and reduce daytime physical activity; fatigue may reduce engagement with smoking cessation, exercise, and preventive care [28-30]. At the same time, the independent cognitive-affective signal suggests that the association is not confined to symptom overlap with respiratory complaints but reflects a broader mood-related pathway. This is consistent with the two-cohort findings of Chen et al., in which both somatic and cognitive-affective dimensions were significantly associated with incident CLD [13]. The present study extends this work by adding the SHARE cohort, which yielded nearly identical effect sizes (HR 1.52), and by using a stricter exposure–follow-up design for trajectory analyses. In Chen et al., the decreasing trajectory showed no significant association with CLD, whereas our rule-based decreasing group retained an elevated HR of 1.4 to 1.6; this difference may reflect our shorter exposure window (3 waves vs. 2) or different trajectory classification thresholds, and should be interpreted cautiously given that we did not use data-driven GBTM. The HRS consistently high HR in our analysis (2.10) was lower than that reported by Chen et al. (approximately 3.3), likely because we excluded baseline asthma and applied more comprehensive covariate adjustment including BMI, diabetes, heart disease, and stroke.

The trajectory analysis adds a further dimension and addresses a key methodological concern. By designating the first three waves as the exposure period, excluding participants who developed CLD during this period, and starting follow-up only after the exposure period ended, we minimized immortal time and protopathic bias. Participants with persistently high depressive symptoms during this exposure-free interval had HRs of 2.1 to 3.0, substantially higher than the HR of 1.6 associated with a single baseline assessment. This finding is consistent with prior trajectory studies showing that chronic, unremitting depressive symptoms confer the greatest risk for incident chronic disease and mortality [16,18]. The decreasing trajectory showed an attenuated but still elevated HR, which suggests that the detrimental respiratory consequences of depression may be partly modifiable if mood symptoms improve over time.

Several mechanisms may underlie the observed association. First, chronic depression is associated with elevated pro-inflammatory cytokines, including interleukin-6 and C-reactive protein, which have been implicated in airway inflammation and COPD pathogenesis [10,27]. Second, HPA axis hyperactivity and glucocorticoid resistance in depression may alter immune regulation and respiratory mucosal defenses [11]. Third, behavioral pathways are likely important: individuals with depressive symptoms are more likely to smoke, less likely to exercise, more likely to be overweight, and less likely to adhere to preventive

care [31,32]. Our adjustment for smoking status and education attenuated but did not eliminate the association, suggesting that residual behavioral and biological pathways may operate together.

The impact of depressive symptoms on COPD outcomes has also been evaluated in relation to lung function and composite severity indices such as the BODE index [33,35], and the bidirectional, self-reinforcing relationship between COPD and depression has been described as a vicious cycle [34].Similar bidirectional associations have been reported between depression and other chronic conditions, including chronic kidney disease and arthritis [36,37], and depression has been linked to the accumulation of multiple chronic conditions [39]. Cross-national differences in physical health and disability have also been documented [40].

These findings have several clinical and public health implications. First, routine screening for depressive symptoms—particularly persistent somatic symptoms such as sleep disturbance and fatigue—in middle-aged and older adults may help identify those at elevated risk of CLD. Second, respiratory clinicians should be aware that patients with persistently high depressive symptoms may be at substantially higher risk of disease progression. Third, the consistency of the association across China, the United States, and Europe strengthens the case for embedding mental health assessment within chronic respiratory disease prevention strategies. Finally, future intervention studies should examine whether effective treatment of persistent depressive symptoms reduces incident CLD.

Strengths and limitations

This study has several strengths. It used three large, nationally representative cohorts (117,160 participants; 9,275 incident CLD events) from China, the United States, and Europe, with consistent effect estimates across cohorts ($I^2 = 0\%$). The trajectory analysis used a prespecified exposure–follow-up design that minimized immortal time and protopathic bias, and item-level data in two cohorts permitted symptom subtype decomposition.

Several limitations should be noted. CLD and depressive symptoms were self-reported, and the three cohorts used different depression instruments and cutoffs, so cross-national estimates are broadly comparable rather than identical. Residual confounding cannot be excluded, although E-values (2.4–2.5) indicated that a relatively strong unmeasured confounder would be needed to explain away the association. Death was not modeled as a competing risk, and the proportional hazards assumption was violated in HRS ($P = 0.001$). Subtype analyses were limited to CHARLS and HRS, with only one somatic item in HRS; trajectory groups used rule-based definitions rather than GBTM, adjusted for fewer covariates, and were not corrected for multiple comparisons. Complete-case analysis and structural BMI missingness in CHARLS may have introduced selection bias, and multiple imputation was not performed. Finally, only three cohorts were meta-analyzed, the trajectory sample was smaller, and findings may not apply to younger adults.

Conclusions

In this three-cohort cross-national analysis of 117,160 adults, depressive symptoms, particularly persistently elevated symptoms assessed during a defined exposure period, were consistently associated with incident chronic lung disease after comprehensive covariate adjustment. Both somatic and cognitive-affective symptom dimensions contributed independently, with somatic symptoms showing modestly stronger effect sizes. The association was of broadly similar magnitude across China, the United States, and Europe, although differences in depression instruments across cohorts warrant cautious cross-national interpretation. These findings support the integration of depressive symptom screening into population-based respiratory prevention strategies and motivate longitudinal studies examining whether treatment of persistent depressive symptoms reduces incident chronic lung disease.

Declarations

Ethics approval and consent to participate: All methods were performed in accordance with the relevant guidelines and regulations, including the Declaration of Helsinki. All three cohorts (CHARLS, HRS, and SHARE) obtained ethics approval from their respective institutional review boards, and informed consent was obtained from all participants. The present analysis used publicly available, de-identified data; therefore, no additional ethics approval was required.

Consent for publication: Not applicable.

Availability of data and materials: The datasets analyzed in this study are publicly available from the CHARLS (http://charls.pku.edu.cn), HRS (https://hrs.isr.umich.edu/), and SHARE (http://www.share-project.org/) repositories. No new datasets were generated.

Competing interests: The authors declare that they have no competing interests.

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Authors contributions: TG and XZ contributed equally to the study. WW and AZ conceived and supervised the study. TG analyzed the data and drafted the manuscript. XZ, BL,YZ,TJ, JS, LZ, and QL reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Figures

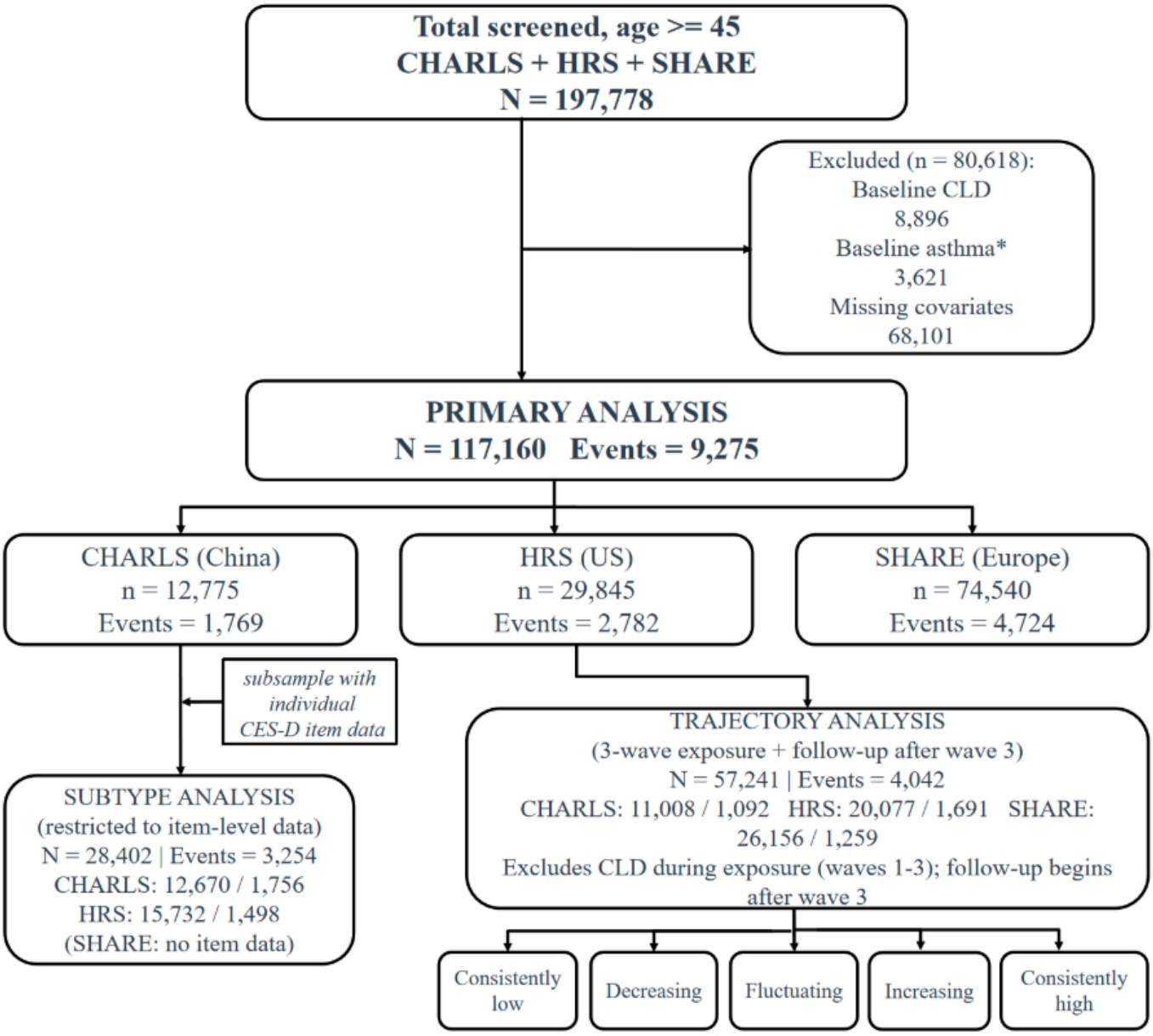


Figure 1

Flow diagram of participant selection for the primary, symptom subtype, and trajectory analyses in CHARLS, HRS, and SHARE.

*Baseline asthma was excluded in CHARLS and SHARE; HRS harmonized data do not distinguish asthma from CLD, so only baseline CLD was excluded in HRS. Subtype analysis was restricted to

participants with item-level CES-D data (CHARLS n=12,670; HRS n=15,732). Trajectory analysis required three exposure waves plus at least one follow-up wave (n=57,241).

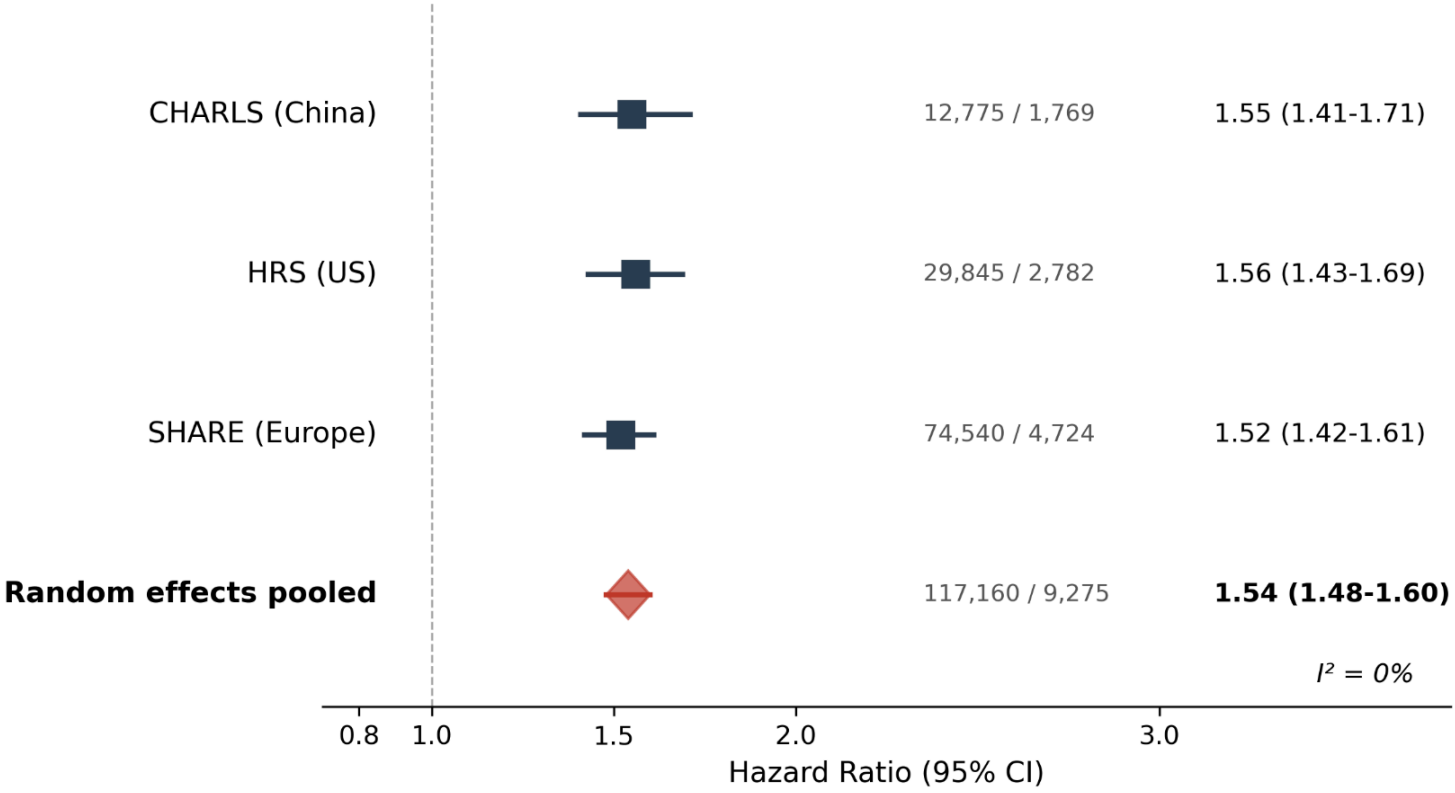


Figure 2

Random-effects meta-analysis of the association between baseline depressive symptoms and incident chronic lung disease across CHARLS, HRS, and SHARE.

HRs were adjusted for age, sex, smoking status, educational attainment, BMI, diabetes, heart disease, stroke, and alcohol consumption. Baseline asthma was excluded in CHARLS and SHARE; HRS did not distinguish asthma. The pooled adjusted HR was 1.54 (95% CI 1.48–1.60), with no evidence of between-cohort heterogeneity (I^2 = 0%, τ^2 = 0, Q = 0.05, P = 0.97). Abbreviations: HR, hazard ratio; CI, confidence interval.

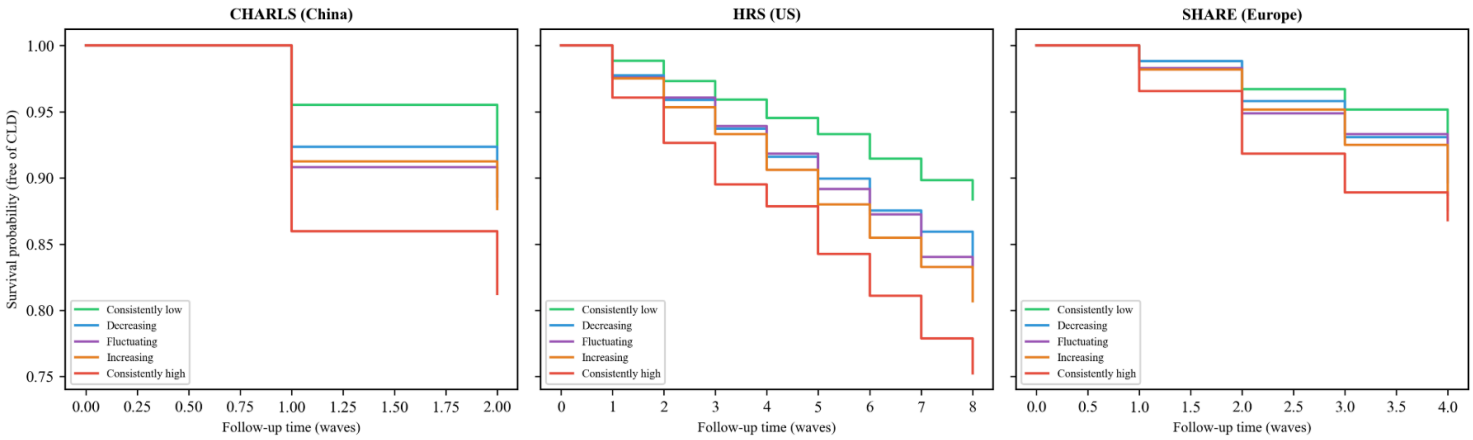


Figure 3

Kaplan-Meier curves for incident chronic lung disease by depressive symptom trajectory group across the three cohorts.