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## Depression, Posttraumatic Stress Disorder, and Functional Disability in Survivors of Critical Illness: results from the BRAIN ICU (Bringing to light the Risk Factors And Incidence of Neuropsychological dysfunction in ICU survivors) Investigation: A Longitudinal Cohort Study

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## Abstract

**Background**—Critical illness is associated with cognitive impairment, but mental health and functional disabilities in general intensive care unit (ICU) survivors are inadequately characterized and there are a paucity of data regarding the relationship between age and delirium and these outcomes.

**Methods**—In this prospective, multisite cohort study, we enrolled medical/surgical ICU patients with respiratory failure or shock, collected detailed demographics and in-hospital variables, and assessed survivors at 3 and 12 months with measures of depression, posttraumatic stress disorder (PTSD) and functional disability. We used linear and proportional odds logistic regression to examine the independent associations between age and delirium duration versus mental health and functional disabilities.

**Findings**—We enrolled 821 patients with a median (interquartile range) age of 61 (51, 71), assessing 448 patients and 382 patients 3 and 12 months after discharge. At 3- and 12-month follow-up, 37% (149/407) and 33% (116/347) of subjects reported at least mild depression, driven primarily by somatic rather than cognitive symptoms. Depressive symptoms were common even among those with no proxy reported history of depression, reported at 3- and 12-month follow-up by 30% (76/255) and 29% (62/217) of these individuals. At either follow-up assessment, only 7% (27/415, 24/361) of subjects had symptoms consistent with PTSD. Disabilities in basic activities of daily living (ADLs) and instrumental activities of daily living (IADLs) were present in 32% (139/428) and 26% (108/422) of individuals at 3 months and in 27% (102/374) and 23% (87/372) at 12 months. Mental health and functional difficulties were prevalent in young and old patients. Although older age was frequently associated with mental health and functional disabilities, no consistent association was observed between delirium and these outcomes.

**Interpretation**—In contrast with early single-center reports, data from this large, multicenter investigation reveal depression is much more common than PTSD after critical illness and is driven by somatic symptoms indicative of physical disabilities rather than by cognitive symptoms. Poor mental health and functional disability were common, and persistent in up to a quarter of patients.

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## Introduction

Well over 5 million individuals are admitted to medical/surgical critical care units in North America annually and approximately 80% survive – more than are diagnosed annually with cancer.<sup>1, 2</sup> For them, critical illness may be a gateway to Post-Intensive Care Syndrome (PICS)<sup>3</sup> – cognitive impairment, depression, post-traumatic stress disorder (PTSD), functional disabilities and quality of life decrements.<sup>4-9</sup>

The aforementioned outcomes have been studied in specialized critically ill populations (e.g., sepsis and Acute Respiratory Distress Syndrome - ARDS), typically with individuals of a narrow age range (preventing an understanding of whether these outcomes differ in young versus old patients), yet they have rarely been evaluated in general medical and general surgical intensive care unit cohorts.<sup>10,11</sup> Depression has been observed in a third of survivors of ARDS, but the precise nature of their symptoms or those of medical and surgical intensive care unit (ICU) survivors is unknown.<sup>4</sup> Select studies have reported PTSD symptoms in up to half of survivors of critical illness, yet PTSD prevalence using Diagnostic and Statistical Manual (DSM) criteria in general medical and surgical populations is also unknown, particularly in the context of critical illness as a traumatic stressor.<sup>5</sup> Functional disability in critical care survivors beyond ARDS is poorly understood, though it has been evaluated in some other specific contexts (e.g. septic patients).<sup>12</sup> Lastly, few investigations have explored ICU delirium—a potentially *modifiable* risk factor—in the emergence of mental health and functional difficulties.<sup>4, 5,13</sup>

We undertook this investigation for 3 reasons. First, in a *general* ICU population, we wanted to characterize mental health outcomes and functional disabilities and explore the hypothesis that depressive symptoms after discharge are more somatic than cognitive. Secondly, we wanted to study the effects of age across outcomes, testing the hypothesis that younger patients experience symptoms of depression, PTSD, and functional disability similarly to those of older patients at 3 and 12 months. Finally, we sought to determine if delirium is a risk factor for poor mental health and functional outcomes at 3 and 12-month follow-up, testing the hypothesis that delirium is associated with depression, PTSD, and functional disabilities.

## Methods

### Patients and Setting

This institutional review board (IRB) approved prospective observational cohort (NCT00392795) study screened patients in the ICUs at Vanderbilt University Medical Center and Saint Thomas Hospital in Nashville, Tennessee. We included adults admitted to medical/surgical ICUs with respiratory failure, cardiogenic shock, or septic shock. We excluded individuals mechanically ventilated at any time two months before the current ICU admission, spent >5 days in an ICU during the month before the current ICU admission, or spent >72 hours with organ dysfunction in the current ICU admission, and individuals with significant preexisting cognitive impairment identified using the Short Informant Questionnaire on Cognitive Decline in the Elderly [IQCODE]<sup>14</sup> and the Clinical Dementia Rating [CDR] Scale.<sup>15</sup> Specifically, patients who were suspected to have preexisting cognitive impairment on the basis of a score of 3.3 or more on the Short Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE; on a scale from 1.0 to 5.0, with 5.0 indicating severe cognitive impairment) were assessed by certified evaluators with the use of the Clinical Dementia Rating (CDR) scale (with scores ranging from 0 to 3.0, and higher scores indicating more severe dementia). Patients with a CDR score of more than 2.0 (moderate dementia) were excluded.<sup>11</sup> We additionally excluded individuals at high risk for preexisting cognitive deficits owing with neurodegenerative disease, recent cardiac surgery

(within the past 3 months), or suspected anoxic injury; blindness, deafness, or non-English speaking; individuals for whom follow-up would be difficult due to substance abuse, psychosis, homelessness, or residence > 200 miles from Nashville; those unlikely to survive 24 hours; and those for whom informed consent could not be obtained. Informed consent was obtained from patients or their healthcare proxy (hereafter referred to simply as “proxy”); if consent was initially obtained from a proxy, the patient provided informed consent when mentally competent. The index presentation of data from this BRAIN-ICU study included cognitive outcomes but did not contain any mental health, functional or quality of life outcomes.<sup>11</sup> All of the data presented in this manuscript other than demographics and in-hospital descriptive data are original – i.e. they have not been previously published.

We collected baseline patient characteristics: age, preexisting cognitive impairment,<sup>14</sup> history of proxy reported depression and other mental health illnesses (using questions that inquired about whether a patient had ever been diagnosed with specific psychiatric conditions by a healthcare professional), education, activities of daily living and instrumental activities of daily living (IADLs) at enrollment using the Katz Activities of Daily Living (ADL)<sup>16</sup> and Pfeffer Functional Activities Questionnaire<sup>17</sup> (FAQ) questionnaires (completed by a proxy), illness severity using the Acute Physiology and Chronic Health Evaluation (APACHE) II score,<sup>18</sup> comorbidities using the Charlson Comorbidity Index<sup>19</sup> and admission diagnoses. Up to 30 days while in the hospital, we evaluated patients twice daily in the ICU and once daily in the wards, assessing level of consciousness using the Richmond Agitation-Sedation Scale (RASS)<sup>20</sup> and delirium using the Confusion Assessment Method for the ICU (CAM-ICU).<sup>21</sup> Patients were delirious if they were responsive to verbal stimuli (RASS -3 or more alert) and CAM-ICU positive.<sup>21</sup> Patients were comatose if they were unresponsive to verbal stimuli (RASS -4 or -5). Data on ongoing organ dysfunctions via the Sequential Organ Failure Assessment score (SOFA),<sup>22</sup> severe sepsis, and vital signs were collected daily through ICU discharge. Throughout the hospitalization, we collected information about sedative and analgesic exposure from the medication administration record.

At 3 and 12 months (+/-1 month) after hospital discharge, a doctoral level neuropsychologist or masters level professional assessed patients using a battery including: 1) the Beck Depression Inventory-II (BDI-II),<sup>23</sup> 2) the Post-Traumatic Stress Checklist – Specific Version (PCL-S),<sup>24</sup> 3) the Katz Activities of Daily Living (ADL) Scale,<sup>16</sup> 4) the Pfeffer Functional Activities Questionnaire (FAQ), assessing IADLs<sup>17</sup> and 5) the Short Form-36 (SF-36) Health Survey – Mental Component Score (MCS) and Physical Component Score (PCS), assessing quality of life<sup>25</sup> (see Table 1). On the BDI-II, we characterized depressive symptoms as either cognitive or somatic, following the approach of test developers, Beck and Steer.<sup>26</sup> On the PCL-S, we used an item mapping approach to determine if individuals met the DSM-IV criteria for PTSD<sup>27</sup> (described in the *footnotes* of Table 1).

### Statistical Analysis/Covariates

Continuous data are presented as medians and interquartile ranges; categorical variables are presented as frequencies and proportions. In addition to descriptive data, we sought to

determine whether age and delirium duration were independent risk factors for our key outcomes. Delirium duration was calculated as the number of days a patient was CAM-ICU positive during the 30-day study period. Simple imputation was used for missing delirium and coma evaluations (3% of all assessments) – for example, on the few days with missing data, we took a random draw from the patient's mean mental status conditioned on his or her status on the days immediately prior to and after the missing day in the computations. We used multiple imputation to assign values to missing risk factors and outcomes in regression modeling and to reduce potential bias resulting from loss to follow-up, a conservative approach. In the imputation, we included all covariates used in the models as well as other variables which might predict missingness (including additional information on hospital illness, such as worst severity of illness and time on the ventilator, or cognitive and HRQL test scores from non-missing follow-up data). We again used the `aregImpute` function provided in R's `Hmisc` library, which is an approximation to full Bayesian multiple imputation procedures using the bootstrap. We specified ten imputations in `aregImpute` and used the results in conjunction with the `fit.mult.impute` function, also in `Hmisc`, which replaces individual model coefficient vectors with the average of all coefficient estimates and creates an imputation-corrected variance-covariance matrix. We specified five imputations in `fit.mult.impute`. The method we used in multiple imputation is thought to be valid under MAR.<sup>28</sup> We did not, however, impute data for patients who had no mental health and functional data (e.g., due to death or withdrawal). We used R version 3.0.1 for all analyses.

Outcome variables were: BDI-II, PCL-S, Katz ADL, FAQ and SF-36 physical component scores (PCS) and mental component scores (MCS). Since missing data are rarely random and patients who had partial missing outcome data were different from those with complete data, we used multiple imputation during modeling to reduce bias.<sup>28</sup> Model covariates were chosen *a priori* as potential confounders, i.e., they had known or suspected relationships with both the independent and outcome variables. Covariates included age, education level, Short IQCODE,<sup>14</sup> depression and other mental health illnesses history, baseline ADL,<sup>16</sup> baseline Charlson Comorbidities Index,<sup>19</sup> cerebrovascular disease burden via the Framingham Stroke Risk Profile,<sup>29</sup> mean modified SOFA score (using RASS rather than GCS scores) over ICU duration,<sup>22</sup> duration of severe sepsis and coma, episodes of hypoxemia, and mean daily doses of benzodiazepines, propofol, dexmedetomidine, opiates and haloperidol.

We used multivariable regression models to study the independent association of age and delirium duration with functional and mental health outcomes, using separate models for 3- and 12-month time points. SF-36 PCS and MCS were normally distributed, and we used linear regression for these outcomes. Because all other outcomes were not normally distributed and assumptions for linear regression would not be satisfied, we used proportional odds logistic regression for all other models. In all models, drug doses were transformed with the use of their cube root to reduce the influence of extreme outliers, and continuous variables were modeled with the use of restricted cubic splines to allow for nonlinear associations (with the exception of dexmedetomidine and haloperidol doses, used so infrequently that the number of unique doses was too small for splines). We examined

model diagnostics, using residual plots versus predicted plots and quantile-quantile plots for linear regression models and graphically examining the proportional odds assumption for proportional odds logistic regression models. All model assumptions were met adequately. Variance inflation due to multiple imputation was not problematic.

Prior to initiation of the BRAIN-ICU study, we developed formal estimates with regard to enrollment and generated sample size and power analysis calculations based on 12-month follow-up. We anticipated enrolling 800 subjects in the study and assessing 320 at 12 month follow-up; we calculated *a priori* that the assessment of 285 patients at 12 month follow-up would provide us at least 80% power to answer key questions of interest related to the association between the primary risk factor of interest (delirium) and mental health, functional, and quality of life outcomes.

The sponsor of the study had no role in study design, data collection, analysis, or interpretation, or paper writing. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Between March 1, 2007 and June 30, 2010, we enrolled 826 patients. Five withdrew consent and permission to use collected data; thus, we had 821 patients with in-hospital data and assessments. Between enrollment and the 3-month follow-up, 252 patients (31%) died; 448 of the 569 surviving patients (79%) participated in follow-up testing 3 months after discharge. Another 59 patients (7% of the original cohort) died before the 12-month follow-up, and 382 of the 510 remaining survivors (75%) were tested 12 months after discharge. For a full description of details to enrollment, reasons for loss to follow-up, death, and withdrawals, refer to our CONSORT diagram (Appendix, Supplemental Figure - SF1).<sup>11</sup>

The enrolled 821 patients had a median age of 61 years and high severity of illness (median APACHE II score of 25). Only 6% (51/821) of patients had preexisting cognitive impairment (score of 3.6 or greater on the Short IQCODE or medical history). Demographic data and descriptive data for all patients that had assessments at either follow-up time points are presented in Table 2. Of the outcomes assessed at 3 and 12 month follow-up (BDI-II, PCL-S, Katz ADL, FAQ, SF-36 PCS and MCS) complete data were obtained in at least 91% of patients (408/448 at 3 month follow-up and 347/382 at 12 month follow-up). (Appendix, Supplemental Table - ST1). Small but potentially meaningful differences were observed with regard to specific baseline and enrollment characteristics between those with and without complete outcome data. Individuals with partial HRQL outcomes had poorer proxy reported ADL and IADL functioning at enrollment and had higher Framingham stroke risk scores (ST2). Additionally, they were older and were more likely to experience delirium. The median age of patients with complete vs. partial outcomes data was 64 (IQR of 51, 72) vs. 49 (48, 68) and delirium occurred in 74% (282/383) of individuals with complete outcomes data vs. 83% (70/84), respectively (ST2). For a description of additional characteristics of those with complete versus partial outcomes data, refer to ST3-ST4).



## Mental Health Outcomes (Depression and PTSD)

### Depression

A total of 37% (149/407) and 33% (116/347) of respondents reported at least mild depressive symptoms (BDI-II >13) at 3 and 12 month follow-up respectively (Table 3). Mild and moderate symptoms were similarly prevalent at 3 months and 12 months and severe depressive symptoms were relatively uncommon (Table 3). Depressive symptoms existed among both younger and older patients (Figure, *for an additional presentation of outcome data across ages ranges in histogram form, refer to SF2, in the Appendix*). At 3-month follow-up, BDI-II scores >13 were present in 52% (71/137) of patients with a reported depression history and 30% (76/255) without such a history. At 12-month follow-up, BDI-II scores > 13 were present in 43% (49/115) and 29% (62/217) of those with and without a reported history of depression. Among the 117 patients reporting depressive symptoms at 3 months with 12 month data, 73 (62%) had depressive symptoms at 12 months. Only 15% (30/200) of those without depressive symptoms at initial follow-up displayed such symptoms at 12 months; in only 2% (3/200) of individuals with no depression at 3 months were depressive symptoms severe at 12 months. In contrast, 80% (20/25) of those with severe depression at 3 months had symptoms of depression at 12 month follow-up, though depression at 12 months was severe in only 36% (9/25) of patients with severe depression at 3 months.

### Somatic versus Cognitive Depression Criteria

Even though somatic items account for only 21 of 63 points on the BDI-II, test scores on the BDI-II were much higher on the somatic than the cognitive/affective scale at 3 [8.0 (5.0, 13.0) vs. 2.0 (0.0 vs. 4.0)] and 12 months; [8.0 (4.0, 13.0) vs. 1.0 (0.0, 5.0)](Table 3). Among the 149 patients with at least mild depression at 3 months, 66% (99/149 patients) would have met criteria for depression based entirely on the 7 items comprising the somatic subscale, while only 8% (12/149 patients) would have met criteria based entirely on the cognitive-affective subscale. Among the 116 patients with at least mild depression at 12 months, 72% (83/116 patients) would have met depression criteria based only on the somatic items and 4% (5/116 patients) would have met criteria using only cognitive-affective items.

### PTSD

At both 3- and 12-month follow-up, 7% (27/415 and 24/361) of individuals had probable critical illness-related PTSD, using PCL-S scoring criteria based on the DSM-IV (see footnote Table 1).<sup>25</sup> Clinically significant elevations on the PCL-S were rare (Figure), with 3% (13/415) of respondents scoring >50 at 3 month follow-up and 3% (10/361) at 12 month follow-up (Figure).

**Co-Morbid Depression and PTSD**—A total of 6% of patients had symptoms of both depression and PTSD at both 3 (23/404) and 12 months (21/346) (BDI-II >13 and PCL-S DSM-IV defined criteria). Among patients with severe depression (BDI-II >29), 25% (9/36) had PTSD symptoms at 3 months and 42% (10/24) had PTSD symptoms at 12 months. Of

the 251 patients without depression at 3 months, only two had symptoms of PTSD; at 12 months, only 1 patient out of 231 had PTSD without depression.

## Functional Status (ADL and IADL) and Health-Related Quality of Life (HRQL)

At least partial ADL disability (>0 on the Katz ADL), was seen in 32% (139/428) and 27% (102/374) of individuals at 3 and 12 months (Table 3). Among those fully independent at enrollment, at least partial ADL disability was observed in 27% (98/367) and 22% (69/319) of patients at 3- and 12-month follow-up. IADL disability (>8 on the FAQ) was seen in 26% (108/422) and 23% (87/372) of individuals at 3 and 12 months. When comparing patients with and without baseline IADL disability, respectively, we found that 56% (19/34) vs. 23% (87/384) had IADL disability at 3 months follow-up. Similarly at 12 months, 62% (21/34) vs. 20% (66/333) had IADL disability among those with and without baseline IADL disability.

SF-36 PCS scores were approximately 2 standard deviations below the mean of the general US population of  $50 \pm 10$ , whereas MCS scores were consistent with those reported by general US population (Table 3).

## Age as a Risk Factor for Mental Health and Functional Outcomes

After adjusting for covariates, younger age was associated with a probability of higher scores (worse PTSD) on the PCL-S at 3 and 12-month follow-up (Table 4). Older age was independently associated with a probability of higher BDI-II scores at 12-month follow-up, higher ADL scores at 3-month follow-up, higher FAQ scores at 3 and 12 month follow-up, and lower SF-36 MCS scores at 12-month follow-up (Table 4). No association was observed between age and a variety of other outcomes/time points.

## Delirium as a Risk Factor for Mental Health and Functional Outcomes

At 3 months, no significant associations were observed between delirium duration and depression, PTSD symptoms, ADL, IADLs, or quality of life after adjusting for covariates (Table 4). At 12-month follow-up, longer delirium duration was associated with higher BDI-II scores (i.e., greater depression) and lower SF-36 MCS scores (i.e., worse mental health status) after adjusting for covariates (Table 4). We found no consistent associations between delirium and any other 12 month outcomes, and at neither 3 nor 12 months did we find any consistent associations between sedative and analgesic medications and outcomes.

## Discussion

This large prospective cohort investigation has yielded two main sets of observations related to mental health and functional outcomes in ICU survivors. First, we found that depression was 4 times more frequent than PTSD, and its symptoms were driven dramatically more often by somatic rather than cognitive components. Second, we found that patients in this large cohort (including a substantial number with no previous history of psychiatric treatment per proxy report) demonstrated the presence of mental health and functional



deficits across the entire spectrum of age (although depression, functional disability and mental health quality of life were worse with older age), and we did not observe a consistent relationship between delirium and our long-term outcomes of interest.

Our investigation highlights the finding that depression is substantially more prevalent than PTSD after critical illness, although these conditions are admittedly frequently comorbid as reflected in the fact that in our cohort virtually everyone who had PTSD symptoms also suffered from depression. Our study also suggests that individuals with more severe expressions of depression in the early post-critical illness recovery period (3 months) tend to experience persistent depressive symptoms at 1 year, though symptom severity may decrease slightly. Given our data and the configuration of somatic symptoms (pervasive) versus cognitive-affective symptoms (uncommon) in this population of ICU survivors (an overall difference of at least 5 points on the BDI-II is clinically significant<sup>30</sup> and the difference on somatic and cognitive-affective scales exceeded this), it appears that a significant portion of our “depressed” patients were manifesting symptoms of physical debility. Studies have shown that medically ill individuals with chronic physical problems are misdiagnosed as having depression when their complaints may be illness-driven.<sup>31</sup> Our data support the hypothesis that survivors of critical illness, as in cardiac patients,<sup>32</sup> largely experience depression through somatic complaints (this hypothesis has been previously unexplored in cohorts of survivors of critical illness, perhaps in part because investigators<sup>9,33,34</sup> have frequently used the Hospital Anxiety and Depression Scale – HADS – which does not contain questions about somatic symptoms of depression). Literature to date<sup>4</sup> has focused on risk factors and mechanisms of post-ICU depression mainly in the realm of inflammation or neurotransmitter imbalances with virtually no studies attempting to explicate roles of psychopathology versus physical pathology. These findings are of utmost importance in that somatic depression tends to be resistant to antidepressant medications, which are often frequently used both in the ICU and thereafter.<sup>35</sup> The management of somatically depressed ICU survivors represents an untapped opportunity for non-pharmacological intervention through physical and occupational rehabilitation,<sup>36</sup> although this is a hypothesis in need of further testing.

In the same way that critical illness may be a gateway to the development of dementia-like cognitive impairment<sup>11</sup>, these data support that critical illness is also a gateway to the develop of persistent physical disability that may be a driver of a closely-related somatic-type of depression in the young and the old. Physical disability, reflected in ADL deficits, has been studied widely in individuals after intensive care, but IADL functioning, particularly in general medical and surgical ICU populations has not.<sup>12,37</sup> Using conservative criteria, which potentially underestimate disability rates, we found that a quarter of patients had Pfeffer FAQ scores suggestive of IADL disability and, indeed, the IADL scores in this cohort were significantly worse than individuals with early dementia.<sup>38</sup>

These findings challenge conventional thinking about the prevalence of PTSD. Early studies reported that PTSD occurred in 50% of ICU survivors and more recent reports suggest rates close to 20%,<sup>5</sup> though a few studies done with general critically ill patients have described rates between 5% and 13%.<sup>39,40</sup> We found a 7% rate of PTSD symptoms – lower than was has typically been reported, though this is not to diminish the importance of this malady in

ICU survivors as it is still twice as high as the overall prevalence rates of 3% in the general population.<sup>27</sup> Reasons for the discrepancy could include the larger sample size of our study and inclusion of general ICU patients, as opposed to just one category of ICU illness such as ARDS. Importantly, we identified individuals as having probable PTSD only if they met pertinent DSM-IV criteria (the definitive criteria employed at the time of this investigation). We also asked individuals about symptoms *in reference to the trauma specific to intensive care and critical illness*—an approach different than that used in most ICU studies, although there are a few investigations that have focused explicitly on the critical illness as the traumatic stressor of interest.<sup>39, 40</sup> This approach, while effective in identifying individuals with PTSD symptoms due to critical illness related trauma, likely failed to capture the effects of critical illness on individuals with pre-existing PTSD due to other causes. Evidence suggests that for such individuals, the stress of intensive care and critical illness could exacerbate underlying symptoms. Substantial time and energy been invested in addressing PTSD in survivors of critical illness, yet our findings suggest that among mental health concerns, it is less pervasive than depression. These data suggest at a minimum that for ICU survivors, it is likely in the interest of public health to focus with added emphasis on the prevention and management of depression rather than so pointedly on PTSD, though these conditions often overlap considerably – particularly in the context of high symptom severity - and cannot be optimally studied, treated, or understood in isolation. Indeed, it may be individuals with both severe depression and PTSD who represent the group most pointedly in need of clinical intervention.

Evidence suggests that advanced age confers unique risks for the ability of older adults to recover from critical illness.<sup>41</sup> Whereas older age was a risk factor for depression and functional disability, younger patients were not immune to these outcomes; we found that ADLs and IADLs, usually impaired predominantly in geriatric populations, were affected in both young and middle age patients. Thus, as previously reported among ARDS survivors,<sup>10</sup> functional disability among survivors of critical illness is not only an “old age” problem. These findings have potential implications for those who develop ADL/IADL disability during “working years,” since it may adversely affect an individual’s ability to hold a job or alter their vocational trajectory. Future research is needed to identify interventions that can effectively rehabilitate functional disability, enabling critical illness survivors to return to work and engage in many other activities that are prevented by these disabilities.

Our study had strengths, including reliance on a large, mixed ICU population, and the use of a comprehensive battery comprised on instruments with robust psychometric properties which have been used extensively with medical populations though in some cases their validity has not specifically been studied in survivors of critical illness. The BDI-II, for instance, has not been validated with general medical and general surgical ICU populations but has been validated in other medical cohorts (e.g. cardiac, HIV, chronic fatigue, and general medical patients)<sup>42</sup> and we believe that findings from these validation studies – which highlight the possibility that the BDI-II may slightly overestimate depression prevalence due to its inclusion of somatic items – likely apply to critically ill populations as well.

Our study also had other limitations. We identified pre-existing depression and mental health by asking proxys whether the individual patient in question had *ever* been diagnosed with particular psychiatric conditions of interest and this approach may have resulted in an underestimation of the true prevalence of premorbid depression and related difficulties. It was not feasible to directly observe patient behaviors, thus we relied on self-report measures. In this cohort that has previously been reported as having high levels of newly-acquired cognitive impairment<sup>11</sup>, the duration of delirium was not associated with either disability outcome (i.e., IADL or ADL status), a finding in contrast to disability outcomes in populations with similar levels of cognitive impairment such as mild cognitive impairment and Alzheimer's disease.<sup>43</sup> While in need of further study in survivors of critical illness, the difference in these outcomes could be explained by differing underlying pathologies between these syndromes, the potential for functional disability to be expressed differently in cognitively impaired ICU survivors than individuals with progressive dementia, the neuropsychiatric domains that are impaired, or simply that the data supporting an association between cognition and functional status are conflicting and in some cases modest.<sup>44</sup> At least 2 studies in medically ill cohorts – one in ICU patients<sup>45</sup> and one in patients following surgery<sup>46</sup> – have demonstrated an association between delirium and ADL disability, in contrast to the current study. Reasons for this discrepancy are unclear, though in light of the findings from these two studies – one of them which was quite large<sup>46</sup> – it is possible that the absence of an association between delirium and ADL and IADL functioning in the BRAIN-ICU study reflects a Type II error. Yet another limitation in our investigation is that patients had unplanned critical illnesses that did not allow pre-ICU testing thus, like other studies<sup>10</sup> we relied both on patients and qualifying proxys.

## Conclusion

Depression and PTSD are important mental health problems after significant critical illness, yet our findings reveal that depression is at least 4 times more common than PTSD and largely somatic in nature. This suggests that physical disability<sup>47</sup> contributes predominantly to this depression, which has implications for scientific discovery related to the roles of physical rehabilitation versus anti-depressant medications in the prevention and management of post-ICU depression. Our data further indicate that monitoring these outcomes is relevant for young and old survivors, and that non-pharmacological interventions during the ICU stay<sup>36</sup> previously found to improve physical outcomes in ICU survivors should be tested in terms of their ability to alter mental health and functional outcomes.

## Research In Context

### Systematic Review

No formal systematic review was conducted prior to the initiation of the BRAIN-ICU cohort study. However, we knew from our engagement with relevant literature over the previous decade that little if any evidence existed exploring the association between delirium and long-term mental health and functional outcomes, even as a dearth of information existed – particularly in the context of large cohort studies – related to the prevalence of depression, PTSD, and ADL and IADL functioning in survivors of critical illness. At the time of the BRAIN-ICU's inception, evidence from numerous investigations suggested that significant

depression occurred in approximately a third of survivors of critical illness and that PTSD symptoms impacted between 15% and 50% of individuals following intensive care. None of these investigations focused on determining the relative prevalence of somatic versus cognitive depression symptoms and few evaluated PTSD using instruments oriented to DSM-based diagnostic criteria.

### Interpretation

Our investigation represents one of the largest cohort studies to evaluate wide-ranging mental health and functional outcomes in survivors of critical illness and to explore delirium as a risk factor these outcomes over time. Our results show that depression is more common than PTSD after critical illness and more common than in the general population (where the prevalence of depression is estimated to be ~ 10%) and that it is driven predominantly by somatic rather than cognitive symptoms. These results underscore the importance of addressing mental health difficulties and functional disabilities should be monitored across the age range and that physical and non-pharmacologic interventions may to impact depression symptoms in particular merit further study.

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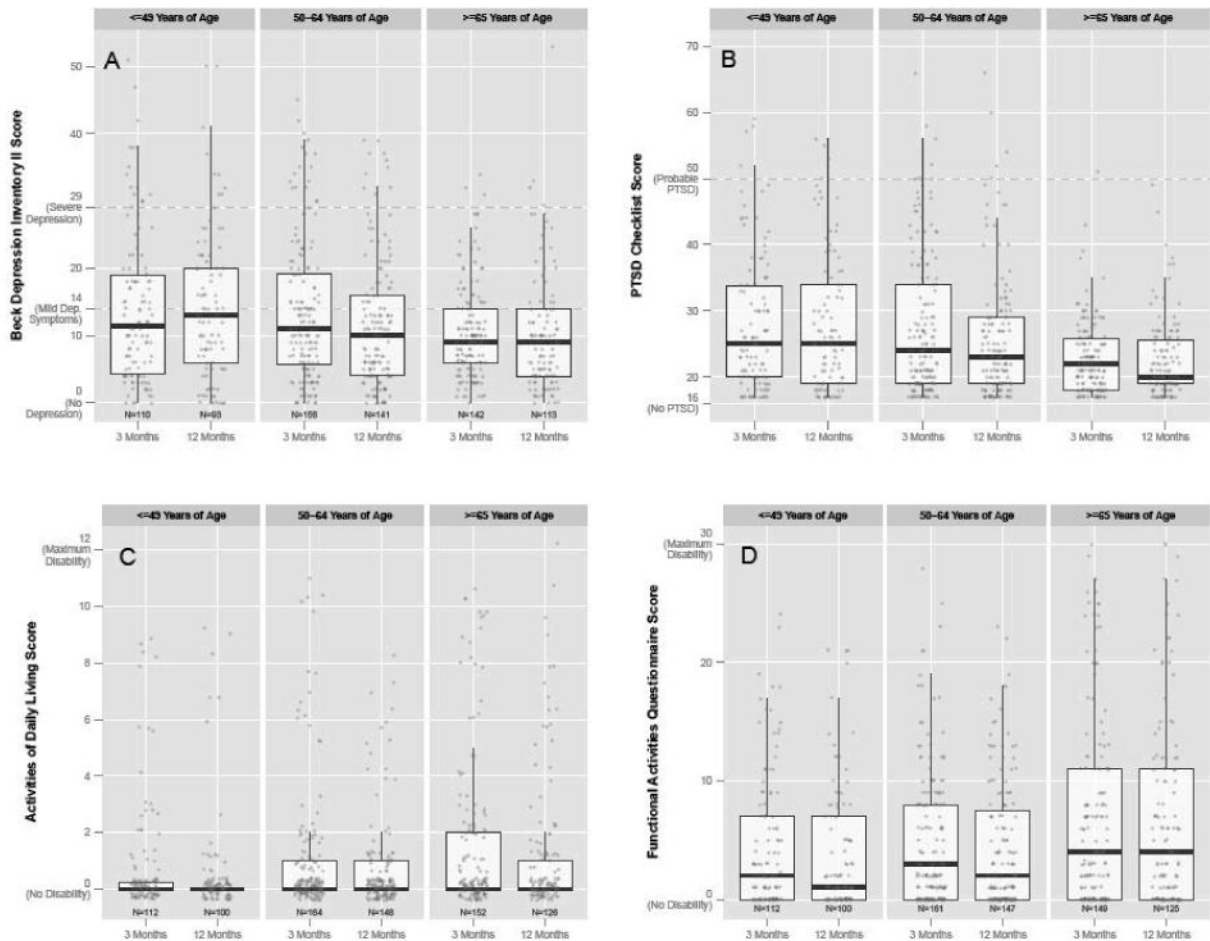
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**Figure. A Comparison of Mental Health and Functional Related Scores by Age at 3 and 12 Months**

This figure displays scores on our 4 primary outcome measures separated by age group (< 49, 50-64, and ≥ 65 years): A) Beck Depression Inventory II (BDI-II), which assesses depressive symptoms; B) PTSD Checklist (PCL), which assesses symptoms of PTSD; C) Katz Activities of Daily Living (ADL), which assesses disability in activities of daily living; and D) Pfeffer Functional Activities Questionnaire (FAQ), which assesses disability in instrumental activities of daily living (IADLs). †Jittering was used to prevent overplotting of equivalent points at integer values.

**Table 1**  
**Description of Follow Up Data**

Test	Description	Area Measured	Scoring
BDI-II <sup>1</sup>	Assesses the presence and severity of depressive symptoms	Depression	21 questions with a range of 1-3 each (total range, 0-63), with scores >13 suggesting depression. Items 1-14 address cognitive/affective symptoms while items 15-21 pertain to somatic symptoms
PCL-S <sup>2</sup>	Assesses the presence and severity of PTSD symptoms	PTSD	DSM-IV- based, 17 questions range of 1-5 each (total range, 17-85), with high scores indicating high likelihood of PTSD
Katz ADL	Assesses basic abilities such as bathing, feeding and transferring	Basic functional abilities	6 questions (total range, 0-18), with high scores indicating dependence
FAQ	Assesses higher order functioning (e.g., managing finances, medications, etc.)	Instrumental Activities of daily living	10 questions with a range of 0-3 each (total range, 0-30), with scores >9 indicating impaired functioning
SF-36	Assesses quality of life and overall functioning across physical and mental health domains	Generic quality of life	36 questions across 8 domains, each with a range of 0-100, with low scores indicating poor quality of life

Definition of abbreviations: ADL = activities of daily living; BDI-II = Beck Depression Inventory – II; FAQ = Functional Activities Questionnaire; PCL-S = Posttraumatic Stress Disorder Checklist, Event Specific Version; SF-36 = Short Form-36.

<sup>1</sup>BDI-II: The BDI-II is comprised of 2 primary factors, cognitive/affective and somatic. Cognitive/affective questions (1-14) pertain to symptoms such as sadness, tearfulness, and feelings of failure; somatic questions (15-21) pertain to symptoms such as loss of energy, changes in appetite, and fatigue.

<sup>2</sup>The PCL-S comprises 17 questions that map onto the Diagnostic and Statistical Manual (DSM)-IV criteria for PTSD (the DSM-IV was the version of the DSM current at the time this study was begun. Questions 1-5 on the PCL map to Criterion B (intrusion symptoms), questions 6-12 map to Criterion C (avoidance), and questions 13-17 map to Criterion D (negative alterations in cognition and mood). All patients met Criterion A (exposed to stressor) since all were survivors of critical illness. We used the mapped DSM-IV criteria as the main determinant of prevalence of PTSD: to be diagnosed with PTSD, patients were required to have at least 1 positive symptom (defined as > 3 on a 5 point scale indicating being moderately affected) from the PCL questions mapping to Criterion B, at least 3 positive symptoms from items correlating to Criterion C, and at least 2 positive symptoms from items matching Criterion D, where “positive” is defined as > 3 on a 5-point scale (indicating being at least moderately affected). We also used a PCL threshold of > 50 as a secondary measure of PTSD symptom prevalence.

**Table 2**  
**Demographic and In-Hospital Data\* ¶**

Variable	In hospital cohort (N=821)	Follow-up cohort (N=467)
Age at enrollment (years)	61 (51, 71)	59 (49, 69)
Caucasian, N (%) <sup>+</sup>	740 (90%)	413 (88%)
Males, N (%)	420 (51%)	234 (50%)
Education (years)	12 (12, 14)	12 (12, 14)
IQCODE at enrollment <sup>±</sup>	3.0 (3.0, 3.1)	3.0 (3.0, 3.1)
History of depression, N (%)	261 (33%)	159 (35%)
History of mental health illness (not depression), N (%)	66 (8%)	44 (10%)
History of ADL disability	229 (29%)	120 (26%)
History of IADL disability	93 (12%)	44 (10%)
Charlson comorbidity score <sup>†</sup>	2 (1,4)	2 (1,4)
Framingham stroke risk	9 (6, 14)	9 (5, 14)
APACHE II Score at enrollment <sup>§</sup>	25 (19, 31)	24 (19, 30)
SOFA Score at enrollment <sup>  </sup>	9 (7, 12)	9 (7, 12)
Admission Diagnosis, N (%)		
Sepsis	244 (30%)	136 (29%)
Acute respiratory failure <sup>††</sup>	135 (16%)	71 (15)
Cardiogenic shock, myocardial ischemia, or arrhythmia	141 (17%)	79 (17%)
Upper-airway obstruction <sup>†††</sup>	87 (11%)	49 (10%)
Gastric/colonic surgery	63 (8%)	29 (6%)
Neurologic disease or seizure	11 (1%)	7 (1%)
Other surgical procedure <sup>††</sup>	82 (10%)	65 (14%)
Other diagnosis	58 (7%)	31 (7%)
ICU Type, N (%)		
Medical ICU	559 (68%)	298 (64%)
Surgical ICU	262 (32%)	169 (36%)
Mechanical ventilation during study period, N (%)	746 (91%)	421 (90%)
Days of mechanical ventilation among exposed to MV	3 (1, 8)	2 (1, 6)
Delirium during study period, N (%)	606 (74%)	352 (75%)
Delirium days among those with delirium	4 (2, 7)	3 (2, 7)
Coma during study period, N (%)	517 (63%)	265 (57%)
Coma days among those with coma	3 (2, 6)	3 (1, 5)
Severe sepsis during study period, N (%)	572 (70%)	297 (64%)
ICU length of stay (days)	5 (3, 11)	5 (3, 10)
Hospital length of stay (days)	10 (6, 17)	10 (6, 18)

Abbreviations: IQCODE, Informant Questionnaire On Cognitive Decline in the Elderly; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, Intensive Care Unit; SOFA, Sequential Organ Failure Score; MV, mechanical ventilation

\* Percentages may not sum to 100, owing to rounding. Of the 821 patients with in-hospital data, 448 patients were assessed at 3 months and 382 patients were assessed at 12 months. Nineteen patients were not assessed at 3 months, but were available at 12 months, making the total number of patients who had follow-up at either one or both time points 467.

<sup>¶</sup> Median (interquartile range) unless otherwise indicated

<sup>+</sup> Race was determined according to the medical record or was reported by the patient's surrogate.

<sup>±</sup> Scores on the Short Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) range from 1 to 5, with a score of 3 indicating no change in cognition over the past 10 years, a score lower than 3 indicating improvement, and a score higher than 3 indicating decline in cognition, as compared with 10 years before. A score of 3.3 or higher indicates an increased probability of cognitive impairment, and a score of 3.6 or higher indicates preexisting cognitive impairment

<sup>†</sup> Scores on the Charlson comorbidity index range from 0 to 33, with higher scores indicating a greater burden of illness; a score of 1 or 2 is associated with mortality of approximately 25% at 10 years.

<sup>§</sup> Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating worse outcomes.

<sup>||</sup> Scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24 (from 0 to 4 for each of six organ systems), with higher scores indicating more severe organ dysfunction. We used a modified SOFA score in our regression models, which excluded the Glasgow Coma Scale components, since coma was included separately in our models.

<sup>††</sup> Acute respiratory failure included the acute respiratory distress syndrome, acute exacerbations of chronic obstructive pulmonary disease or asthma, pulmonary edema, and fibrosis.

<sup>†††</sup> Upper airway obstruction refers to patients with airway swelling or obstruction due to otolaryngeal, tracheal or maxillofacial pathology or surgery, sleep apnea, angioedema, inability to protect airway from secretions, etc.

<sup>†††</sup> Other surgical procedures included hepatobiliary surgery, liver transplantation, and orthopedic, obstetrical or gynecologic, vascular, otolaryngologic, and urologic surgery.

**Table 3**  
**Long-Term Outcomes at 3 and 12 months**

Outcome	3-Month Follow-Up Cohort (N = 448)	12-Month Follow-Up Cohort (N = 382)
Psychological (N/%)		
Depression		
BDI-II (N:407, 347) <sup>×</sup>	10.0 (5.0, 17)	10.0 (4.6, 16.5)
Somatic-affective	8 (5, 13)	8 (4, 13)
Cognitive	2 (0, 4)	1 (0, 5)
No Dep. (0-13)	257 (63%)	231 (67%)
Mild Dep. (14-19)	66 (16%)	43 (12%)
Mod. Dep. (20-28)	47 (12%)	48 (14%)
Severe Dep.(29 <sup>+</sup> )	36 (9%)	25 (7%)
BDI-II (History Dep/No Dep) <sup>*</sup>	14.0 (9, 24) vs. 9.0 (4, 14.8)	12 (5, 22) vs. 9 (4, 15)
BDI-II (History Dep/No Dep)	52% vs. 30%	42% vs. 29%
PTSD		
PCL-S (N:415, 361) <sup>×</sup>	23 (19, 29)	22 (19, 28)
Probable PTSD <sup>+</sup>	27 (7%)	24 (7%)
Functional		
ADLs		
Katz ADL (N:428, 371) <sup>×</sup>	0 (0, 1) N = 428	0 (0, 1) N = 374
Partial disability <sup>±</sup>	139 (32%)	102 (27%)
ADLs (History Dis/No Dis) <sup>∞</sup>	77% vs. 27%	55% vs. 22%
IADLs		
FAQ (N:422, 372) <sup>×</sup>	3 (0, 9)	2 (0, 8)
Functional Disability <sup>§</sup>		
FAQ (History Dis./No Dis) <sup>£</sup>	9.5 (7.0, 16.8) vs. 2.2 (0.0, 8.0)	10 (6.0, 14.0) vs. 2.0 (0.0, 7.0)
Functional Disability (History of Dis/No Dis) <sup>β</sup>	56% vs. 23%	62% vs. 20%
Quality of Life		
SF-36 (N:416, 361) <sup>×</sup>		
Mental Component	56 (40, 62)	55 (45,60)
Physical Component	29 (22, 38)	32 (25, 43)

<sup>×</sup> refers to the total N for the patients who completed these assessments at 3 and 12 months, reflecting the fact that a small percentage of patients did not complete every test in the battery at each follow-up time point.

<sup>\*</sup> BDI-II (History Dep/No Dep) refers to % with at least mild depression symptoms by baseline depression status versus no depression symptoms at baseline.

<sup>+</sup> - Probable PTSD was defined as at least 1 positive symptom (defined as > 3 on a 5 point scale indicating being "moderately affected") from the PCL-S questions mapping on to Criterion B, at least 3 positive symptoms mapping on to Criterion C, and at least 2 positive symptoms from items mapping onto Criterion D,

<sup>±</sup> - At least partial disability in activities of daily living is defined as a score of >0 on 1 of 6 ADL items.

$\infty$  - ADLs (History Dis/No Dis) refers to % of individuals with at least partial disability among those with a baseline history of at least partial disability (dependence) vs. those with no disability (dependence).

$\S$  - Functional disability was defined as score of  $>9$  on the FAQ.

$\pounds$  - FAQ (History Dis./No Dis) refers to FAQ scores by baseline functional status (disability vs. no disability)

$\beta$  - Functional Disability (History of Dis/No Dis) refers to % functional disability by baseline functional status (disability vs. no disability).



**Table 4**  
**Effect of Duration of Delirium on Mental Health and Functional Outcomes**

<b>Delirium: 25th percentile (0 delirium days) vs. 75th percentile (5 delirium days)</b>				
<b>Outcome</b>	<b>3 Mo F/Up</b>	<b>P Value</b>	<b>12 Mo F/Up</b>	<b>P Value</b>
BDI-II <sup>‡</sup>	1.63 (0.94 to 2.85)	0.38	2.31 (1.25 to 4.27)	0.05
PCL-S <sup>‡</sup>	1.39 (0.78 to 2.47)	0.59	1.92 (1.03 to 3.55)	0.18
Katz ADL <sup>‡</sup>	1.50 (0.63 to 3.57)	0.18	0.63 (0.27 to 1.46)	0.51
FAQ <sup>‡</sup>	1.57 (0.89 to 2.77)	0.35	1.84 (0.96 to 3.54)	0.21
SF-36 PCS <sup>‡ †</sup>	0.79 (-2.59 to 4.18)	0.77	-3.72 (-8.60 to 1.16)	0.09
SF-36 MCS <sup>‡ †</sup>	-4.53 (-8.81 to -0.24)	0.10	-5.79 (-10.26 to -1.31)	0.18

Definition of abbreviations: ADL = activities of daily living; BDI-II = Beck Depression Inventory – II; FAQ = Functional Activities Questionnaire; PCL-S = Posttraumatic Stress Disorder Checklist; SF-36 = Short Form-36

Results shown are from linear regression models in which outcome variables were scores on the BDI, PCL, Katz ADL, FAQ, and SF-36 PCS and MCS. The independent variables were duration of delirium and age and covariates were the following potential confounders, which were selected a priori: age, education level, Short IQCODE, 10 history of depression and other mental health illnesses, baseline ADL, baseline Charlson Comorbidities Index, cerebrovascular disease burden via the Framingham Stroke Risk Profile, mean modified SOFA score over ICU duration, duration of severe sepsis and coma, episodes of hypoxemia, and mean daily doses of benzodiazepines, propofol, dexmedetomidine, opiates and haloperidol.

<sup>‡</sup>Proportional Odds Logistic Regression (POLR): Proportional odds logistic regression (POLR) was used for the BDI-II, PCL, Katz ADL and FAQ models. Therefore, the point estimates indicate odds ratios (95% Confidence Intervals); here, they indicate the odds ratio between the 75th and 25th percentiles of the exposure in question, holding all other covariates constant. For example, a patient with 5 days of delirium (our 75th percentile) had, on average, 2.3 times the odds of a higher (worse) score on the BDI-II at 12-month follow-up than a patient with no days of delirium (our 25th percentile), assuming all other covariates were equal. Similarly, a 71-year-old patient (our 75th percentile) had, on average, 0.3 times the odds of a higher BDI-II score at 12 months than a 51-year-old patient (our 25th percentile).

<sup>† †</sup>Linear (note: not logistic) regression was used for the SF-36 PCS and MCS models; therefore, the point estimates (95% Confidence Intervals) indicate the average difference in SF-36 component scores for patients at the 75th percentile of the exposure compared to patients at the 25th percentile. For example, a patient with 5 days of delirium (our 75th percentile) had, on average, a 12-month SF-36 MCS score 5.8 points lower than a patient with no delirium (our 25th percentile).

Although p-values may indicate significance (and is correct), due to the use of nonlinear terms for continuous exposures, the comparison of the 25th and 75th percentiles may yield a point estimate with a confidence interval that crosses zero, or vice versa.

**Table 5**  
**Effect of Age on Mental Health and Functional Outcomes**

Age: 25th percentile (51 years) vs. 75th percentile (71 years)				
Outcome	3 Mo F/Up	P Value	12 Mo F/Up	P Value
BDI-II <sup>‡</sup>	0.52 (0.29 to 0.97)	0.10	0.34 (0.17 to 0.69)	0.005
PCL-S <sup>‡</sup>	0.39 (0.21 to 0.74)	0.02	0.43 (0.22 to 0.84)	0.02
Katz ADL <sup>‡</sup>	1.41 (0.63 to 3.16)	0.01	3.94 (0.78 to 4.38)	0.10
FAQ <sup>‡</sup>	0.89 (0.49 to 1.62)	<0.0001	0.93 (0.47 to 1.81)	<0.0003
SF-36 PCS <sup>‡ †</sup>	0.50 (-3.15 to 4.16)	0.79	-0.13 (-4.37 to 4.12)	0.18
SF-36 MCS <sup>‡ †</sup>	1.58 (-3.02 to 6.19)	0.56	5.15 (0.42 to 9.89)	0.04

Definition of abbreviations: ADL = activities of daily living; BDI-II = Beck Depression Inventory – II; FAQ = Functional Activities Questionnaire; PCL-S = Posttraumatic Stress Disorder Checklist; SF-36 = Short Form-36

Results shown are from linear regression models in which outcome variables were scores on the BDI, PCL, Katz ADL, FAQ, and SF-36 PCS and MCS. The independent variables were duration of delirium and age and covariates were the following potential confounders, which were selected a priori: age, education level, Short IQCODE, 10 history of depression and other mental health illnesses, baseline ADL, baseline Charlson Comorbidities Index, cerebrovascular disease burden via the Framingham Stroke Risk Profile, mean modified SOFA score over ICU duration, duration of severe sepsis and coma, episodes of hypoxemia, and mean daily doses of benzodiazepines, propofol, dexmedetomidine, opiates and haloperidol.

<sup>‡</sup>Proportional Odds Logistic Regression (POLR): Proportional odds logistic regression (POLR) was used for the BDI-II, PCL, Katz ADL and FAQ models. Therefore, the point estimates indicate odds ratios (95% Confidence Intervals); here, they indicate the odds ratio between the 75th and 25th percentiles of the exposure in question, holding all other covariates constant. For example, a patient with 5 days of delirium (our 75th percentile) had, on average, 2.3 times the odds of a higher (worse) score on the BDI-II at 12-month follow-up than a patient with no days of delirium (our 25th percentile), assuming all other covariates were equal. Similarly, a 71-year-old patient (our 75th percentile) had, on average, 0.3 times the odds of a higher BDI-II score at 12 months than a 51-year-old patient (our 25th percentile).

<sup>† †</sup>Linear (note: not logistic) regression was used for the SF-36 PCS and MCS models; therefore, the point estimates (95% Confidence Intervals) indicate the average difference in SF-36 component scores for patients at the 75th percentile of the exposure compared to patients at the 25th percentile. For example, a patient with 5 days of delirium (our 75th percentile) had, on average, a 12-month SF-36 MCS score 5.8 points lower than a patient with no delirium (our 25th percentile).

Although p-values may indicate significance (and is correct), due to the use of nonlinear terms for continuous exposures, the comparison of the 25th and 75th percentiles may yield a point estimate with a confidence interval that crosses zero, or vice versa.