




# Prognostic models for depression and post-traumatic stress disorder symptoms following traumatic brain injury: a CENTER-TBI study

Ana Mikolić <sup>1,2</sup>, David van Klaveren,<sup>1</sup> Mathilde Jost,<sup>1</sup> Andrew IR Maas <sup>3,4</sup>, Shuyuan Shi <sup>2</sup>, Noah D Silverberg <sup>2,5</sup>, Lindsay Wilson <sup>6</sup>, Hester F Lingsma,<sup>1</sup> Ewout W Steyerberg,<sup>7</sup> CENTER-TBI Participants and Investigators

► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/bmjment-2024-301181>).

<sup>1</sup>Department of Public Health, Erasmus MC, Rotterdam, The Netherlands

<sup>2</sup>Department of Psychology, University of British Columbia, Vancouver, British Columbia, Canada

<sup>3</sup>Department of Neurosurgery, University Hospital Antwerp, Edegem, Belgium

<sup>4</sup>Department of Translational Neuroscience, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

<sup>5</sup>Rehabilitation Research Program, Centre for Aging SMART, Vancouver Coastal Health, Vancouver, British Columbia, Canada

<sup>6</sup>Department of Psychology, University of Stirling, Stirling, UK

<sup>7</sup>Department of Biomedical Data Sciences, Leiden University Medical Centre, Leiden, The Netherlands

## Correspondence to

Dr Ana Mikolić, Public Health, Erasmus MC, Rotterdam, Netherlands; [a.mikolic@erasmusmc.nl](mailto:a.mikolic@erasmusmc.nl)

Received 29 May 2024

Accepted 25 October 2024



© Author(s) (or their employer(s)) 2025. Re-use permitted under CC BY-NC. Published by BMJ.

**To cite:** Mikolić A, van Klaveren D, Jost M, et al. *BMJ Ment Health* 2025;**28**:1–11.

## ABSTRACT

**Background** Traumatic brain injury (TBI) is associated with an increased risk of major depressive disorder (MDD) and post-traumatic stress disorder (PTSD). We aimed to identify predictors and develop models for the prediction of depression and PTSD symptoms at 6 months post-TBI.

**Methods** We analysed data from the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury study. We used linear regression to model the relationship between predictors and depression (Patient Health Questionnaire-9) and PTSD symptoms (PTSD Checklist for Diagnostic and Statistical Manual for Mental Health Disorders Fifth Edition). Predictors were selected based on Akaike's Information Criterion. Additionally, we fitted logistic models for the endpoints 'probable MDD' and 'probable PTSD'. We also examined the incremental prognostic value of 2–3 weeks of symptoms.

**Results** We included 2163 adults (76% Glasgow Coma Scale=13–15). Depending on the scoring criteria, 7–18% screened positive for probable MDD and about 10% for probable PTSD. For both outcomes, the selected models included psychiatric history, employment status, sex, injury cause, alcohol intoxication and total injury severity; and for depression symptoms also preinjury health and education. The performance of the models was modest (proportion of explained variance= $R^2$  8% and 7% for depression and PTSD, respectively). Symptoms assessed at 2–3 weeks had a large incremental prognostic value (delta  $R^2$ =0.25, 95% CI 0.24 to 0.26 for depression symptoms; delta  $R^2$ =0.30, 95% CI 0.29 to 0.31 for PTSD).

**Conclusion** Preinjury characteristics, such as psychiatric history and unemployment, and injury characteristics, such as violent injury cause, can increase the risk of mental health problems after TBI. The identification of patients at risk should be guided by early screening of mental health.

## INTRODUCTION

Traumatic brain injury (TBI), generally defined as 'an alteration in brain function or other evidence of brain pathology, caused by an external force',<sup>1</sup> is a leading cause of death and disability worldwide. After a TBI, mental health symptoms are common.<sup>2–4</sup>

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The rates of depression and post-traumatic stress disorder (PTSD) are high in the first year after traumatic brain injury (TBI).

## WHAT THIS STUDY ADDS

⇒ This study identified baseline predictors of depression and PTSD after TBI and developed prognostic models.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Assessing risk for depression and PTSD before hospital discharge may support early referrals to mental health assessment and specialist care. Screening for mental health symptoms in the first weeks after injury would enable more accurate predictions of depression and PTSD after TBI.

Approximately 9%–30% of adults meet diagnostic criteria for major depressive disorder (MDD) within the first year post-TBI,<sup>5–9</sup> compared with a 12-month prevalence of 6% in the general population.<sup>10</sup> Similarly, post-traumatic stress disorder (PTSD) is more prevalent after TBI (16%)<sup>11</sup> than in the general population (1%–12%).<sup>12</sup> The prevalence of psychiatric disorders may be higher among individuals who sustain TBI even before the TBI occurs.<sup>13</sup>

Depression and PTSD are causes of burden on their own,<sup>14</sup> but co-occurrence with a TBI can lead to greater disability<sup>15–17</sup> and healthcare use.<sup>18–19</sup> Addressing mental health early after TBI may prevent poor clinical outcomes.<sup>20–21</sup> Accurately identifying who is at risk of mental health complications at hospital presentation or in the first weeks after injury can support a timely referral to a mental health specialist for diagnosis and treatment. Nevertheless, in contrast to other outcomes after TBI,<sup>22–23</sup> prognostic models for mental health disorders are lacking.

A systematic review and meta-analysis of predictors of mental health disorders following TBI<sup>2</sup> identified female sex/gender, preinjury depression, postinjury unemployment, and lower brain volume

as risk factors for MDD. Additionally, shorter post-traumatic amnesia (PTA), memory of the traumatic event and early post-traumatic stress symptoms were identified as risk factors for PTSD. However, the majority of analysed studies had important methodological limitations and only a few used multivariable models to predict MDD or PTSD. More recently, Stein *et al*<sup>7</sup> investigated risk factors for probable MDD and PTSD after mild TBI (Glasgow Coma Scale (GCS) Score 13–15) in a large US-based cohort. The authors identified lower education, being black, prior mental health problems and injury cause involving violence as the strongest multivariable predictors of probable PTSD and, except injury cause, of probable MDD.

We aimed to identify predictors of depression and PTSD symptoms after TBI of all severities and to develop prognostic models for the early identification of at-risk adults. Additionally, we aimed to develop prognostic models for MDD and PTSD, using criteria on validated screening questionnaires that showed satisfactory diagnostic accuracy for clinical diagnosis (referred to as 'probable MDD' and 'probable PTSD').

## METHODS

### Study population

We analysed data from the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI, Core V.3.0) study.<sup>24</sup> CENTER-TBI is a prospective, multicentre, longitudinal, observational study. The participants' data were collected in 65 sites (trauma centres) in Europe and Israel from December 2014 to December 2017. Patients with a clinical diagnosis of TBI, who presented to study centre within 24 hours of injury and had an indication for CT scan were included in the study. Patients with a pre-existing severe neurological disorder that would confound outcome assessments were excluded. In CENTER-TBI, participants were differentiated by care pathway into three strata: emergency room (ER) stratum (assessed in the ER and discharged), admission stratum (admitted to a hospital ward) or intensive care unit (ICU) stratum (admitted to the ICU).<sup>25</sup>

For this study, we included participants aged 16 years or older who completed at least one of the outcome assessments at 6 months post-TBI. In subgroup analyses, we analysed participants with baseline GCS=3–12 and 13–15 separately. Further, we analysed a subgroup of participants assessed at 2–3 weeks (according to the study protocol, assessment was scheduled for all patients enrolled in the ER stratum and a proportion of the admission stratum).

### Outcomes

Patients were asked to complete self-report questionnaires measuring depression and PTSD symptoms at 6 months post injury. If not available in local languages, the questionnaires were translated and linguistically validated.<sup>26</sup> The assessments could take place face to face, by telephone or by (postal) questionnaire.

#### Depression symptoms and probable diagnosis of MDD

The Patient Health Questionnaire-9 (PHQ-9)<sup>27</sup> was used to assess the presence and the severity of depressive symptoms. It is a self-report instrument containing nine items that can be scored on a 4-point Likert scale ranging from 0 (not at all) to 3 (nearly every day). The range of the total score is 0–27, with a higher score indicating more severe symptoms. The cut-off scores of 10 and 15 indicate moderate and moderately severe symptoms of depression, respectively.<sup>27</sup> We operationalised probable MDD in three ways. We used a cut-off score  $\geq 10$  that demonstrated

excellent diagnostic sensitivity and specificity for MDD.<sup>28–30</sup> In line with Stein *et al*,<sup>7</sup> we also used the cut-off score  $\geq 15$  as indicative of probable MDD. Finally, following the Diagnostic and Statistical Manual for Mental Health Disorders Fifth Edition (DSM-5),<sup>31</sup> we defined probable MDD by five or more items checked at least 'several days' (except suicidal ideation that can be checked 'some days'), with at least one measuring depressive mood or anhedonia (items 1 or 2).<sup>28</sup>

#### PTSD symptoms and probable diagnosis of PTSD

The PTSD Checklist for DSM-5 Score (PCL-5) was used to assess PTSD symptoms.<sup>32</sup> It contains 20 items measuring PTSD symptoms across four clusters, as defined in the DSM-5. Each item is scored on a 5-point Likert scale ranging from 0 (not at all) to 4 (extremely). The total score ranges from 0 to 80, with a higher score indicating more pronounced symptoms. A score of  $\geq 33$  is considered indicative of probable PTSD.<sup>7 33</sup> We also employed an alternative definition of probable PTSD according to the DSM-5 criteria: a score of 2 (moderate) or higher on at least one item from criterion B (questions 1–5), one item from criterion C (questions 6–7), two items from criterion D (questions 8–14) and two items from criterion E (questions 15–20). As a sensitivity analysis, we defined PTSD as positive only for those who responded positively to: 'Were your answers in reference to the stressful experience which caused your traumatic brain injury?'.

#### Candidate predictors

Candidate predictors were prespecified based on the previous studies<sup>2 4 7 9 34–36</sup>: age (years), sex ('male'/'female'), education (years), employment status ('employed'/'not working'/'retired'/'student'), psychiatric history ('yes'/'no'), prior TBI ('yes'/'no'), cause of injury ('traffic accidents'/'falls or other incidental injuries'/'violence'), GCS (3–15), PTA ('yes or suspected'/'no'), loss of consciousness (LOC, 'yes or suspected'/'no'), alcohol intoxication at the time of injury ('yes or suspected'/'no'), total Injury Severity Score (ISS) (1–75 for brain-injured patients), any intracranial abnormality on CT ('yes'/'no'). In addition, preinjury physical health ('healthy'/'systemic disease') was considered as a candidate predictor for depression,<sup>37</sup> and retrograde amnesia<sup>2</sup> ('yes or suspected'/'no') for PTSD. Because of skewed distribution, race/ethnicity<sup>7</sup> was only analysed as a predictor in univariable analyses.

Baseline variables were prospectively collected. Detailed description of candidate predictors is available in online supplemental table 1. In subgroups in whom these symptoms were assessed (ER stratum and part of admission stratum), we examined the predictive value of PHQ-9 total score and PCL-5 total score at 2–3 weeks (median 20 days) following injury. The Generalized Anxiety Disorder 7-item scale (GAD-7)<sup>38</sup> was also administered at the 2–3 weeks of assessment. The GAD-7 consists of 7 items that can be answered from 0=not at all to 3=nearly every day, and the total score (sum of all items) ranges 0–21. Postconcussion symptoms at 2–3 weeks were assessed using the Rivermead Post-concussion Symptoms Questionnaire (RPQ). The RPQ<sup>39</sup> includes 16 items that represent common symptoms after a (mild) TBI and can be rated from 0=not experienced at all to 4=severe. The total score was calculated as a sum of all items, with responses '1' (same as before the injury) treated as 0.

#### Statistical analysis

We described candidate predictors and outcomes in terms of medians with IQRs for continuous variables and percentages for categorical variables. For other analysis, missing values in

baseline predictor variables were imputed using multiple imputation (multivariate imputation by chain equations, mice)<sup>40</sup> with 10 iterations and all predictors, outcomes and auxiliary variables (online supplemental table 1). If scores on all analysed 2–3 weeks of questionnaires were missing, they were not imputed because they were not measured for over half of participants (>60%). Imputed 6-month outcomes were used when only one of the two questionnaires (PHQ-9 or PCL-5) were missing (<4%).

### Model development

We used linear regression to model the relationship between all baseline predictors, and depression (PHQ-9 total score) and PTSD symptoms (PCL-5 total score). We examined associations in univariable and multivariable regression analyses and quantified them by regression coefficients.

We assessed non-linear terms with polynomials for age and ISS. To account for potentially different predictor effects by TBI severity, we assessed the interaction terms between GCS (continuous) and other variables in multivariable analyses. To develop a more robust model, we only included interactions when the *p* value for all interactions with GCS (overall interaction term) and individual interaction term(s) were significant (*p*<0.05).<sup>41 42</sup> To select the strongest predictors in the final model while balancing out the model fit with model complexity, we used backward selection based on Akaike's Information Criterion (AIC) as a stopping rule (see online supplemental table 2–3 for more details). The strength of predictors was also reported in terms of statistical significance (online supplemental table 2–3) and by partial *R*<sup>2</sup>: overall and separately in GCS=13–15 and GCS=3–12 subgroups.

To estimate a uniform shrinkage factor and model optimism, we used an internal validation procedure with 500 bootstrap samples. We reported model equations with optimism-corrected regression coefficients of the final models (coefficient multiplied by a shrinkage factor) and re-estimated model intercept (online supplemental table 4). The performance was quantified with the proportion of explained variance (*R*<sup>2</sup>) and calculated across imputed datasets. CIs were estimated using 500 bootstrap samples.

The selected model for depression symptoms was refitted to an endpoint 'probable MDD' by using cut-off≥10 on PHQ-9; cut-off≥15 on PHQ-9 and mapping items to DSM-5 criteria. The selected model for PTSD symptoms was refitted to an endpoint 'probable PTSD' by using cut-off≥33 on PCL-5; and mapping items to DSM-5 diagnosis. The equations of these logistic models were multiplied by the same shrinkage factor obtained for linear models (online supplemental table 4). The classification performance of binary logistic models was quantified with the area under the receiver operating characteristic curve (AUC) across imputed datasets, with optimism and CIs estimated using bootstrapping. To illustrate model performance and utility, we presented contingency tables for selected risk thresholds, and reported sensitivity, specificity and net benefit<sup>43</sup> (online supplemental table 5–6).

To assess the incremental value of 2–3-week symptoms for the prediction of depression in a subset for whom these were assessed, we compared the performance (delta *R*<sup>2</sup>) of the following models: (1) final baseline model, (2) final baseline model + 2–3-week PHQ-9, (3) final model + all 2–3-week questionnaires (PHQ-9, PCL-5, GAD-7 and RPQ). To assess the incremental value of 2–3-week symptoms for the prediction of PTSD, the same approach was taken with the PCL-5 instead of the PHQ-9.

## RESULTS

### Study population

The CENTER-TBI Core study included 4509 participants. Of 4306 adults (age 16+ years), *n*=2163 (50%) had completed 6-month questionnaires and were included in the analysis. The majority of included participants were men (65%), had white race (97%) and GCS=13–15 (table 1). About 12% reported a history of psychiatric disorder. Participants who survived to 6 months but did not respond to the questionnaires did not substantially differ from the participants who responded; however, they were somewhat younger, more frequently unemployed and with higher rates of psychiatric history, intoxication at the time of injury and injuries due to violence.

At 6 months, 18% had probable MDD according to the PHQ-9≥10, 7% according to PHQ-9≥15 and 9% based on mapping to the DSM-5 criteria (online supplemental table 7). The prevalence of probable PTSD was 10% according to both criteria. When counting only participants who responded to PCL-5 in reference to their TBI, that percentage was slightly lower (8%). There were no large differences in the prevalence of MDD/PTSD based on the TBI severity; however, symptoms of depression and PTSD and the rates of PHQ-9≥10 were somewhat higher after more severe TBI.

### Depression: predictors and model development

In univariable analyses, female sex, identifying as black/Asian, fewer years of education, unemployment, systemic disease, psychiatric history, being intoxicated at the time of injury, more severe injuries (by GCS, ISS and CT abnormalities) and injuries due to traffic accidents and violence were associated with more severe depression symptoms. In multivariable analyses, according to our prespecified criteria, the interactions between GCS and other candidate predictors (overall *F*=0.86, *df*=16, *p*=0.62), and non-linear effects of age (*p*=0.63) and ISS (*p*=0.22) were not included in the model. The following predictors were selected based on the AIC: psychiatric history, employment, ISS, sex, education, preinjury health, injury cause and alcohol intoxication (figure 1). Psychiatric history was the strongest predictor (figure 1 online supplemental figure 1). The overall model performance was very modest (optimism-corrected *R*<sup>2</sup>=0.08, 95% CI 0.08 to 0.08).

Based on the partial *R*<sup>2</sup>, psychiatric history and employment were the strongest predictors of depression symptoms in GCS=13–15. In the GCS=3–12 subgroup, the strongest predictor was injury cause, followed by employment and psychiatric history (online supplemental figure 1).

For probable MDD, the optimism-corrected AUC ranged 0.64–0.66 (table 2). Similar predictors were important for all endpoints, with psychiatric history and unemployment being associated with the highest odds of probable MDD (table 2).

In the subset of participants with 2–3 weeks of symptoms assessed (*n*=655), the baseline model for depression symptoms had an *R*<sup>2</sup>=0.11, 95% CI 0.10 to 0.12; after validation *R*<sup>2</sup>=0.07, 95% CI 0.07 to 0.08. The addition of 2–3 weeks of PHQ-9 markedly improved the performance (delta *R*<sup>2</sup>=0.25, 95% CI 0.24 to 0.26). The extension with additional questionnaires (PCL-5, GAD-7 and RPQ) did not further improve the model (delta *R*<sup>2</sup>=0.00, 95% CI 0.00 to 0.01).

### PTSD: predictors and model development

In univariable analyses, female sex, identifying as black/Asian, unemployment, psychiatric history, injuries caused by traffic accidents and violence, sustaining LOC, intoxication at the time

**Table 1** CENTER-TBI participants by the response to 6-month questionnaires

	Responders to 6-month questionnaires	Missing %	Not responded to 6-month questionnaires	Death by 6 months
N	2163		1726	471
Baseline variables				
Age (median (IQR))	51 (32, 64)	0	47 (29, 65)	68 (52, 78)
Sex=M (%)	1413 (65.3)	0	1186 (68.7)	335 (71.1)
Race=white (%)	2034 (97.2)	3.3	1569 (96.0)	419 (97.2)
Education, years (median (IQR))	13 (11, 16)	18.5	12 (10, 15)	12 (8, 14)
Employment (%)		6.3		
Working	1156 (57.0)		745 (49.7)	75 (23.3)
Retired	496 (24.5)		403 (26.9)	213 (66.1)
Student	202 (10.0)		156 (10.4)	8 (2.5)
Not working*	173 (8.5)		196 (13.1)	26 (8.1)
Psychiatric history (%)	265 (12.4)	1.2	257 (15.6)	75 (17.9)
Preinjury health=no systemic disease (%)	866 (40.4)	0.9	716 (43.3)	284 (66.7)
Prior TBI/concussions (%)	217 (10.5)	4.7	145 (9.2)	29 (7.8)
Cause of injury (%)		2.1		
Fall and other unintentional cause	1124 (53.1)		911 (54.6)	273 (60.8)
Traffic	886 (41.9)		600 (35.9)	148 (33.0)
Violence	107 (5.1)		158 (9.5)	28 (6.2)
GCS (median (IQR))	15 (13, 15)	2.9	15 (11, 15)	6 (3, 11)
GCS<13 (%)	507 (24.1)	2.9	479 (28.9)	347 (79.6)
Total Injury Severity Score (median (IQR))	14 (9, 26)	1.1	16 (8, 26)	34 (25, 57)
Loss of consciousness (%)	1278 (65.7)	10.1	954 (63.0)	329 (82.2)
Post-traumatic amnesia (%)	891 (53.2)	22.6	500 (42.0)	49 (36.0)
Retrograde amnesia (%)	637 (40.3)	27	419 (37.0)	28 (23.3)
Alcohol intoxication	466 (22.9)	8	468 (29.8)	103 (25.6)
Any intracranial traumatic abnormality (%)	1163 (57.5)	6.5	826 (54.2)	375 (93.5)
2–3-week symptoms (median (IQR))				
PHQ-9 Total Score (min–max: 0–27)	5 (2, 10)	78.3	5 (0.50, 10)	/†
PCL-5 Total Score (min–max: 0–33)	9 (3, 19)	78.2	8 (2, 17.25)	/
GAD-7 Total Score (min–max: 0–21)	2 (0, 6)	78.4	2 (0, 7)	/
RPQ Total Score (min–max: 0–64)	8 (2, 21)	77.9	6 (0, 18.25)	/

\*Unemployed, looking for work, unable to work, homemaker.  
†Small frequencies.

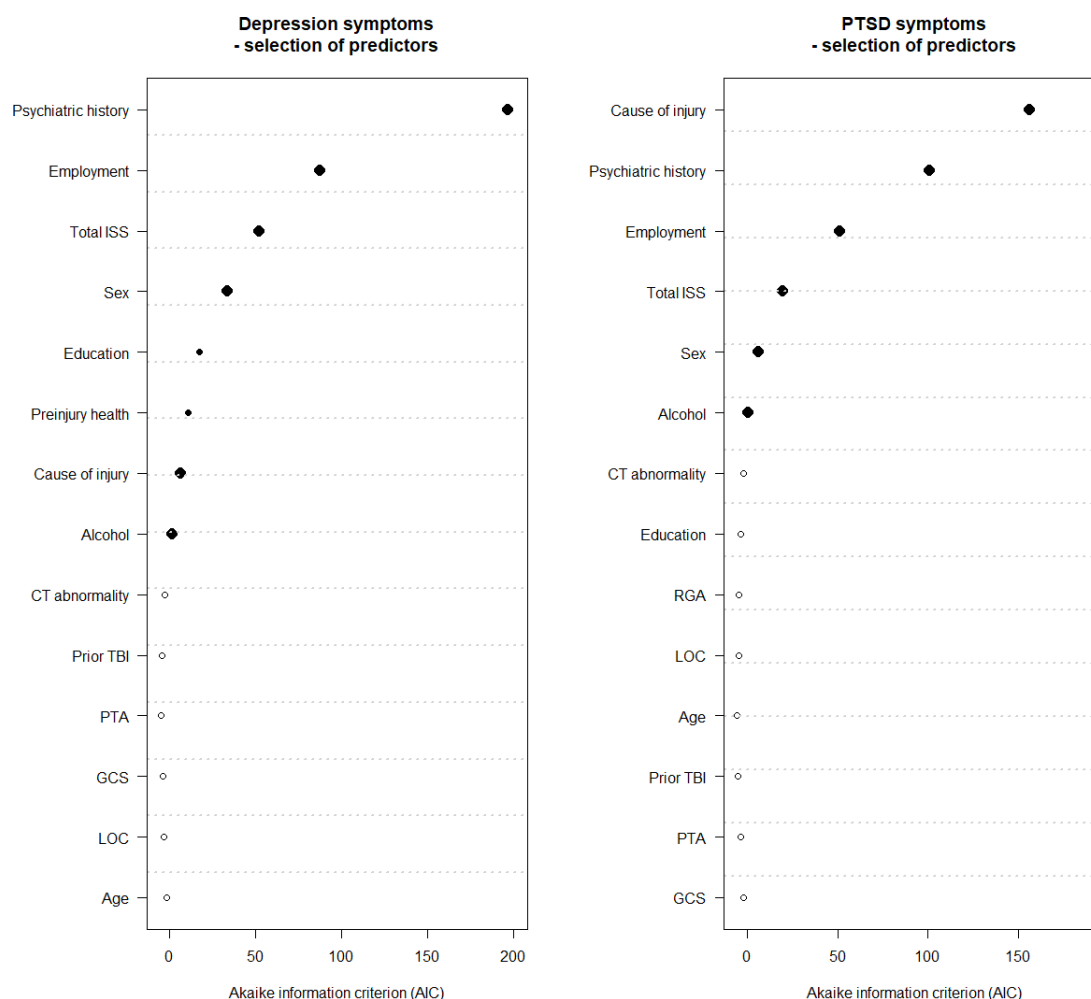
CENTER-TBI, Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury; GAD-7, Generalized Anxiety Disorder-9; GCS, Glasgow Coma Scale Score; PCL-5, Post-Traumatic Stress Disorder Checklist for Diagnostic and Statistical Manual for Mental Health Disorders Fifth Edition; PHQ-9, Patient Health Questionnaire-9; RPQ, Rivermead Post-concussion Symptoms Questionnaire.

of injury and more severe injuries (lower GCS, higher ISS and CT abnormalities) were associated with more severe PTSD symptoms. Being retired and an increase in age after 40 were associated with less severe PTSD symptoms (table 3; online supplemental figure 2). In multivariable analysis, the overall interaction terms for GCS (overall  $F=1.14$ ,  $df=16$ ,  $p=0.315$ ) were not significant. The non-linear effects of age ( $p=0.34$ ) and ISS ( $p=0.70$ ) were weak. The selected model had optimism-corrected  $R^2$  of 0.07 and included: cause of injury, psychiatric history, employment status, sex, total ISS and alcohol intoxication (figure 1). The strongest predictors that explained the largest proportion of the variance in PTSD symptoms were injury cause, psychiatric history and employment status (online supplemental figure 3).

For probable PTSD, the model performance was modest ( $AUC=0.62$ – $0.64$ ; table 3). Psychiatric history, unemployment and traffic and violence as injury cases were associated with higher odds of PTSD, while being retired was associated with lower odds of PTSD. The sensitivity analysis of TBI-related

probable PTSD showed mostly consistent results for both endpoints; however, while psychiatric history remained a significant predictor of  $PCL-5 \geq 33$ , it was not a significant predictor for PTSD mapped to DSM-5 ( $OR=1.22$ , 95% CI 0.8 to 1.9; Online supplemental table 8). In both  $GCS=13$ – $15$  and  $GCS=3$ – $12$ , injury cause was the strongest predictor with the largest partial  $R^2$ , followed by psychiatric history ( $GCS=13$ – $15$ ) and employment ( $GCS=3$ – $12$ ; online supplemental figure 3).

In the subset with patients whose symptoms were assessed at 2–3 weeks ( $n=655$ ), the performance of the model for PTSD symptoms with baseline variables was  $R^2=0.08$ , 95% CI 0.08 to 0.09; after validation  $R^2=0.05$ , 95% CI 0.05 to 0.06). The addition of 2–3-week PCL-5 increased the performance substantially (delta  $R^2=0.30$ , 95% CI 0.29 to 0.31). The addition of other 2–3-week questionnaires (PHQ-9, GAD-7 and RPQ) to baseline variables and PCL-5 led to a delta  $R^2$  of 0.005, 95% CI 0.003 to 0.007.



**Figure 1** Prediction of depression and post-traumatic stress disorder symptoms: selection of predictors based on the Akaike information criterion for the pooled residual  $\chi^2$ . Selected predictors are indicated with black circles. Predictors selected for both outcomes are shown with larger circles. GCS, Glasgow Coma Score; ISS, Injury Severity Score; LOC, loss of consciousness; PTA, post-traumatic amnesia; PTSD, post-traumatic stress disorder; RGA, retrograde amnesia; TBI, traumatic brain injury.

## DISCUSSION

We examined predictors and developed prognostic models for depression symptoms (including probable MDD) and PTSD symptoms (including probable PTSD) at 6 months post-TBI. Using validated screening questionnaires, between 7% and 18% of patients (dependent on chosen cut-off value) had an indication for MDD and about 10% for PTSD. Psychiatric history was a strong predictor of both depression and PTSD symptoms following TBI. Although the baseline models for the prediction of both outcomes had only modest performance, some socio-demographic variables (eg, employment status) and injury variables (eg, injury cause) were associated with outcomes. Including 2–3-week symptoms for predicting later depression/PTSD symptoms improved model performance.

The strong incremental value of 2–3-weeks symptoms confirms the importance of screening for mental health symptoms in the weeks after TBI, which has been recommended by clinical practice guidelines.<sup>44</sup> Brief validated screening questionnaires for mental health disorders could be used in primary care settings<sup>21</sup> or using remote assessment<sup>45</sup>, or after more severe TBIs, in hospital and rehabilitation settings. Without the screening, it is difficult to identify patients at risk of depression and PTSD symptoms at 6 months.

Although baseline variables do not enable accurate predictions on postinjury mental health, the presence of some risk factors can suggest a need for systematic follow-up. We found an association between psychiatric history and mental health problems after TBI, as supported by other evidence.<sup>7 46</sup> Further, the importance of social determinants of health for outcomes after TBI<sup>7 47 48</sup> has been confirmed in this study. Unemployment at the time of injury may increase the risk of mental health problems by elevated financial burden and levels of stress, hindering the ability to cope with an unexpected condition and further lowering the possibility to find paid employment. Similarly, lower education may be an indicator of lower socioeconomic status. Race,<sup>47</sup> one of the most studied factors, was not examined in our multivariable models due to a highly skewed distribution (97% white); however, the results from our univariable analyses suggest that racial minorities in Europe may have a higher likelihood of mental health disorders after TBI, echoing findings from other regions.<sup>7 49</sup> As in most previous studies, female sex was associated with higher risk of mental health problems after TBI.<sup>2</sup>

In line with the TRACK-TBI cohort, violent injury cause was a prominent predictor of PTSD, but a weaker predictor of depression.<sup>7</sup> While the TRACK-TBI study combined other injury causes, we examined traffic incidents separately and found them

**Table 2** Predictors and model performance for depression symptoms and probable major depressive disorder according to three criteria (n=2163)

	Depression symptoms (Patient Health Questionnaire-9, (PHQ-9) total score)			PHQ-9≥10	PHQ-9≥15	PHQ-9 DSM-5
	Regression coefficient (95% CI)			Odds ratio (95% CI)		
	Univariable analyses	Full model	Selected model	Selected model		
Age, 67 vs 32 years*	−0.2 (−0.61, 0.21)	−0.18 (−0.87, 0.51)	Not selected			
Sex, female versus male	1.04 (0.56, 1.51)	1.06 (0.60, 1.53)	1.05 (0.58, 1.51)	1.47 (1.15 to 1.87)	1.43 (1.00 to 2.02)	1.55 (1.13 to 2.13)
Race, black/Asian versus white	2.2 (0.77, 3.63)	Not assessed	Not assessed			
Education, 16 vs 11 years*	−0.59 (−0.88, −0.29)	−0.42 (−0.72, −0.13)	−0.45 (−0.75, −0.16)	0.85 (0.72 to 1.01)	0.76 (0.59 to 0.97)	0.83 (0.66 to 1.03)
Employment, ref=working						
Retired	−0.18 (−0.72, 0.37)	−0.39 (−1.13, 0.34)	−0.45 (−1.03, 0.13)	0.84 (0.61 to 1.16)	1.13 (0.71 to 1.78)	0.92 (0.61 to 1.41)
Student	−0.07 (−0.86, 0.73)	−0.05 (−0.97, 0.87)	0.05 (−0.74, 0.83)	1.30 (0.87 to 1.95)	1.14 (0.61 to 2.14)	1.07 (0.61 to 1.89)
Not working†	3.08 (2.25, 3.91)	2.06 (1.23, 2.90)	2.07 (1.24, 2.90)	2.39 (1.65 to 3.46)	2.38 (1.46 to 3.89)	1.99 (1.23 to 3.21)
Psychiatric history, yes versus no	3.53 (2.85, 4.21)	2.64 (1.94, 3.34)	2.71 (2.01, 3.41)	2.37 (1.75 to 3.22)	1.82 (1.20 to 2.78)	2.02 (1.37 to 2.98)
Preinjury systemic disease versus healthy	0.9 (0.44, 1.36)	0.69 (0.17, 1.20)	0.65 (0.16, 1.15)	1.46 (1.13 to 1.89)	1.31 (0.91 to 1.91)	1.39 (0.98 to 1.96)
Prior TBI, yes versus no	0.64 (−0.11, 1.39)	0.65 (−0.08, 1.38)	Not selected			
Cause of injury, ref=fall						
Traffic	0.71 (0.24, 1.17)	0.72 (0.24, 1.20)	0.70 (0.23, 1.17)	1.26 (0.98 to 1.63)	1.46 (1.01 to 2.12)	1.52 (1.08 to 2.12)
Violence	1.53 (0.46, 2.60)	0.82 (−0.26, 1.90)	0.81 (−0.25, 1.87)	1.35 (0.81 to 2.24)	1.77 (0.97 to 3.44)	1.21 (0.60 to 2.43)
Glasgow Coma Scale, 15 vs 9*	−0.76 (−1.12, −0.4)	−0.28 (−0.75, 0.18)	Not selected			
Total Injury Severity Score, 29 vs 9*	0.7 (0.4, 1)	0.41 (0.01, 0.80)	0.66 (0.36, 0.96)	1.18 (1.01 to 1.38)	1.20 (0.97 to 1.49)	1.08 (0.88 to 1.33)
Loss of consciousness, yes or suspected versus no	0.08 (−0.41, 0.57)	−0.15 (−0.67, 0.38)	Not selected			
Post-traumatic amnesia, yes or suspected versus no	−0.07 (−0.59, 0.45)	−0.31 (−0.89, 0.27)	Not selected			
Alcohol intoxication, yes or suspected versus no	1.11 (0.57, 1.65)	0.64 (0.08, 1.19)	0.67 (0.13, 1.21)	1.40 (1.07 to 1.84)	1.58 (1.09 to 2.30)	1.43 (1.00 to 2.04)
Intracranial abnormality, present versus absent	0.93 (0.47, 1.39)	0.54 (0.03, 1.05)	Not selected			
Model performance, 95% CI		R <sup>2</sup> =0.10, 0.10 to 0.10	R <sup>2</sup> =0.10, 0.09 to 0.10	AUC=0.68 0.66 to 0.70	AUC=0.68, 0.65 to 0.73	AUC=0.66, 0.63 to 0.70
Optimism-corrected performance, 95% CI			R <sup>2</sup> =0.08, 0.08 to 0.09	AUC=0.66, 0.64 to 0.68	AUC=0.64, 0.61 to 0.69	AUC=0.62, 0.59 to 0.66

\*IQR coefficients, scaled to 75:25 percentile.

†Unemployed, unable to work, homemaker.

DSM-5, Diagnostic and Statistical Manual for Mental Health Disorders Fifth Edition; TBI, traumatic brain injury.

predictive of PTSD at 6 months post-TBI. Our findings suggest that TBIs caused by psychologically traumatic events that induce fear and feeling of loss of control should trigger follow-up screening for PTSD. Interestingly, we also found associations between higher total injury severity (including extracranial injuries) and lower GCS (in univariable analyses) with more severe PTSD/depression symptoms, while we did not find strong associations between retrograde/PTA and PTSD symptoms. It was previously hypothesised that amnesia for injury event decreases the likelihood of PTSD by preventing memory encoding; however, it is now more widely accepted that amnesia/LOC do not preclude post-traumatic reactions.<sup>17</sup> While our finding

is consistent with some studies,<sup>7</sup> considerable missingness and lack of granularity (eg, assessment by standardised instruments, incorporation of duration) prevent strong conclusions.

The baseline models developed in this study had only modest performance. However, they contain predictors identified in other studies.<sup>7 50</sup> As preinjury mental health problems are consistent predictors of postinjury symptoms, particular attention should be given to patients with this comorbidity. Given the small proportion of variance explained by the baseline models, we recommend improving the model fit by refining the assessment of predictors identified by this study and including additional variables. Future studies should include a detailed

**Table 3** Predictors and model performance for post-traumatic stress disorder (PTSD) symptoms and probable PTSD according to two criteria (n=2163)

	PTSD symptoms (PTSD Checklist for DSM-5 (PCL-5) total score)			PCL-5≥33	PCL-5 DSM-5
	Regression coefficient (95% CI)			Odds ratio (95% CI)	
	Univariable	Full model	Selected	Selected	
Age, 67 vs 32 years*	−2.5 (−3.55, −1.44)	−1.21 (−2.99, 0.57)	Not selected		
Sex, female versus male	1.25 (0.03 to 2.48)	1.84 (0.62 to 3.05)	1.81 (0.60 to 3.02)	1.11 (0.81 to 1.52)	1.21 (0.89 to 1.64)
Race, black/Asian versus white	7.01 (3.36, 10.66)	Not assessed	Not assessed		
Education, 16 vs 11 years*	−0.85 (−1.66, −0.03)	−0.79 (−1.59, 0.01)	Not selected		
Employment, ref=working					
Retired	−2.72 (−4.13, −1.31)	−1.22 (−3.12, 0.68)	−1.78 (−3.19, −0.38)	0.58 (0.38 to 0.91)	0.53 (0.34 to 0.83)
Student	−0.12 (−2.21, 1.97)	−0.97 (−3.47, 1.53)	0.03 (−2.00, 2.06)	0.84 (0.48 to 1.47)	0.80 (0.46 to 1.39)
Not working†	6.97 (4.68, 9.25)	4.96 (2.71, 7.22)	5.30 (3.05, 7.56)	1.85 (1.18 to 2.90)	2.15 (1.37 to 3.36)
Psychiatric history, yes versus no	6.65 (4.88, 8.42)	5.05 (3.28, 6.82)	5.17 (3.41, 6.93)	2.23 (1.55 to 3.23)	1.58 (1.11 to 2.33)
Prior TBI, yes versus no	0.53 (−1.39, 2.46)	0.57 (−1.29, 2.44)	Not selected		
Cause of injury, ref=fall					
Traffic	3.52 (2.32, 4.72)	3.16 (1.90 to 4.42)	2.94 (1.72, 4.16)	1.51 (1.09, 2.10)	1.36 (0.99 to 1.88)
Violence	9.12 (6.35, 11.89)	6.63 (3.84 to 9.41)	6.96 (4.20, 9.72)	2.39 (1.39, 4.10)	2.02 (1.14 to 3.58)
Glasgow Coma Scale, 15 vs 9*	−1.78 (−2.7, −0.86)	0.18 (−1.00, 1.36)	Not selected		
Total Injury Severity Score, 29 vs 9*	2.13 (1.36, 2.91)	1.35 (0.33, 2.37)	1.70 (0.92, 2.47)	0.95 (0.78, 1.17)	0.98 (0.81 to 1.20)
Loss of consciousness, yes or suspected versus no	1.59 (0.34, 2.83)	1.21 (−0.14, 2.57)	Not selected		
Post-traumatic amnesia, yes or suspected versus no	0.62 (−0.66, 1.9)	−0.40 (−1.87, 1.07)	Not selected		
Retrograde amnesia, yes or suspected versus no	−0.19 (−1.67, 1.28)	−1.20 (−2.82, 0.43)	Not selected		
Alcohol intoxication, yes or suspected versus no	2.68 (1.26, 4.1)	1.33 (−0.14, 2.80)	1.43 (−0.01, 2.87)	1.39 (0.97, 1.97)	1.17 (0.81 to 1.68)
Intracranial abnormality, present versus absent	2.34 (1.14, 3.54)	1.46 (0.14, 2.79)	Not selected		
Model performance, 95% CI		R <sup>2</sup> =0.09, 0.09 to 0.09	R <sup>2</sup> =0.08, 0.08 to 0.08	AUC=0.66, 0.63 to 0.70	AUC=0.64, 0.61 to 0.68;
Optimism-corrected performance, 95% CI			R <sup>2</sup> =0.07, 0.07 to 0.08	AUC=0.64, 0.61 to 0.68	AUC=0.62, 0.59 to 0.66

\*IQR coefficients, scaled to 75:25 percentile.

†Unemployed, unable to work, homemaker.

AUC, area under the receiver operating characteristic curve; DSM-5, The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; TBI, traumatic brain injury.

assessment of preinjury mental health and the psychological impact of the TBI. Using tools developed for screening of trauma survivors, such as the Predictive Screening Tool for Depression and PTSD<sup>51</sup> or the Injured Trauma Survivor Screen,<sup>52</sup> within the hospital setting may also improve the prediction of depression and PTSD before discharge and optimise follow-up.<sup>53</sup> The feasibility of these instruments and their predictive performance should be examined in the TBI population. In larger datasets, analysing more granular baseline variables (eg, detailed medical history, specific lesions and medical procedures) using modern

analytical techniques, including machine learning, may enable more satisfactory baseline models.

This study has limitations. The outcomes were not assessed by structured clinical interviews, which are necessary for confirming the diagnosis of mental health disorders. Nevertheless, we used validated screening questionnaires that showed satisfactory sensitivity and specificity for clinical diagnosis of MDD and PTSD.<sup>28 29 54</sup> Further, there was a substantial proportion of missing data on outcomes, with participants with the highest and lowest disability levels having more missing data.<sup>55</sup>

Imputation of missing predictor values was performed under missing at random assumption, which would lead to bias under missing not at random mechanism. We did not consider clustering or random effects for sites in the imputation of missing values and modelling. Our sample consisted mostly of patients with GCS=13–15, and 2–3-week symptoms were not assessed in patients admitted to ICU. Our findings, in particular the predictive value of early symptoms and the optimal timing to assess them after more severe TBI, require validation.

In conclusion, we identified baseline predictors of depression and PTSD symptoms after TBI, such as psychiatric history, employment status and injury cause. Prognostic models that include only sociodemographic and baseline clinical variables have modest performance. Screening for mental health symptoms 2–3 weeks after TBI strongly improves prognostication of later mental health problems and it should guide systematic follow-up after TBI.

**Collaborators** CENTER-TBI Participants and Investigators: Cecilia Åkerlund (Department of Physiology and Pharmacology, Section of Perioperative Medicine and Intensive Care, Karolinska Institutet, Stockholm, Sweden), Krisztina Amrein (János Szentágothai Research Centre, University of Pécs, Pécs, Hungary), Nada Andelic (Division of Surgery and Clinical Neuroscience, Department of Physical Medicine and Rehabilitation, Oslo University Hospital and University of Oslo, Oslo, Norway), Lasse Andreassen (Department of Neurosurgery, University Hospital Northern Norway, Tromsø, Norway), Audny Anke (Department of Physical Medicine and Rehabilitation, University Hospital Northern Norway, Tromsø, Norway), Anna Antoni (Trauma Surgery, Medical University Vienna, Vienna, Austria), Gérard Audibert (Department of Anesthesiology & Intensive Care, University Hospital Nancy, Nancy, France), Philippe Azouvi (Raymond Poincaré hospital, Assistance Publique – Hôpitaux de Paris, Paris, France), Maria Luisa Azzolini (Department of Anesthesiology & Intensive Care, S Raffaele University Hospital, Milan, Italy), Ronald Bartels (Department of Neurosurgery, Radboud University Medical Center, Nijmegen, The Netherlands), Pál Barzó (Department of Neurosurgery, University of Szeged, Szeged, Hungary), Romuald Beauvais (International Projects Management, ARTTIC, Munchen, Germany), Ronny Beer (Department of Neurology, Neurological Intensive Care Unit, Medical University of Innsbruck, Innsbruck, Austria), Bo-Michael Bellander (Department of Neurosurgery & Anesthesia & intensive care medicine, Karolinska University Hospital, Stockholm, Sweden), Antonio Belli (NIHR Surgical Reconstruction and Microbiology Research Centre, Birmingham, UK), Habib Benali (Anesthésie-Réanimation, Assistance Publique – Hôpitaux de Paris, Paris, France), Maurizio Berardino (Department of Anesthesia & ICU, AOU Città della Salute e della Scienza di Torino - Orthopedic and Trauma Center, Torino, Italy), Luigi Beretta (Department of Anesthesiology & Intensive Care, S Raffaele University Hospital, Milan, Italy), Morten Blaabjerg (Department of Neurology, Odense University Hospital, Odense, Denmark), Peter Bragge (BehaviourWorks Australia, Monash Sustainability Institute, Monash University, Victoria, Australia), Alexandra Brazinova (Department of Public Health, Faculty of Health Sciences and Social Work, Trnava University, Trnava, Slovakia), Vibeke Brinck (Quesgen Systems Inc., Burlingame, California, USA), Joanne Brooker (Australian & New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia), Camilla Brorsson (Department of Surgery and Perioperative Science, Umeå University, Umeå, Sweden), Andras Buki (Department of Neurosurgery, Medical School, University of Pécs, Hungary and Neurotrauma Research Group, János Szentágothai Research Centre, University of Pécs, Hungary), Monika Bullinger (Department of Medical Psychology, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany), Manuel Cabeleira (Brain Physics Lab, Division of Neurosurgery, Dept of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK), Alessio Caccioppola (Neuro ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy), Emiliana Calappi (Neuro ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy), Maria Rosa Calvi (Department of Anesthesiology & Intensive Care, S Raffaele University Hospital, Milan, Italy), Peter Cameron (ANZIC Research Centre, Monash University, Department of Epidemiology and Preventive Medicine, Melbourne, Victoria, Australia), Guillermo Carbayo Lozano (Department of Neurosurgery, Hospital of Cruces, Bilbao, Spain), Marco Carbonara (Neuro ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy), Simona Cavallo (Department of Anesthesia & ICU, AOU Città della Salute e della Scienza di Torino - Orthopedic and Trauma Center, Torino, Italy), Giorgio Chevallard (NeuroIntensive Care, Niguarda Hospital, Milan, Italy), Arturo Chierogato (NeuroIntensive Care, Niguarda Hospital, Milan, Italy), Giuseppe Citerio (School of Medicine and Surgery, Università Milano Bicocca, Milano, Italy), Hans Clusmann (NeuroIntensive Care, ASST di Monza, Monza, Italy), Mark Coburn (Department of Neurosurgery, Medical Faculty RWTH Aachen University, Aachen, Germany), Jonathan Coles (Department of Anesthesiology and Intensive Care Medicine,

University Hospital Bonn, Bonn, Germany), Jamie D Cooper (Department of Anesthesia & Neurointensive Care, Cambridge University Hospital NHS Foundation Trust, Cambridge, UK), Marta Correia (School of Public Health & PM, Monash University and The Alfred Hospital, Melbourne, Victoria, Australia), Amra Čović (Radiology/MRI department, MRC Cognition and Brain Sciences Unit, Cambridge, UK), Nicola Curry (Institute of Medical Psychology and Medical Sociology, Universitätsmedizin Göttingen, Göttingen, Germany), Endre Czeiter (Oxford University Hospitals NHS Trust, Oxford, UK), Marek Czosnyka (Department of Neurosurgery, Medical School, University of Pécs, Hungary and Neurotrauma Research Group, János Szentágothai Research Centre, University of Pécs, Hungary), Claire Dahyot Fizelier (Brain Physics Lab, Division of Neurosurgery, Dept of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK), Paul Dark (Intensive Care Unit, CHU Poitiers, Poitiers, France), Helen Dawes (University of Manchester NIHR Biomedical Research Centre, Critical Care Directorate, Salford Royal Hospital NHS Foundation Trust, Salford, UK), Véronique De Keyser (Movement Science Group, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK), Vincent Degos (Anesthésie-Réanimation, Assistance Publique – Hôpitaux de Paris, Paris, France), Francesco Della Corte (Department of Anesthesia & Intensive Care, Maggiore Della Carità Hospital, Novara, Italy), Hugo den Boogert (Department of Neurosurgery, Radboud University Medical Center, Nijmegen, The Netherlands), Bart Depreitere (Department of Neurosurgery, University Hospitals Leuven, Leuven, Belgium), Dula Dilvesi (Department of Neurosurgery, Clinical centre of Vojvodina, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia), Abhishek Dixit (Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK), Emma Donoghue (Australian & New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia), Jens Dreier (Center for Stroke Research Berlin, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany), Guy Loup Dulière (Intensive Care Unit, CHR Citadelle, Liège, Belgium), Ari Ercole (Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK), Patrick Esser (Movement Science Group, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK), Erzsébet Ezer (Department of Anaesthesiology and Intensive Therapy, University of Pécs, Pécs, Hungary), Martin Fabricius (Departments of Neurology, Clinical Neurophysiology and Neuroanesthesiology, Region Hovedstaden Rigshospitalet, Copenhagen, Denmark), Valery L Feigin (National Institute for Stroke and Applied Neurosciences, Faculty of Health and Environmental Studies, Auckland University of Technology, Auckland, New Zealand), Kelly Foks (Department of Neurology, Erasmus MC, Rotterdam, the Netherlands), Shirin Frisvold (Department of Anesthesiology and Intensive care, University Hospital Northern Norway, Tromsø, Norway), Alex Furmanov (Department of Neurosurgery, Hadassah-hebrew University Medical center, Jerusalem, Israel), Pablo Gagliardo (Fundación Instituto Valenciano de Neurorrehabilitación (FIVAN), Valencia, Spain), Damien Galanaud (Anesthésie-Réanimation, Assistance Publique – Hôpitaux de Paris, Paris, France), Dashiell Gantner (ANZIC Research Centre, Monash University, Department of Epidemiology and Preventive Medicine, Melbourne, Victoria, Australia), Guoyi Gao (Department of Neurosurgery, Shanghai Renji hospital, Shanghai Jiaotong University/school of medicine, Shanghai, China), Pradeep George (Karolinska Institutet, INCF International Neuroinformatics Coordinating Facility, Stockholm, Sweden), Alexandre Ghuyssen (Emergency Department, CHU, Liège, Belgium), Lelde Giga (Neurosurgery clinic, Pauls Stradins Clinical University Hospital, Riga, Latvia), Ben Glocker (Department of Computing, Imperial College London, London, UK), Jagoš Golubovic (Department of Neurosurgery, Clinical centre of Vojvodina, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia), Pedro A Gomez (Department of Neurosurgery, Hospital Universitario 12 de Octubre, Madrid, Spain), Johannes Gratz (Department of Anesthesia, Critical Care and Pain Medicine, Medical University of Vienna, Austria), Benjamin Gravesteijn (Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, The Netherlands), Francesca Grossi (Department of Anesthesia & Intensive Care, Maggiore Della Carità Hospital, Novara, Italy), Russell L Gruen (College of Health and Medicine, Australian National University, Canberra, Australia), Deepak Gupta (Department of Neurosurgery, Neurosciences Centre & JPN Apex trauma centre, All India Institute of Medical Sciences, New Delhi-110029, India), Juanita A Haagsma (Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, The Netherlands), Iain Haitsma (Department of Neurosurgery, Erasmus MC, Rotterdam, the Netherlands), Raimund Helbok (Department of Neurology, Neurological Intensive Care Unit, Medical University of Innsbruck, Innsbruck, Austria), Eirik Helseth (Department of Neurosurgery, Oslo University Hospital, Oslo, Norway), Lindsay Horton (Division of Psychology, University of Stirling, Stirling, UK), Jilke Huijben (Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, The Netherlands), Peter J Hutchinson (Division of Neurosurgery, Department of Clinical Neurosciences, Addenbrooke's Hospital & University of Cambridge, Cambridge, UK), Bram Jacobs (Department of Neurology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands), Stefan Jankowski (Neurointensive Care, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK), Mike Jarrett (Quesgen Systems Inc., Burlingame, California, USA), Ji yao Jiang (Karolinska Institutet, INCF International Neuroinformatics Coordinating

Facility, Stockholm, Sweden), Faye Johnson (Salford Royal Hospital NHS Foundation Trust Acute Research Delivery Team, Salford, UK), Kelly Jones (National Institute for Stroke and Applied Neurosciences, Faculty of Health and Environmental Studies, Auckland University of Technology, Auckland, New Zealand), Mladen Karan (Department of Neurosurgery, Clinical centre of Vojvodina, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia), Angelos G Kolias (Division of Neurosurgery, Department of Clinical Neurosciences, Addenbrooke's Hospital & University of Cambridge, Cambridge, UK), Erwin Kompanje (Department of Intensive Care and Department of Ethics and Philosophy of Medicine, Erasmus Medical Center, Rotterdam, The Netherlands), Daniel Kondziella (Departments of Neurology, Clinical Neurophysiology and Neuroanesthesiology, Region Hovedstaden Rigshospitalet, Copenhagen, Denmark), Evgenios Kornaropoulos (Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK), Lars Owe Koskinen (Department of Clinical Neuroscience, Neurosurgery, Umeå University, Umeå, Sweden), Noémi Kovács (Hungarian Brain Research Program - Grant No. KTI13\_13\_NAP-A-II/8, University of Pécs, Pécs, Hungary), Ana Kowark (Department of Anaesthesiology, University Hospital of Aachen, Aachen, Germany), Alfonso Lagares (Department of Neurosurgery, Hospital Universitario 12 de Octubre, Madrid, Spain), Linda Lanyon (Cyclotron Research Center, University of Liège, Liège, Belgium), Steven Laureys (Cyclotron Research Center, University of Liège, Liège, Belgium), Fiona Lecky (Centre for Urgent and Emergency Care Research (CURE), Health Services Research Section, School of Health and Related Research (SchARR), University of Sheffield, Sheffield, UK), Didier Ledoux (Cyclotron Research Center, University of Liège, Liège, Belgium), Rolf Lefering (Institute of Research in Operative Medicine (IFOM), Witten/Herdecke University, Cologne, Germany), Valerie Legrand (VP Global Project Management CNS, ICON, Paris, France), Aurelie Lejeune (Department of Anesthesiology-Intensive Care, Lille University Hospital, Lille, France), Leon Levi (Department of Neurosurgery, Rambam Medical Center, Haifa, Israel), Roger Lightfoot (Department of Anesthesiology & Intensive Care, University Hospitals Southampton NHS Trust, Southampton, UK), Hester Lingsma (Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, The Netherlands), Andrew I R Maas (Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Edegem, Belgium), Ana M Castaño León (Department of Anesthesia & Intensive Care, M. Bufalini Hospital, Cesena, Italy), Marc Maegele (Cologne-Merheim Medical Center (CMC), Department of Traumatology, Orthopedic Surgery and Sportmedicine, Witten/Herdecke University, Cologne, Germany), Marek Majdan (Department of Public Health, Faculty of Health Sciences and Social Work, Trnava University, Trnava, Slovakia), Alex Manara (Intensive Care Unit, Southmead Hospital, Bristol, Bristol, UK), Geoffrey Manley (Department of Neurological Surgery, University of California, San Francisco, California, USA), Costanza Martino (Department of Anesthesia & Intensive Care, M. Bufalini Hospital, Cesena, Italy), Hugues Maréchal (Intensive Care Unit, CHR Citadelle, Liège, Belgium), Julia Mattern (Department of Neurosurgery, University Hospital Heidelberg, Heidelberg, Germany), Catherine McMahon (Department of Neurosurgery, The Walton centre NHS Foundation Trust, Liverpool, UK), Béla Meleg (Department of Medical Genetics, University of Pécs, Pécs, Hungary), David Menon (Department of Physiology and Pharmacology, Section of Perioperative Medicine and Intensive Care, Karolinska Institutet, Stockholm, Sweden), Tomas Menovsky (Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Edegem, Belgium), Ana Mikolic (Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, The Netherlands), Benoit Misset (Cyclotron Research Center, University of Liège, Liège, Belgium), Visakh Muraleedharan (Karolinska Institutet, INCF International Neuroinformatics Coordinating Facility, Stockholm, Sweden), Lynnette Murray (ANZIC Research Centre, Monash University, Department of Epidemiology and Preventive Medicine, Melbourne, Victoria, Australia), Ancuta Negru (Department of Neurosurgery, Emergency County Hospital Timisoara, Timisoara, Romania), David Nelson (Department of Anesthesiology & Intensive Care, University Hospitals Southampton NHS Trust, Southampton, UK), Virginia Newcombe (Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK), Daan Nieboer (Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, The Netherlands), József Nyírádi (János Szentágotthai Research Centre, University of Pécs, Pécs, Hungary), Otesile Olubukola (Centre for Urgent and Emergency Care Research (CURE), Health Services Research Section, School of Health and Related Research (SchARR), University of Sheffield, Sheffield, UK), Matej Oresic (School of Medical Sciences, Örebro University, Örebro, Sweden), Fabrizio Ortolano (Neuro ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy), Aarno Palotie (Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland), Paul M Parizel (Department of Radiology, University of Antwerp, Edegem, Belgium), Jean François Payen (Department of Anesthesiology & Intensive Care, University Hospital of Grenoble, Grenoble, France), Natascha Perera (International Projects Management, ARTTIC, Munchen, Germany), Vincent Perlberg (Anesthésie-Réanimation, Assistance Publique – Hôpitaux de Paris, Paris, France), Paolo Persona (Department of Anesthesia & Intensive Care, Azienda Ospedaliera Università di Padova, Padova, Italy), Wilco Peul (Dept. of Neurosurgery, Leiden University Medical Center, Leiden, The Netherlands and Dept. of Neurosurgery, Medical Center Haaglanden, The Hague, The Netherlands), Anna Piippo-Karjalainen (Department of Neurosurgery, Helsinki University Central Hospital/Institute for Molecular Medicine Finland, University of

Helsinki, Helsinki, Finland), Matti Pirinen (Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland), Dana Pisica (Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, The Netherlands), Horia Ples (Department of Neurosurgery, Emergency County Hospital Timisoara, Timisoara, Romania), Suzanne Polinder (Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, The Netherlands), Inigo Pomposo (Department of Neurosurgery, Hospital de Cruces, Bilbao, Spain), Jussi P Posti (Division of Clinical Neurosciences, Department of Neurosurgery and Turku Brain Injury Centre, Turku University Hospital and University of Turku, Turku, Finland), Louis Puybasset (Department of Anesthesiology and Critical Care, Pitié-Salpêtrière Teaching Hospital, Assistance Publique, Hôpitaux de Paris and University Pierre et Marie Curie, Paris, France), Andreea Radoi (Neurotraumatology and Neurosurgery Research Unit (UNINN), Vall d'Hebron Research Institute, Barcelona, Spain), Arminas Ragauskas (Department of Neurosurgery, Kaunas University of technology and Vilnius University, Vilnius, Lithuania), Rahul Raj (Department of Neurosurgery, Helsinki University Central Hospital), Malinka Rambadagalla (Department of Neurosurgery, Rezekne Hospital, Latvia), Isabel Retel Helmrich (Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, The Netherlands), Jonathan Rhodes (Department of Anaesthesia, Critical Care & Pain Medicine NHS Lothian & University of Edinburgh, Edinburgh, UK), Sylvia Richardson (Director, MRC Biostatistics Unit, Cambridge Institute of Public Health, Cambridge, UK), Sophie Richter (Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK), Samuli Ripatti (Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland), Saulius Rocka (Department of Neurosurgery, Kaunas University of technology and Vilnius University, Vilnius, Lithuania), Cecilie Roe (Department of Physical Medicine and Rehabilitation, Oslo University Hospital/University of Oslo, Oslo, Norway), Olav Roise (Division of Orthopedics, Oslo University Hospital, Oslo, Norway), Jonathan Rosand (Broad Institute, Cambridge MA Harvard Medical School, Boston MA, Massachusetts General Hospital, Boston MA, USA), Jeffrey V Rosenfeld (National Trauma Research Institute, The Alfred Hospital, Monash University, Melbourne, Victoria, Australia), Christina Rosenlund (Department of Neurosurgery, Odense University Hospital, Odense, Denmark), Guy Rosenthal (Department of Neurosurgery, Hadassah-hebrew University Medical center, Jerusalem, Israel), Rolf Rossaint (Department of Anaesthesiology, University Hospital of Aachen, Aachen, Germany), Sandra Rossi (Department of Anesthesia & Intensive Care, Azienda Ospedaliera Università di Padova, Padova, Italy), Daniel Rueckert Martin Rusnák (Department of Computing, Imperial College London, London, UK), Juan Sahuquillo (International Neurotrauma Research Organisation, Vienna, Austria), Oliver Sakowitz (Neurotraumatology and Neurosurgery Research Unit (UNINN), Vall d'Hebron Research Institute, Barcelona, Spain), Renan Sanchez Porras (Klinik für Neurochirurgie, Klinikum Ludwigsburg, Ludwigsburg, Germany), Janos Sándor (Division of Biostatistics and Epidemiology, Department of Preventive Medicine, University of Debrecen, Debrecen, Hungary), Nadine Schäfer (Institute of Research in Operative Medicine (IFOM), Witten/Herdecke University, Cologne, Germany), Silke Schmidt (Department Health and Prevention, University Greifswald, Greifswald, Germany), Herbert Schoechl (Department of Anaesthesiology and Intensive Care, AUA Trauma Hospital, Salzburg, Austria), Guus Schoonman (Department of Neurology, Elisabeth-TweeSteden Ziekenhuis, Tilburg, the Netherlands), Rico Frederik Schou (Department of Neuroanesthesia and Neurointensive Care, Odense University Hospital, Odense, Denmark), Elisabeth Schwendenwein (Trauma Surgery, Medical University Vienna, Vienna, Austria), Charlie Sewalt (Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, The Netherlands), Toril Skandsen (Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, NTNU, Trondheim, Norway), Peter Smielewski (Brain Physics Lab, Division of Neurosurgery, Dept of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK), Abayomi Sorinola (Department of Neurosurgery, University of Pécs, Pécs, Hungary), Emmanuel Stamatakis (Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK), Simon Stanworth (Oxford University Hospitals NHS Trust, Oxford, UK), Robert Stevens (Division of Neuroscience Critical Care, John Hopkins University School of Medicine, Baltimore, USA), William Stewart (Department of Neuropathology, Queen Elizabeth University Hospital and University of Glasgow, Glasgow, UK), Ewout W Steyerberg (Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, The Netherlands), Nino Stocchetti (Department of Pathophysiology and Transplantation, Milan University, and Neuroscience ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Italy), Nina Sundström (Department of Radiation Sciences, Biomedical Engineering, Umeå University, Umeå, Sweden), Riikka Takala (Perioperative Services, Intensive Care Medicine and Pain Management, Turku University Hospital and University of Turku, Turku, Finland), Viktória Tamás (Department of Neurosurgery, University of Pécs, Pécs, Hungary), Tomas Tamosiutis (Department of Neurosurgery, Kaunas University of Health Sciences, Kaunas, Lithuania), Mark Steven Taylor (Department of Public Health, Faculty of Health Sciences and Social Work, Trnava University, Trnava, Slovakia), Braden Te Ao (National Institute for Stroke and Applied Neurosciences, Faculty of Health and Environmental Studies, Auckland University of Technology, Auckland, New Zealand), Olli Tenovu (Division of Clinical Neurosciences, Department of Neurosurgery and Turku Brain Injury Centre, Turku University Hospital and University of Turku, Turku, Finland), Alice Theadom (National

Institute for Stroke and Applied Neurosciences, Faculty of Health and Environmental Studies, Auckland University of Technology, Auckland, New Zealand), Matt Thomas (Division of Clinical Neurosciences, Department of Neurosurgery and Turku Brain Injury Centre, Turku University Hospital and University of Turku, Turku, Finland), Dick Tibboel (National Institute for Stroke and Applied Neurosciences, Faculty of Health and Environmental Studies, Auckland University of Technology, Auckland, New Zealand), Marjolijn Timmers (Intensive Care Unit, Southmead Hospital, Bristol, Bristol, UK), Christos Toliás (Intensive Care and Department of Pediatric Surgery, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands), Tony Trapani (Department of Intensive Care and Department of Ethics and Philosophy of Medicine, Erasmus Medical Center, Rotterdam, The Netherlands), Cristina Maria Tudora (Department of Neurosurgery, Kings college London, London, UK), Andreas Unterberg (ANZIC Research Centre, Monash University, Department of Epidemiology and Preventive Medicine, Melbourne, Victoria, Australia), Peter Vajkoczy (Department of Neurosurgery, Emergency County Hospital Timisoara, Timisoara, Romania), Shirley Vallance (ANZIC Research Centre, Monash University, Department of Epidemiology and Preventive Medicine, Melbourne, Victoria, Australia), Egils Valeinis (Neurosurgery clinic, Pauls Stradins Clinical University Hospital, Riga, Latvia), Zoltán Vámos (Department of Anaesthesiology and Intensive Therapy, University of Pécs, Pécs, Hungary), Mathieu van der Jagt (Department of Intensive Care Adults, Erasmus MC—University Medical Center Rotterdam, Rotterdam, the Netherlands), Gregory Van der Steen (Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Edegem, Belgium), Joukje van der Naalt (Department of Neurology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands), Jeroen T J M van Dijk (Dept. of Neurosurgery, Leiden University Medical Center, Leiden, The Netherlands and Dept. of Neurosurgery, Medical Center Haaglanden, The Hague, The Netherlands), Thomas A van Essen (Dept. of Neurosurgery, Leiden University Medical Center, Leiden, The Netherlands and Dept. of Neurosurgery, Medical Center Haaglanden, The Hague, The Netherlands), Wim Van Hecke (icoMetrix NV, Leuven, Belgium), Caroline van Heugten (Movement Science Group, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK), Dominique Van Praag (Psychology Department, Antwerp University Hospital, Edegem, Belgium), Ernest van Veen (Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, The Netherlands), Thijs Vande Vyvere (icoMetrix NV, Leuven, Belgium), Roel P J van Wijk (Dept. of Neurosurgery, Leiden University Medical Center, Leiden, The Netherlands and Dept. of Neurosurgery, Medical Center Haaglanden, The Hague, The Netherlands), Alessia Vargiolu (NeuroIntensive Care, ASST di Monza, Monza, Italy), Emmanuel Vega (Department of Anesthesiology-Intensive Care, Lille University Hospital, Lille, France), Kimberley Velt (Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, The Netherlands), Jan Verheyden (Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK), Paul M Vespa (Department of Neurosurgery, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany), Anne Vik (Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, NTNU, Trondheim, Norway), Rimantas Vilcinis (Department of Neurosurgery, St.Olavs Hospital, Trondheim University Hospital, Trondheim, Norway), Victor Volovici (Department of Neurosurgery, Kaunas University of Health Sciences, Kaunas, Lithuania), Nicole von Steinbüchel (Department of Neurosurgery, Erasmus MC, Rotterdam, the Netherlands), Daphne Voormolen (Institute of Medical Psychology and Medical Sociology, Universitätsmedizin Göttingen, Göttingen, Germany), Petar Vulekovic (Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, The Netherlands), Kevin K W Wang (Department of Neurosurgery, Clinical centre of Vojvodina, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia), Eveline Wieggers (Department of Emergency Medicine, University of Florida, Gainesville, Florida, USA), Guy Williams (Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, The Netherlands), Lindsay Wilson (Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK), Stefan Winzeck (Department of Neurosurgery, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany), Stefan Wolf (Broad Institute, Cambridge MA Harvard Medical School, Boston MA, Massachusetts General Hospital, Boston MA, USA), Zhihui Yang (Broad Institute, Cambridge MA Harvard Medical School, Boston MA, Massachusetts General Hospital, Boston MA, USA), Peter Ylén (VTT Technical Research Centre, Tampere, Finland), Alexander Younsi (Department of Neurosurgery, University Hospital Heidelberg, Heidelberg, Germany), Frederick A Zeiler (Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK), Veronika Zelinkova (Department of Public Health, Faculty of Health Sciences and Social Work, Trnava University, Trnava, Slovakia), Agate Ziverte (Neurosurgery clinic, Pauls Stradins Clinical University Hospital, Riga, Latvia), Tommaso Zoerle (Neuro ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy).

**Contributors** Contributions to conception/design: AMikolić, DvK, AMAas, NDS, LW, HL and ES. Contributions to acquisition/analysis/interpretation: AMikolić, DvK, MJ, SS and ES. Drafting the work/revising critically: AMikolić, DvK, MJ, AMAas, NDS, SS, LW, HL and ES. Final improvement: AMikolić, DvK, MJ, AMAas, NDS, SS, LW, HL and ES.

Agreement to be accountable: AMikolić, DvK, MJ, AMAas, NDS, SS, LW, HL and ES. Guarantor: ES.

**Funding** This study was supported by the European Commission Seventh Framework program (grant number 602150). Additional support was obtained by ZNS—Hannelore Kohl Stiftung (n/a), OneMind (n/a), Integra LifeSciences (n/a) and NeuroTrauma Sciences (n/a).

**Competing interests** AMikolić reports the University of British Columbia Institute of Mental Health Marshall Fellows Program Postdoctoral fellowship. NDS reports grants from the Canadian Institutes of Health Research, Canadian Foundation for Innovation, Ontario Brain Institute, Weston Brain Institute, Heart and Stroke Foundation of Canada, MITACS, VGH+UBC Hospital Foundation and WorkSafeBC; clinical consulting fees from the National Hockey League and Major League Soccer, and speakers fees from NYU Langone, WorkSafeBC, Yukon Workers' Safety and Compensation Board, International Academy of Independent Medical Examiners and Canadian Concussion Network. AMAas declares personal fees from NeuroTrauma Sciences and Novartis and participation on the DSMB of Presura Neuro. LW reports consulting fees for Neurotrauma Sciences, Novartis and Mass General Brigham. ES reports royalties for text book with Springer: Clinical Prediction Models.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants. The CENTER-TBI study (EC grant 602150) has been conducted in accordance with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws of the country where the recruiting sites were located, including but not limited to, the relevant privacy and data protection laws and regulations (the 'Privacy Law'), the relevant laws and regulations on the use of human materials and all relevant guidance relating to clinical studies from time to time in force including, but not limited to, the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) ('ICH GCP') and the World Medical Association Declaration of Helsinki entitled 'Ethical principles for medical research involving human subjects'. Informed consent by the patients and/or the legal representative/next of kin was obtained, accordingly to the local legislations, for all patients recruited in the Core Dataset of CENTER-TBI and documented in the e-CRF. Ethical approval was obtained for each recruiting sites. The list of sites, ethical committees, approval numbers and approval dates can be found below: <https://www.center-tbi.eu/project/ethical-approval>. Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data may be obtained from a third party and are not publicly available. Access to the CENTER-TBI dataset can be granted after approval of a study plan proposal, submitted through the online system: <https://www.center-tbi.eu/data>.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

#### ORCID iDs

Ana Mikolić <http://orcid.org/0000-0002-3476-096X>

Andrew IR Maas <http://orcid.org/0000-0003-1612-1264>

Shuyuan Shi <http://orcid.org/0000-0001-9138-9805>

Noah D Silverberg <http://orcid.org/0000-0001-6378-148X>

Lindsay Wilson <http://orcid.org/0000-0003-4113-2328>

#### REFERENCES

- Menon DK, Schwab K, Wright DW, *et al*. Position statement: definition of traumatic brain injury. *Arch Phys Med Rehabil* 2010;91:1637–40.
- Cnossen MC, Scholten AC, Lingsma HF, *et al*. Predictors of Major Depression and Posttraumatic Stress Disorder Following Traumatic Brain Injury: A Systematic Review and Meta-Analysis. *J Neuropsychiatry Clin Neurosci* 2017;29:206–24.
- Howlett JR, Nelson LD, Stein MB. Mental Health Consequences of Traumatic Brain Injury. *Biol Psychiatry* 2022;91:413–20.
- Scholten AC, Haagsma JA, Cnossen MC, *et al*. Prevalence of and Risk Factors for Anxiety and Depressive Disorders after Traumatic Brain Injury: A Systematic Review. *J Neurotrauma* 2016;33:1969–94.

- 5 Ouellet M-C, Beaulieu-Bonneau S, Sirois M-J, *et al.* Depression in the First Year after Traumatic Brain Injury. *J Neurotrauma* 2018;35:1620–9.
- 6 Gould KR, Ponsford JL, Johnston L, *et al.* The nature, frequency and course of psychiatric disorders in the first year after traumatic brain injury: a prospective study. *Psychol Med* 2011;41:2099–109.
- 7 Stein MB, Jain S, Giacino JT, *et al.* Risk of Posttraumatic Stress Disorder and Major Depression in Civilian Patients After Mild Traumatic Brain Injury: A TRACK-TBI Study. *JAMA Psychiatry* 2019;76:249–58.
- 8 Delmonico RL, Theodore BR, Sandel ME, *et al.* Prevalence of depression and anxiety disorders following mild traumatic brain injury. *PM R* 2022;14:753–63.
- 9 Alway Y, Gould KR, Johnston L, *et al.* A prospective examination of Axis I psychiatric disorders in the first 5 years following moderate to severe traumatic brain injury. *Psychol Med* 2016;46:1331–41.
- 10 Malhi GS, Mann JJ. Depression. *The Lancet* 2018;392:2299–312.
- 11 Van Praag DLG, Cnossen MC, Polinder S, *et al.* Post-Traumatic Stress Disorder after Civilian Traumatic Brain Injury: A Systematic Review and Meta-Analysis of Prevalence Rates. *J Neurotrauma* 2019;36:3220–32.
- 12 Shalev A, Liberzon I, Marmar C. Post-Traumatic Stress Disorder. *N Engl J Med* 2017;376:2459–69.
- 13 Albrecht JS, Abariga SA, Rao V, *et al.* Incidence of New Neuropsychiatric Disorder Diagnoses Following Traumatic Brain Injury. *J Head Trauma Rehabil* 2020;35:E352–60.
- 14 Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry* 2022;9:137–50.
- 15 Combs HL, Berry DTR, Pape T, *et al.* The Effects of Mild Traumatic Brain Injury, Post-Traumatic Stress Disorder, and Combined Mild Traumatic Brain Injury/Post-Traumatic Stress Disorder on Returning Veterans. *J Neurotrauma* 2015;32:956–66.
- 16 Haagsma JA, Scholten AC, Andriessen TMJC, *et al.* Impact of depression and post-traumatic stress disorder on functional outcome and health-related quality of life of patients with mild traumatic brain injury. *J Neurotrauma* 2015;32:853–62.
- 17 Vasterling JJ, Jacob SN, Rasmusson A. Traumatic Brain Injury and Posttraumatic Stress Disorder: Conceptual, Diagnostic, and Therapeutic Considerations in the Context of Co-Occurrence. *J Neuropsychiatry Clin Neurosci* 2018;30:91–100.
- 18 van der Vlegel M, Polinder S, Mikolic A, *et al.* The Association of Post-Concussion and Post-Traumatic Stress Disorder Symptoms with Health-Related Quality of Life, Health Care Use and Return-to-Work after Mild Traumatic Brain Injury. *J Clin Med* 2021;10:2473.
- 19 O'Donovan A, Cohen BE, Seal KH, *et al.* Elevated risk for autoimmune disorders in Iraq and Afghanistan veterans with posttraumatic stress disorder. *Biol Psychiatry* 2015;77:365–74.
- 20 Silverberg ND, Mikolic A. Management of Psychological Complications Following Mild Traumatic Brain Injury. *Curr Neurol Neurosci Rep* 2023;23:49–58.
- 21 Silverberg ND, Otamendi T, Brasher PM, *et al.* Effectiveness of a guideline implementation tool for supporting management of mental health complications after mild traumatic brain injury in primary care: protocol for a randomised controlled trial. *BMJ Open* 2022;12:e062527.
- 22 Dijkland SA, Foks KA, Polinder S, *et al.* Prognosis in Moderate and Severe Traumatic Brain Injury: A Systematic Review of Contemporary Models and Validation Studies. *J Neurotrauma* 2020;37:1–13.
- 23 Mikolic A, Polinder S, Steyerberg EW, *et al.* Prediction of Global Functional Outcome and Post-Concussive Symptoms after Mild Traumatic Brain Injury: External Validation of Prognostic Models in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) Study. *J Neurotrauma* 2021;38:196–209.
- 24 Maas AIR, Menon DK, Steyerberg EW, *et al.* Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. *Neurosurgery* 2015;76:67–80.
- 25 Steyerberg EW, Wiegers E, Sewalt C, *et al.* Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study. *Lancet Neurol* 2019;18:923–34.
- 26 von Steinbuechel N, Rauen K, Krenz U, *et al.* Translation and Linguistic Validation of Outcome Instruments for Traumatic Brain Injury Research and Clinical Practice: A Step-by-Step Approach within the Observational CENTER-TBI Study. *J Clin Med* 2021;10:2863.
- 27 Kroenke K, Spitzer RL. The PHQ-9: A New Depression Diagnostic and Severity Measure. *Psychiatr Ann* 2002;32:509–15.
- 28 Fann JR, Bombardier CH, Dikmen S, *et al.* Validity of the Patient Health Questionnaire-9 in Assessing Depression Following Traumatic Brain Injury. *J Head Trauma Rehab* 2005;20:501–11.
- 29 Donders J, Pendery A. Clinical Utility of the Patient Health Questionnaire-9 in the Assessment of Major Depression After Broad-Spectrum Traumatic Brain Injury. *Arch Phys Med Rehabil* 2017;98:2514–9.
- 30 Manea L, Gilbody S, McMillan D. Optimal cut-off score for diagnosing depression with the Patient Health Questionnaire (PHQ-9): a meta-analysis. *CMAJ* 2012;184:E191–6.
- 31 *Diagnostic and statistical manual of mental disorders: DSM-5.* Washington, DC: American Psychiatric Publishing, Division of American Psychiatric Association, 2013.
- 32 Weathers FW, Litz BT, Keane TM, *et al.* The PTSD checklist for DSM-5 (PCL-5)—standard [measurement instrument]. 2013.
- 33 Bovin MJ, Kimerling R, Weathers FW, *et al.* Diagnostic Accuracy and Acceptability of the Primary Care Posttraumatic Stress Disorder Screen for the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) Among US Veterans. *JAMA Netw Open* 2021;4:e2036733.
- 34 Singh R, Mason S, Lecky F, *et al.* Comparison of early and late depression after TBI; (the SHEFBIT study). *Brain Inj* 2019;33:584–91.
- 35 Singh R, Mason S, Lecky F, *et al.* Prevalence of depression after TBI in a prospective cohort: The SHEFBIT study. *Brain Inj* 2018;32:84–90.
- 36 Yue JK, Phelps RRL, Winkler EA, *et al.* Substance use on admission toxicology screen is associated with peri-injury factors and six-month outcome after traumatic brain injury: A TRACK-TBI Pilot study. *J Clin Neurosci* 2020;75:149–56.
- 37 Handing EP, Strobl C, Jiao Y, *et al.* Predictors of depression among middle-aged and older men and women in Europe: A machine learning approach. *Lancet Reg Health Eur* 2022;18:100391.
- 38 Spitzer RL, Kroenke K, Williams JBW, *et al.* A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006;166:1092–7.
- 39 King NS, Crawford S, Wenden FJ, *et al.* The Rivermead Post Concussion Symptoms Questionnaire: a measure of symptoms commonly experienced after head injury and its reliability. *J Neurol* 1995;242:587–92.
- 40 Buuren S, Groothuis-Oudshoorn K, Robitzsch A, *et al.* Package 'mice. *Comp softw* 2015.
- 41 Steyerberg EW. *Clinical prediction models: a practical approach to development, validation, and updating.* Cham: Springer International Publishing, 2019.
- 42 Núñez E, Steyerberg EW, Núñez J. Regression Modeling Strategies. *Rev Esp Cardiol (Eng Ed)* 2011;64:501–7.
- 43 Vickers AJ, Van Calster B, Steyerberg EW. Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests. *BMJ* 2016;352:i6.
- 44 Marshall S, Lithopoulos A, Curran D, *et al.* Living concussion guidelines: guideline for concussion & prolonged symptoms for adults 18 years of age or older. 2023. Available: <https://concussionsontario.org> [Accessed 1 Dec 2023].
- 45 Smith BG, Tumpa S, Mantle O, *et al.* Remote Follow-Up Technologies in Traumatic Brain Injury: A Scoping Review. *J Neurotrauma* 2022;39:1289–317.
- 46 Silverberg ND, Gardner AJ, Brubacher JR, *et al.* Systematic review of multivariable prognostic models for mild traumatic brain injury. *J Neurotrauma* 2015;32:517–26.
- 47 Johnson LW, Diaz I. Exploring the Social Determinants of Health and Health Disparities in Traumatic Brain Injury: A Scoping Review. *Brain Sci* 2023;13:707.
- 48 Yue JK, Rick JW, Morrissey MR, *et al.* Preinjury employment status as a risk factor for symptomatology and disability in mild traumatic brain injury: A TRACK-TBI analysis. *NeuroRehabilitation* 2018;43:169–82.
- 49 Eagle SR, Brent D, Covassin T, *et al.* Exploration of Race and Ethnicity, Sex, Sport-Related Concussion, Depression History, and Suicide Attempts in US Youth. *JAMA Netw Open* 2022;5:e2219934.
- 50 Cnossen MC, Scholten AC, Lingsma HF, *et al.* Predictors of Major Depression and Posttraumatic Stress Disorder Following Traumatic Brain Injury: A Systematic Review and Meta-Analysis. *JNP* 2017;29:206–24.
- 51 Richmond TS, Ruzek J, Ackerson T, *et al.* Predicting the future development of depression or PTSD after injury. *Gen Hosp Psychiatry* 2011;33:327–35.
- 52 Hunt JC, Sapp M, Walker C, *et al.* Utility of the injured trauma survivor screen to predict PTSD and depression during hospital admission. *J Trauma Acute Care Surg* 2017;82:93–101.
- 53 Jensen SM, Abrahamsen I, Baumgarten M, *et al.* Screening tools for predicting posttraumatic stress disorder in acutely injured adult trauma patients: A systematic review. *J Trauma Acute Care Surg* 2022;92:e115–26.
- 54 Bovin MJ, Marx BP, Weathers FW, *et al.* Psychometric properties of the PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (PCL-5) in veterans. *Psychol Assess* 2016;28:1379–91.
- 55 Wilson L, Horton L, Polinder S, *et al.* Tailoring Multi-Dimensional Outcomes to Level of Functional Recovery after Traumatic Brain Injury. *J Neurotrauma* 2022;39:1363–81.