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Original Research Article

Associations Between Depression Symptom Burden and Delirium Risk: A Prospective Cohort Study

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Abstract

Background and Objectives: Delirium and depression are prevalent in aging. There is considerable clinical overlap, including shared symptoms and comorbid conditions, including Alzheimer's disease, functional decline, and mortality. Despite this, the long-term relationship between depression and delirium remains unclear. This study assessed the associations of depression symptom burden and its trajectory with delirium risk in a 12-year prospective study of older hospitalized individuals.

Research Design and Methods: A total of 319 141 UK Biobank participants between 2006 and 2010 (mean age 58 years [range 37–74, *SD* = 8], 54% women) reported frequency (0–3) of 4 depressive symptoms (mood, disinterest, tenseness, or lethargy) in the preceding 2 weeks prior to initial assessment visit and aggregated into a depressive symptom burden score (0–12). New-onset delirium was obtained from hospitalization records during 12 years of median follow-up. 40 451 (mean age 57 ± 8; range 40–74 years) had repeat assessment on average 8 years after their first visit. Cox proportional hazard models examined whether depression symptom burden and trajectory predicted incident delirium.

Results: A total of 5 753 (15 per 1 000) newly developed delirium during follow-up. Increased risk for delirium was seen for mild (aggregated scores 1–2, hazards ratio, HR = 1.16, [95% confidence interval (CI): 1.08–1.25], $p < .001$), modest (scores 3–5, 1.30 [CI: 1.19–1.43], $p < .001$), and severe (scores ≥ 5, 1.38 [CI: 1.24–1.55], $p < .001$) depressive symptoms, versus none in the fully adjusted model. These findings were independent of the number of hospitalizations and consistent across settings (eg, surgical, medical, or critical care) and specialty (eg, neuropsychiatric, cardiorespiratory, or other). Worsening depression symptoms (≥1 point increase), compared to no change/improved score, were associated with an additional 39% increased risk (1.39 [1.03–1.88], $p = .03$) independent of baseline depression burden. The association was strongest in those over 65 years at baseline (p for interaction <.001).

Discussion and Implications: Depression symptom burden and worsening trajectory predicted delirium risk during hospitalization. Increased awareness of subclinical depression symptoms may aid delirium prevention.

Translational Significance: Delirium is associated with an increased risk of readmission, cognitive decline, dementia, and mortality. Recognizing early depression symptoms may promote psychological well-being and cognitive resilience. In this study, depression symptom burden is associated with delirium risk during hospitalization. Worsening symptom trajectory was associated with additional risk regardless of initial burden. These findings were consistent across hospitalization settings, and results were strongest in those over 65 years. By bringing attention to the cognitive consequences of depression symptom burden in older persons, screening will be encouraged for optimizing psychological health prior to major surgery or for promoting cognitive resilience for illnesses requiring hospitalization.

Keywords: Altered mental status, Anxiety, Alzheimer's disease, Dementia, Postoperative

Background and Objectives

Delirium is a cognitive insult characterized by its acute onset, fluctuating course of attention and awareness, with hyperactive forms exhibiting increased awareness and hypervigilance, commonly occurring in hospital admissions as frequently as 50% of patients (1,2). Although delirium is a reversible form of cognitive impairment, it is associated with an increased risk for dementia, nursing home placement, functional decline, and mortality (3). Delirium has been linked to noncognitive features, such as sleep disruption (4) and depression symptoms (5). There is a known overlap of syndromal symptoms between delirium and depression and a worse prognosis when symptoms overlap (6,7).

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In older hospitalized patients, depression symptoms can be present in up to half, depending on the population (medical vs surgical) and measurement tools (8,9). Some evidence suggests that depression may be a risk factor for delirium (10,11). Yet, uncertainty remains regarding the long-term relationship between depression symptoms and delirium (12,13), particularly in larger population-based cohorts across therapeutic settings (eg, general medical vs postoperative) and age groups (6). In addition, shared comorbidities prevalent in older individuals, such as dementia or cardiometabolic disease, are also associated with delirium risk (14,15). Whether depression symptoms are a risk factor for delirium or a prodromal marker for neurodegeneration remains unclear (16).

Given that depression symptoms are modifiable, our primary objective was to determine whether earlier life depression symptoms are a risk factor for incident delirium during hospitalization (17). Within a large community sample of middle- to older-aged adults from the UK Biobank, we examined the association between depression symptom burden derived from an aggregate symptom frequency score and new-onset delirium after hospitalization during a median 12 years of follow-up. We examined these relationships in clinically important subsets (postoperative delirium [POD] and after the exclusion of known dementia) and by common comorbidities. Finally, in a follow-up cohort, a median 4 years after the first assessment, we examined whether worsening depression symptom trajectory contributed to additional risk for delirium.

Research Design and Methods

Study Participants and Data Resource

Over 500 000 of the 9.2 million people between the ages of 40–69 who were registered within 25 miles of the 22 assessment centers across the United Kingdom were recruited to participate in the UK Biobank between 2006 and 2010. They completed extensive questionnaires on demographics, lifestyle choices, medical conditions, and psychiatric well-being at the initial recruitment visit by the Biobank team and were followed until February 2021 (median 12 years). They also completed physical exams and submitted biological samples such as blood, urine, and saliva. In sampling this population, no design weights were implemented, and the participants did not undergo poststratification or nonresponse weighting to the data. A total of 319 141 participants completed a psychological assessment and had at least ≥1 hospitalization after the baseline assessment (given that delirium requires a precipitating illness event; Supplementary Figure 1). A subset (n = 40 451, 52% women, mean age 64 ± 8; range 44–83 years) was reassessed with repeated questionnaires by the UK Biobank team between 2012 and 2020 and followed for a median of 4 years. The UK Biobank structure and data validation efforts have been described in detail (18).

Standard Protocol Approvals, Registrations, and Patient Consents

The UK Biobank received National Research Ethics approval, and participants gave written informed consent. This study was conducted under the terms of UK Biobank access number 40556 and Mass General Brigham IRB approval (#2020P002097).

Screening of Depression Symptoms

Participants were asked about depression symptoms frequency with 4 questions: (a) "Over the past two weeks, how often have you felt down, depressed, or hopeless?" (depressed mood); (b) "How often have you had little interest or pleasure in doing things?" (unenthusiasm/disinterest); (c) "How often have you felt tense, fidgety, or restless?" (tenseness/restlessness); and (d) "How often have you felt tired or had little energy?" (tiredness/lethargy). We assigned scores to the responses: not at all (0), several days (1), more than half the days (2), or nearly every day (3). A summed depression symptom score (0–12) was calculated for each participant, which we used to classify depression symptom burden in a way that keeps group power with increments of 2-points (representing 1 *significantly more* or 2 *slightly more* frequent symptoms) as follows: "none" (0), "mild" (1–2), "modest" (3–4) and "severe" (≥5). We excluded participants who responded with "do not know" or "prefer not to answer" (depressed mood [4.6%], unenthusiasm and disinterest [3.6%], tenseness and restlessness [4.2%], and tiredness and lethargy [3.1%]). Depression symptom burden trajectory was calculated as the difference between the follow-up and baseline scores and categorized into "no change/improved" (≤0-point change) or "worsened" (≥1-point change). The distribution and change in scores are shown in Supplementary Figure 3.

Assessment of Delirium Diagnosis

The UK Biobank released linked hospitalization records and International Classification of Disease (ICD-10) diagnoses from the National Health Service during the follow-up period. Incident delirium was the first occurrence of the ICD-10 code F05, included in hospital admissions health records as described in previous studies (4,19–22). We excluded 61 cases where delirium predated the baseline assessment and 27 where delirium predated the follow-up assessment. The hospitalization settings of delirium, that is, surgical (postoperative), medical (nonsurgical), and critical care, were separately identified. We identified POD using linked operation/procedure coding and matching operation dates within 3 days before delirium and tested in separate models (23). We classified a *medical* hospitalization setting as patients with delirium who did not have any associated operations or procedures. Finally, we identified those with delirium after admission to critical care units using critical care admission dates provided by the UK Biobank.

We further identified *non-dementia-related delirium* by excluding a subset of participants within the delirium group who had "delirium superimposed on dementia" (F05.1) or a prior diagnosis of any dementia. Admitting specialist/specialty was used to specify patients with delirium admitted to neuropsychiatric, cardiorespiratory, or other teams. Neuropsychiatric admitting specialty was found under the data field 41 245, described as "Main Specialty of Consultant (recorded) Summary Administration." See Supplementary Methods for specific grouping codes used.

Assessment of Covariates

Covariates were grouped based on (a) demographics, (b) lifestyle factors, (c) significant cardiovascular disease/risks (CVD)/comorbidities, and (d) neuropsychiatric comorbidities.

In selecting covariates, we first established the upper limit number of variable inclusion by the "1 in 10 rule," or 1 variable considered for every event (24). We chose candidate variables based on previously demonstrated prognostic performance with the delirium outcome. For example, we grouped demographic variables based on previously established, a-priori knowledge of differences in the delirium outcome such as age (25), sex (26), and educational outcomes (27).

Demographics included age, sex, education, ethnic background, and controlling for number of hospitalizations post-assessment. Age at recent depression assessment was calculated in years based on the participants' birth dates. Sex and ethnicity were self-reported at baseline. Ethnicity was included as European versus non-European based on the distribution of participants of European descent (94%). Education was based on answering college attendance (yes/no).

Lifestyle factors included the Townsend Deprivation Index (TDI), a material deprivation score classified into higher/lower medians, physical activity (summed metabolic equivalent minutes), alcohol consumption (<4 drinks/≥4 drinks per week), body mass index (BMI, weight [kg] divided by the height squared [m^2]), sleep duration was categorized into short (<6 hours/day), normal (6–9 hours), and long (>9 hours) because of the previously demonstrated U-shape associations with delirium or dementia (4,28), frequency of friend and family visits (never vs any), and falls in the last year (none vs any).

Cardiovascular disease (CVD) is based on hypertension, high cholesterol, smoking, diabetes, ischemic heart disease, and peripheral vascular disease. Comorbidities included a previously described morbidity burden (21,29,30) based on the summed presence of any cancers, respiratory, neurological, gastrointestinal, renal, hematological, endocrine, musculoskeletal, connective tissue, infectious diseases/disorders, and classified as none (0)/modest (1–3)/high (≥4) conditions. Cognitive performance was estimated at initial enrollment using a raw processing speed test involving the mean reaction time to identify card matches correctly (31).

The full final model included serum 25-hydroxyvitamin D (25[OH]D, a proxy for vitamin D levels recently linked to delirium within this cohort, categorized into sufficient > 50 nmol/L, low 25–50 nmol/L, and deficient < 25 nmol/L), and pre-existing dementia/Parkinson's disease, or depression diagnosis/treatment ("any", from seeing a psychiatrist, or a self-reported/ICD-10 diagnosis).

Statistical Analysis

The features of those who developed delirium compared to those who were hospitalized but remained delirium-free during follow-up were compared using Chi-squared tests for categorical variables (eg, sex, ethnicity, presence/absence of comorbidities, and recent smoking) and independent samples *t* tests or the nonparametric, Kruskal–Wallis for continuous variables (eg, age, BMI, TDI, physical activity, reaction time, CVD, depressive symptoms burden score, and frequency of falls in the last month). Cox proportional hazard models were used to evaluate the association between depressive symptoms burden and time to incident delirium (reported as hazard ratios [HRs] and corresponding to 95% confidence intervals [CIs]). The Cox proportional hazards model was selected due to delirium cases occurring at different time points, requiring censoring, thus capturing more information from the data by accounting for "survival time" or the time since baseline depression symptom assessment compared to logistic regression. The proportional hazards assumption was assessed using the global χ^2 test in R-package cox.zph (survival) incorporating methods described by Grambsch and Therneau (32) and Schoenfeld residuals were plotted (Supplementary Figure 4).

The core model (A) controlled for demographics (age, sex, college education, ethnicity, and number of hospitalizations). The lifestyle model (B) additionally controlled for TDI, physical activity, alcohol consumption, BMI, sleep duration, frequency of family and friend visits, and falls in the last year. The significant CVD/comorbidities model (C) further controlled for CVD risk score, morbidity burden, and cognition. The final model (D) controlled for vitamin D levels, Parkinson's/dementia, and depression diagnosis. We again examined the association between depression symptom burden in the follow-up cohort. Using the core model, we adjusted for the baseline depressive score and the time lag between assessments. Sensitivity analysis examined the relationship between the depression score and postoperative (surgical), medical (nonsurgical), non-dementia-related delirium, and critical care delirium in the full cohort in addition to admitting specialty in delirium cases separated into neuropsychiatric, cardiorespiratory and others (noncardiorespiratory, non-neuropsychiatric related admissions). Time-to-event was the years between depressive symptoms assessment and delirium diagnosis. Delirium-free participants were censored in February 2021, the last date of available records. All other statistical analyses were performed using JMP Pro (Ver. 16, SAS Institute, Cary, NC, USA). p Value < .05 was used for statistical significance.

Data are available from the UK Biobank after submitting an application. The syntax for conducting the analysis is available upon reasonable request.

Results

Participant Characteristics

Approximately 500 000 participants aged 37–70 (57 ± 8 years, 54% women) were recruited for the UK Biobank. This prospective study included 319 141 participants (mean [*SD*] age: 57.9 [8.0], range: 37.4–73.8 years; 54.0% women) who had all data available, were hospitalized at least once after the first assessment, and had no prior delirium (Supplementary Figure 1). The cohort was followed for a median period of 12.0 years (interquartile range 11.2–12.7) after baseline depression symptom burden assessment. Within this period, 5 753 (15 per 1 000) developed delirium. A subset (n = 40 451, 52% women, mean age 64 ± 8; range 44–83 years) was reassessed between 2012 and 2020 and followed for a median of 4 years.

Participants with incident delirium were more likely to be older (64.0 years vs 57.9 years), men (57.3% n = 3 296 vs 45.7% n = 145 847), lower chance of college attendance (20.8% n = 1 196 vs 30.0% n = 95 742), were more likely to be of European ancestry (95.4% n = 5 488 vs 94.1% n = 300 3011), lived in areas of greater deprivation (TDI −0.62 vs −1.30), had higher BMI (28.7 vs 27.7) than those who remained delirium-free. The incident delirium participants were less active (1 962.5 vs 2 079.4 MET-minutes), did not have differences in alcohol consumption, and were more likely to sleep outside the recommended 6–9 hours range (<6 hours/day: 8.2% n = 471 vs 6.1% n = 1 9467

and >9 hours/day: 4.5% $n = 258$ vs 2.1% $n = 6\,701$), had a higher percentage of no family visits that year (3.4% $n = 195$ vs 1.8% $n = 5\,744$), and more likely to have fallen that year (31.6% $n = 1\,817$ vs 21.4% $n = 68\,296$). The delirium group was more likely to have 1 or more CVD (68.9% $n = 3\,963$ vs 31.1% $n = 99\,252$), higher morbidity burden with 4 or more conditions (40.5% $n = 2\,329$ vs 32.0% $n = 102\,125$), higher incidence of dementia/Parkinson's disease (2.5 $n = 143$ % vs 0.2% $n = 6\,382$), slower reaction time (613 vs 559 milliseconds), and more likely to be vitamin D deficient (5.7% $n = 327$ vs 3.7% $n = 11\,808$). Participants with delirium were also diagnosed with or self-reported depression more (10% $n = 575$ vs 7% $n = 22\,339$) and had more of the cohort in the severe category of depressive symptom burden scoring (12.2% $n = 701$ vs 9.4% $n = 29\,999$) (Table 1).

Depressive Symptoms and Associations with Incidence of Delirium

Figure 1A shows a stepwise increase in risk for the first occurrence of delirium with increasing depression symptom burden (mild, modest, and severe vs none) for the core model. This translated into a higher cumulative incidence of delirium over the follow-up period (Figure 1B). Compared to no depressive symptoms, those with mild (HR = 1.16, 95% CI [1.08–1.25], $p < .001$), modest (1.30 [1.19–1.43], $p < .001$), or severe (1.38 [1.24–1.55], $p < .001$) depressive burden remained at higher risk for delirium in the fully adjusted model (Table 2). Using coefficients (ratio of the natural log of HRs) from the core model (Supplementary Table 1), the risks of modest and severe depression burden were equivalent to the effects of an additional 4 and 7 years of aging, respectively.

These results remained consistent when considering POD only, after excluding known dementia (ie, nondementia-related diagnoses of delirium), medical (nonsurgical), and critical care. Furthermore, these results were consistent in all cardiorespiratory admitting teams, neuropsychiatric, and all other non-neuropsychiatric or cardiorespiratory admitting teams (Supplementary Figure 2). The effects of individual depression symptoms (daily vs none) are shown in Supplementary Table 2. Those with depressed mood (2.17 [1.84–2.55], $p < .001$), unenthusiasm/disinterest (1.88 [1.61–2.21], $p < .001$), tenseness/restlessness (2.25 [1.84–2.63], $p < .001$), tiredness/lethargy (2.48,

Table 1. Demographics, Lifestyle, and Clinical Comorbidities at Baseline

Covariates	Developed new-onset delirium ($n = 5\,753$)	Did not develop delirium ($n = 319\,141$)
	Mean (*SD*), or *n* (%)	Mean (*SD*), or *n* (%)
Demographics		
Age at baseline	64.0 (5.4)	57.9 (7.9)
Males	57.3	45.7
College attendance	20.8	30.0
Ethnic background (European)	95.4	94.1
Townsend deprivation index*	−0.62 (0.04)	−1.30 (0.01)
Body mass index (kg/m^2)	28.7 (5.4)	27.7 (4.9)
Lifestyle		
Physical activity (MET-mins)†	1 963 (493)	2 079.4 (462)
Alcohol (≥ 4 drinks/wk)	47.5	47.0
Sleep duration		
Short (<6 h/d)	8.2	6.1
Normal (6–9 h)	87.4	91.9
Long (>9 h)	4.5	2.1
Frequency of family visits (never)	3.4	1.8
Falls in the last year (any)	31.6	21.1
Comorbidities		
CVD risk‡ (any)	68.9	31.1
Morbidity burden (high)	40.5	32.0
Dementia/Parkinson's disease	2.5	0.2
Cognition (reaction time)§	613 (145)	559 (118)
Vitamin D (deficient)‖	5.7	3.7
Depression/anxiety¶	10.0	7.0

Notes: CVD = cardiovascular disease; *SD* = standard deviation.
Participant characteristics at baseline by delirium status.
*Higher value = worse deprivation.
†METS-min/wk increase.
‡CVD risk score: summed hypertension, cholesterol, diabetes mellitus, smoking status, and ischemic heart disease.
§Cognition reaction time in milliseconds: average timed tests of symbol matching.
‖Vitamin D levels: sufficient >50 nmol/L, low 25–50 nmol/L, and deficient <25 nmol/L.
¶Participants self-reported depression and anxiety symptoms, or ICD depression diagnosis.

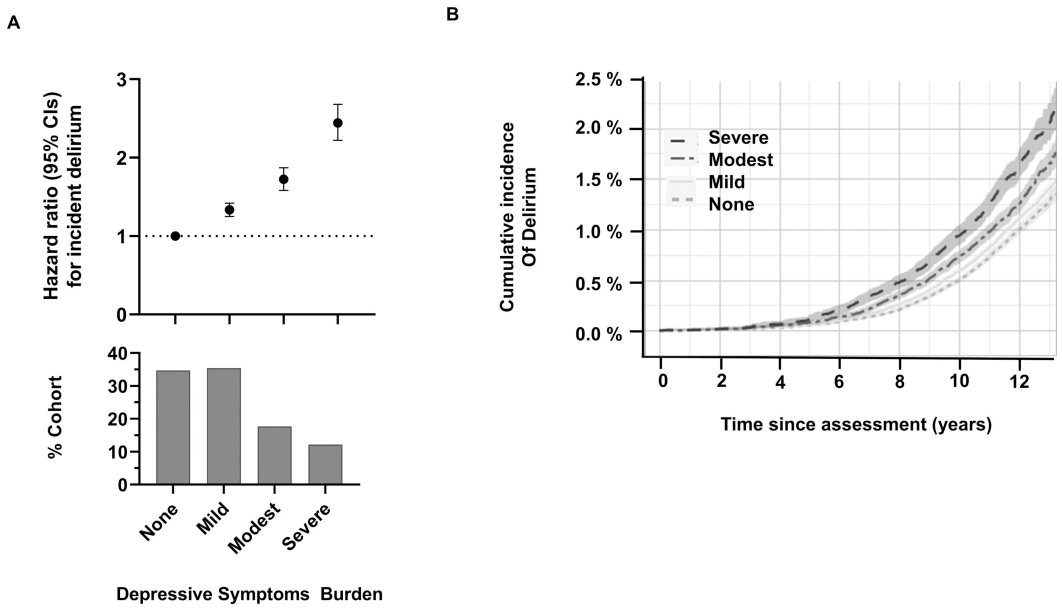

Figure 1. Depressive symptoms burden groups and risk for incident delirium. (**A**) Unadjusted cumulative incidence plot showing the percentage of the cohort with a first diagnosis of delirium over time, in the 4 depressive symptoms categories (none = 0, mild = 1–2, modest = 3–4, and severe risk = ≥5), based on the depression symptom burden score. Hazard ratios (±95% CI) for incident delirium using Cox proportional hazards regression models adjusted for age, sex, education, and ethnicity, percentage of the cohort by depression symptom burden group in the panel below. (**B**) Cumulative incidence plot showing the percentage of the cohort with a first diagnosis of delirium over time in the 4 depressive symptom burden groups.

Table 2. Depressive Symptoms Burden and Associations with Incident Delirium

Model	All delirium *N* = 5 753		Postoperative delirium *n* = 1 689		Nondementia related *n* = 4 064	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Model A						
Mild	1.30 (1.22–1.38)	<.001	1.29 (1.15–1.45)	<.001	1.34 (1.24–1.44)	<.001
Modest	1.70 (1.58–1.84)	<.001	1.71 (1.48–1.96)	<.001	1.75 (1.60–1.92)	<.001
Severe	2.43 (2.22–2.68)	<.001	2.26 (1.92–2.66)	<.001	2.58 (2.33–2.86)	<.001
Model B						
Mild	1.24 (1.16–1.32)	<.001	1.22 (1.09–1.37)	.0007	1.23 (1.15–1.33)	<.001
Modest	1.44 (1.32–1.57)	<.001	1.50 (1.30–1.73)	<.001	1.45 (1.32–1.60)	<.001
Severe	1.70 (1.53–1.88)	<.001	1.67 (1.40–2.00)	<.001	1.75 (1.56–1.96)	<.001
Model C						
Mild	1.19 (1.11–1.27)	<.001	1.17 (1.04–1.32)	.008	1.18 (1.09–1.27)	<.001
Modest	1.35 (1.24–1.47)	<.001	1.40 (1.21–1.63)	<.001	1.36 (1.24–1.49)	<.001
Severe	1.48 (1.33–1.64)	<.001	1.45 (1.21–1.75)	<.001	1.50 (1.34–1.69)	<.001
Model D						
Mild	1.16 (1.08–1.25)	<.001	1.16 (1.02–1.30)	.02	1.15 (1.07–1.25)	<.001
Modest	1.30 (1.19–1.43)	<.001	1.39 (1.19–1.63)	<.001	1.30 (1.18–1.44)	<.001
Severe	1.38 (1.24–1.55)	<.001	1.44 (1.18–1.75)	<.001	1.44 (1.28–1.62)	<.001

Notes: 95% CI = confidence intervals; HR = hazard ratio.
Cox proportional hazard models examining the association between depressive symptoms groups (with None as reference) and all delirium cases, and subgroups.
Model A: demographics.
Model B: additionally includes Townsend deprivation index, physical activity, alcohol consumption, body mass index, sleep duration, frequency of friend and family visits, and falls.
Model C: cardiovascular risk, morbidity burden, and reaction time.
Model D: dementia/Parkinson's, vitamin D levels, and depression/anxiety diagnosis.

[2.26–2.72], $p < .001$) were all at increased risk for incident delirium. However, greater attenuation was seen for those reporting "depressed mood" and the anhedonia-like question on "unenthusiasm/disinterest" in the final models.

Depression Symptoms Trajectory and Risk for Delirium

In the follow-up cohort of 40 451 participants, 213 (5.3 per 1 000) developed incident delirium (median follow-up

time: 3.8 years [range 11 months to 11.2 years; *SD* 2.7]). The median time from the initial depressive symptoms screening was 8.0 years [range 2.6–13.8 years; *SD* 2.7 years]. After adjusting for demographics, those who reported mild (1.51 [1.12–2.05], $p = .008$), modest (1.74 [1.13–2.67], $p = .01$), and severe (2.80 [1.63–4.80], $p < .001$) depression symptoms were again associated with increased delirium risk when compared to those reported none (Table 3). After adjusting for participant baseline depression symptoms burden score and time-lag, a worsening score (≥1) depression symptoms burden score was associated with an additional 39% increased risk (1.39 [1.03–1.88], $p = .03$; Table 3) compared to those reporting no change/improved score. To mitigate the ceiling effect (those scoring high at baseline have no room for worsening), we tested only those within the none and mild groups (baseline depression score 0–2, 74% of the cohort) and confirmed that a worsening score (≥1), was associated with an increased risk (1.45 [1.04–2.02], $p = .03$, Supplementary Table 3).

Incident Delirium Risk by Subgroups

The risk of delirium was further examined by age (<65 years/≥65 years), sex, physical activity (lower/higher), morbidity burden, depression, reaction time, and sleep duration (Figure 2). Comparing participants with modest/severe versus no depressive symptoms, those aged ≥65 years were more strongly associated with delirium risk (1.70 [1.56–1.86]) compared to participants aged <65 years (1.36 [1.24–1.48]) p for interaction <.001. Similarly, patients without a depression diagnosis were more strongly associated (1.65 [1.54–1.76]) compared to those with diagnosed depression (1.29 [1.07–1.54]), p for interaction <.001. Depression symptom burden was equally predictive in men and women, those with above-average and below-average physical activity, morbidity risk, reaction times, and nighttime sleep duration.

Table 3. Follow-up Depressive Symptoms Burden, Trajectory, and Risk for Delirium

Depression symptom burden	*N* (%)	HR (95% CI)	*p* Value
Depressive symptoms burden follow-up (213 delirium cases)			
Score (0–12)*	40 451	1.16 (1.09–1.24)	<.001
None	18 122 (45%)	Ref.	Ref.
Mild	14 774 (36%)	1.51 (1.12–2.05)	.008
Modest	5 172 (13%)	1.74 (1.13–2.67)	.01
Severe	2 383 (6%)	2.80 (1.63–4.80)	<.001
Depressive symptoms burden trajectory (213 delirium cases)			
No change/ improved (0)	28 494 (75%)	Ref.	Ref.
Worsening (≥1)	9 650 (25%)	1.39 (1.03–1.88)	.03

Notes: Cox proportional hazard models for follow-up depression symptom assessment and risk for delirium. "Score" is the continuous symptom score. *Per 1-point increase. Subsequent groups are comparing recent depressive symptoms score groups against the reference group, "None," for all delirium cases using Model A, the core model adjusting for demographics (age, sex, education, ethnic background, and number of hospitalizations). *Ref.* reference category.

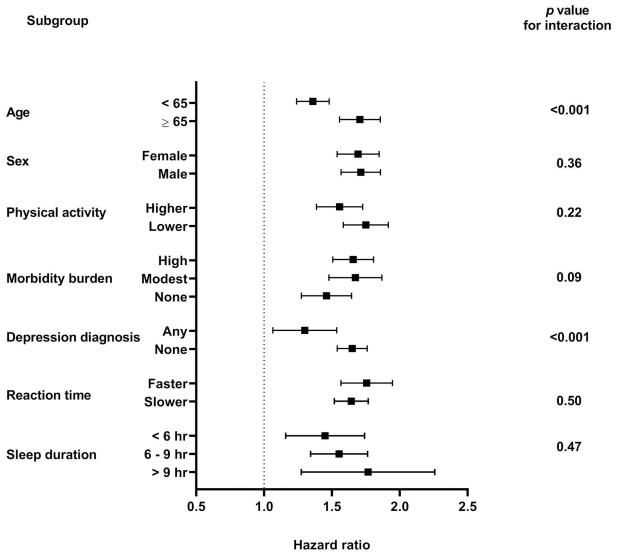

Figure 2. Forrest plot of hazard ratios and 95% confidence intervals for modest/severe depression symptoms burden (vs none/mild) predicting incident delirium based on subgroups of participants by age, sex, physical activity, morbidity burden, diagnosed depression, reaction time, and night-time sleep duration.

Discussion and Implications

Our study of 319 141 community-based UK Biobank participants found that those reporting mild, modest, and severe depression symptom burden were at 16%, 30%, and 38% higher risk for developing hospital-diagnosed delirium over a median 12 years of follow-up when compared to those reporting none. The findings were consistent for POD and after the exclusion of underlying dementia, our main secondary analysis. In nonpostoperative and critical care settings, these results remained consistent. Further sensitivity analysis of consulting/admitting specialty demonstrated that depressive symptoms were equally associated with incident delirium in neuropsychiatric, cardiorespiratory, or other admissions. More recent reporting in a smaller follow-up cohort of 40 451 confirmed the association between depression symptoms and delirium risk; in fact, those reporting worsened depression symptom trajectory were at an additional 39% risk. The association was strongest when depression symptoms were reported after the age of 65 years and in individuals without a history of depression/anxiety.

These findings are consistent with prior work showing that psychiatric well-being measures reliably predict delirium development (11,33). Specifically, POD is more likely in those with baseline depression and depressive symptoms (10,34,35). Dysphoric mood and hopelessness, as components of depression symptoms, also increased the risk for delirium (33). Although all components/questions drove these results, interestingly, tenseness/restlessness and tiredness/lethargy were most strongly associated with delirium in the final models, suggesting that the full spectrum of depression and anxiety-related symptoms reported should be considered (9). The simplicity of the assessment questions captured responses on a large scale, allowing for repeated measures and examining symptom trajectory. Consistent results across 2 separate time points and the additional risk from worsening symptoms support the idea that depression may increase neurocognitive vulnerability to stressors such as illness, surgery, or

hospitalization rather than simply being comorbid with delirium. If replicated, these findings suggest the need for optimizing depression symptom burden in older adults, separately or as part of established multicomponent delirium bundles. For example, despite consistency in our findings across hospitalization settings (Supplementary Figure 2), there is a window of opportunity before major surgery to intervene (9), given that delirium is growing in an aging population with exponential increases in surgical needs (36). Possible interventions that may prove to be efficacious prior to surgery are formal evaluation for psychiatric conditions if indicated by preliminary questionnaire results, and timely treatment with psychotropic medications to reduce the incidence of POD (37,38).

Whether these results point to a causal role or an unmasking of cognitive vulnerability is unclear. Underlying diseases linked to depressive symptomatology may contribute, despite being included in our models. Dementia is commonly comorbid with both delirium and depression (6,14). Neurophysiological disturbances in delirium include aberrations in monoamine neurotransmission and the imbalance of dopaminergic and cholinergic signaling (39). Twin studies have found an association between the serotonin 2A receptor gene promoter A/A genotype and depression in older men (40). Although late-life depression is associated with Alzheimer's dementia, causal links have not been established (41). Other mechanisms include shared vulnerability to inflammation after illness or surgery and the impact on the aging brain and the endocrine system. Elevated endogenous cortisol levels have been observed for depression and in patients with severe dementia and delirium (42,43), and implicated in delirium pathophysiology (44,45). Finally, depression and dementia are often accompanied by sleep and circadian disruptions (46,47). In this study, differences in sleep duration did not modify the association between depression symptoms and delirium. Fluctuations of symptoms and intensity of delirium suggest an altered circadian rhythm (48). Recent evidence also indicates that circadian disturbances predispose to delirium (29), suggesting a bidirectional relationship. In this study, we accounted for sleep duration, and the association between depression symptom burden and delirium remained after controlling for known dementia and excluding preexisting dementia (or "delirium superimposed on dementia" cases). However, the interplay between depression, sleep/circadian health, and delirium risk in the older population is an emerging area of interest (49,50).

The association between delirium and depression symptom burden (significant vs mild/none) was strongest in older participants over 65 years (vs <65 years) and in those *without* a depression diagnosis (vs those with). Although age is one of the strongest independent risk factors for developing delirium, this suggests that concurrent depression burden is even more important to identify in older persons when preventing delirium. One interpretation is that cognitive impairment was underreported in the older cohort and not adequately controlled. Another possibility is that the temporal burden of depression symptoms, which may have been undertreated or underrecognized in those over 65, was not accounted for. This could also apply to participants without a formal diagnosis of depression but still reported significant symptoms, which may have been left untreated, leading to greater delirium vulnerability. Our findings of an increased risk in those with a worsening trajectory of depression symptoms support the latter. Unfortunately, details on treatments were not available in this study. Screening questions in this study may be more sensitive in detecting symptoms in patricians without a diagnosis. Although caution is needed, these results emphasize the importance of addressing older adults' psychiatric well-being, even in the absence of depression/anxiety diagnosis, to enhance neurocognitive reserve in response to acute illness or major surgical procedures. Depressive symptoms should not be regarded as a normal response to aging, as they have neurocognitive consequences (51).

Strengths of this study include large sample size, long prospective follow-up, and repeat assessment. The sample sizes dedicated to delirium are also uniquely large (52). However, there are several limitations. UK Biobank participants are mostly Caucasian of European descent and may have healthier behaviors than the general UK population. This may underestimate the associations since participants agreeing to participate may have healthier habits, fewer comorbidities, and lower rates of psychiatric burden and delirium. For example, the interpretation of dysphoria and other aspects of psychiatric well-being may vary across different ethnicities and socioeconomic backgrounds, cautioning against extrapolating these findings to populations outside this specific demographic. In contrast to this, prior work has shown that risk factor associations in the UK Biobank are generalizable (53).

The questionnaire items were selected by a UK Biobank working group consensus of experts that needed to balance broad utility with low patient burden given the large sample size (54). This study employed a brief rating scale using 4 items related to the patient health questionnaire to assess psychiatric well-being (6,7,34,55,56). The simplicity allows faster assessment on a large scale, but it is not a complete evaluation. The repeat assessment for depression symptom trajectory is limited in power and subject to selection bias in those who agreed to be reassessed. Furthermore, follow-up trajectories may be affected by ceiling and floor effects (eg, quantifying changes in individuals with none or maximum depression symptom burden at baseline is not possible with our fixed scale). Unfortunately, there was no suitable medication use information in our analyses. The UK Biobank does have a self-reported baseline medication use data set, but it remains free-text/uncoded, with over a quarter of participants missing. A complete list of properly coded medications during each hospitalization and delirium diagnosis would have been clinically useful, but it was also unavailable. Given that, earlier, we decided not to include medication use at baseline. Further work by the UK Biobank and our group is planned to process the data for analysis in future studies.

We controlled a wide range of confounders and stratified by subgroups. Still, there is likely residual confounding in the described relationships, given the complex nature of depression symptomatology and heterogeneity of delirium. Although we were able to adjust our models for 1 cognitive test, UK Biobank does not have other cognitive measurements, such as the MiniMental State Examination. We cannot exclude the possibility that many with delirium had undiagnosed cognitive impairment that we could not adjust for. Those with subclinical depression and depressive symptoms may have had maladaptive behaviors and consequences (eg, poor stress tolerance, coping strategies, the higher chance of future substance use, and lack of social support), increasing opportunities for delirium via increased hospitalization numbers or presenting diagnoses more likely to precipitate delirium even when controlling for a number of hospitalizations

during follow-up. Given the potential relationship of those confounding factors with our exposure (ie, depression), we grouped participants by admitting specialty physician/primary team as a proxy for admitting diagnosis (neuropsychiatric and cardiorespiratory) and hospitalization setting (postoperative, nonoperative, and critical).

Carefully designed longitudinal studies tracking depression/anxiety symptoms before hospitalization—for example, a planned, elective major surgery—would help to confirm our observed link between depression symptoms and delirium. On the other hand, our multivariable-adjusted models may have accounted for covariates that could be on the causal pathway—for example, physical activity and alcohol/substance use. Changes in these factors, driven by depression symptoms, can potentially affect delirium risk. Therefore, the results may underestimate the true strength of the relationship. Finally, clinical data in the UK Biobank cohort were limited to ICD coding. Others have used this approach for delirium (19), within this cohort and are highly specific (up to 96%) for delirium (57), but the sensitivity is low–modest at best (6%–56% in recent studies) (57,58). In a previous study, the pairing of ICD coding for delirium with the use of antipsychotic coding was associated with sensitivity as low as 6% (30% sensitivity overall) while maintaining 100% specificity, better detection of severe delirium (73% sensitivity), mixed and hyperactive subtypes (64% sensitivity) (59). The accuracy and completeness of the ICD data available are variable, as criteria-based diagnoses such as delirium rely heavily on clinical observation and protocols. The willingness to make diagnoses and specific disease labeling may change over time. Specific to delirium, barriers include difficulty experienced with delirium screening and identification, screening tool challenges, cultural barriers, and clinical workload (60). We are likely missing many delirium cases during hospitalization in the UK Biobank, contributing to nondifferential classification errors. Although the direction of the association is not considered to be affected, this error may bias the magnitude of the association toward the null hypothesis (61,62).

Our findings provide evidence bridging psychiatric well-being and delirium prevention. Because depression symptoms are modifiable and a noncognitive proxy for resilience to inciting stressors before delirium, it may prove useful for neurological risk stratification alongside traditional risk factors. Additional work is required to determine the underlying mechanisms and whether a causal relationship exists before focusing on screening and treatment. Future work would benefit from examining preoperative psychotherapeutic and behavioral interventions, antidepressants, anxiolytics, or other psychotropic medications in high-risk patients, to optimize neurologic health prior to elective surgeries.

Supplementary Material

Supplementary data are available at *Innovation in Aging* online.

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Conflict of Interest

None.

Data Availability

Data are available from the UK Biobank after submitting an application at https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access. The syntax for conducting the analysis will be provided to UK Biobank and will be freely available to any other researchers upon reasonable request. The conducted research was not preregistered with an analysis plan in an independent, institutional registry.

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Author Contributions

Conception and design of the study: Gaba, Li, Hu, and Gao Lei. Acquisition and analysis of data: Gaba, Li, Zheng, Hu, and Gao Lei. Drafting a significant portion of the manuscript or figures: Gaba, Li, Gao Chenlu, Cai Ruixue, Kun Hu, and Gao Lei.

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