Association between Marshall computed tomography grade and anxiety, depression and post-traumatic stress disorder one-year after moderate-severe traumatic brain injury

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Thesis declaration form

I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature:

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Date: 19/06/2022

Overview

This thesis is concerned with identifying predictors of self-reported psychiatric outcomes after traumatic brain injury (TBI).

Part 1 consists of a systematic review and meta-analysis of predictors of self-reported post-traumatic stress disorder (PTSD) symptoms after TBI. Limitations of the literature are discussed as well as recommendations for future research.

Part 2 is an empirical research paper consisting of a secondary analysis of data from the BIOmarkers of AXonal injury following Traumatic Brain Injury (BIO-AX-TBI) study. This is a prospective longitudinal study of fluid and neuroimaging biomarkers of axonal injury after moderate-severe TBI in adults, recruiting participants across multiple European centres (Graham et al. 2020). The secondary analysis aimed to explore the utility of a brain imaging measure, Marshall computed tomography grade, as a predictor of self-reported psychiatric outcomes one-year after TBI. These outcomes include anxiety, depression and PTSD.

Part 3 presents a critical appraisal of this thesis. It includes reflections on challenges encountered throughout the research process and personal insights gained from these. Also critically discussed are the limitations of the research, generalisability of the findings, and implications for clinical practice and future research.

Impact statement

In the UK, over a million people live with the consequences of traumatic brain injury (TBI), costing the economy around £15 billion a year (Parsonage, 2016). Psychiatric disorders are a disabling consequence of TBI that can hinder recovery and impair functioning (Rogers and Read, 2007).

This thesis examines predictors of self-reported psychiatric outcomes after TBI. Part 1 is a systematic review and meta-analysis investigating predictors of self-reported PTSD symptoms after TBI. It identifies promising predictors of post-TBI PTSD beyond those identified in the meta-analytic review of Cnossen et al (2017). The strengths and limitations of the studies included in the current review are discussed, and recommendations made for how risk of bias can be reduced in future studies. Suggestions are also made for directions of future research.

Part 2 of this thesis is a secondary analysis of a large set of data from the multi-centre, international, longitudinal BIO-AX-TBI study, examining the utility of Marshall computed tomography (CT) grade (a measure of TBI severity based on CT scan features) in predicting self-reported psychiatric outcomes one-year after moderate-severe TBI. These outcomes include anxiety, depression and PTSD. This is the first longitudinal study to investigate the prognostic value of Marshall CT grade for post-TBI psychiatric outcomes.

Together, these pieces of research contribute to the understanding of predictors of psychiatric outcomes after TBI. Dissemination through publication in a peer-reviewed journal would enable the findings to be shared more widely, helping them to inform future research.

The meta-analytic review highlights the need for further research to confirm significant associations identified in the meta-analyses, to investigate other promising predictors, and to explore moderators of these associations. The review also shows that the majority of studies on this topic are conducted in either the United States or European countries, and recruit predominantly Caucasian, male participants. This is problematic since it is therefore uncertain whether the findings generalise to more diverse patient populations.

This emphasises the need for further large-scale prospective cohort studies in more geographically diverse locations and with more demographically diverse samples. This could be complemented by qualitative research with key stakeholders, such as TBI patients, family members, carers and clinicians, investigating their perspectives on risk factors and protective factors for psychiatric disorders after TBI. It could also explore their ideas about underpinning mechanisms, moderating factors, and how this risk could be mitigated.

This research represents a further step towards developing multivariate predictive models to predict psychiatric outcomes after TBI in clinical practice. Such models could serve as a valuable adjunct to diagnosis and clinical judgement, improving predictions about prognosis after TBI. Identifying individuals at risk of psychiatric disorders after TBI would aid their early prevention and treatment, thereby improving outcomes for TBI survivors.

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Part 1: Literature review

Predictors of self-reported post-traumatic stress disorder symptoms after traumatic brain injury: a systematic review and meta-analysis

Abstract

Background: This systematic review and meta-analysis examines predictors of self-reported symptoms of post-traumatic stress disorder (PTSD) in civilians after traumatic brain injury (TBI), assessed using the PTSD Checklist for DSM-IV – Civilian Version (PCL-C) or the PTSD Checklist for DSM-5 (PCL-5).

Methods: A systematic literature search was conducted in MEDLINE, EMBASE, PsycInfo, Web of Science, Cochrane Library and Google Scholar up until August 2021. Studies were identified exploring univariable predictors or multivariable models of self-reported PTSD symptoms after TBI, measured using the PCL-C or PCL-5. Univariate effects were meta-analysed. The review was limited to studies recruiting civilians aged 16-80 with a TBI of any severity. Data were extracted using the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies checklist. Risk of bias assessments were conducted using the Quality in Prognostic Studies tool. Random effects meta-analyses were performed on univariable predictors in RevMan (version 5.4.1).

Results: A total of 19 papers, from 10 different studies, published between 2006-2022 were included. The majority of the studies were prospective cohort studies (n = 6) and based in the US (n = 6). TBI severity ranged from mild to severe. Risk of bias ratings were generally acceptable, though most studies had a moderate risk of bias in the 'study participation' domain, and many in 'statistical analysis and reporting' domain. 12 papers reported multivariable models. 20 univariable predictors were meta-analysed. Pooled effects showed that higher scores on self-report PTSD measures after TBI were significantly associated with: non-Caucasian race (pOR = 1.78; 95% CI: 1.21, 2.62; I^2 = 0%; 3 studies), assault mechanism of injury (pOR = 3.44; 95% CI: 2.37, 5.00; I^2 = 7%; 5 studies), pre-TBI psychiatric history (pOR = 2.95; 95% CI: 2.25, 3.89; I^2 = 0%; 4 studies) and positive toxicology screen on admission (pOR = 3.40; 95% CI: 1.45, 7.95; I^2 = 0%; 2 studies). Years of education was significantly inversely associated with scores on self-report PTSD

measures after TBI (pMD = -1.43; 95% CI: -1.93, -0.94; I^2 = 0%; 2 studies). These findings were robust to sensitivity analyses in which studies with cross-sectional or retrospective designs were excluded.

Discussion: This review and meta-analysis adds to existing research by identifying a number of potential predictors of self-reported PTSD symptoms after TBI. More research in more geographically diverse locations and recruiting more demographically diverse samples is needed to confirm the relevance of these predictors. Future research could also explore moderators of these associations. This would help to develop multivariate models that could identify TBI survivors at risk of PTSD in clinical practice.

1. Introduction

Traumatic brain injury (TBI) is a disruption of the brain's normal structure or function caused by a head impact or external force (Haydel and Lauro, 2022). With an estimated 69 million people sustaining a TBI each year globally (Dewan *et al.*, 2018), it is one of the leading causes of death and life-long disability. TBI is associated with a range of negative outcomes including: physical disability, cognitive impairment, functional impairment and mental health difficulties (Rabinowitz and Levin, 2014; Devi *et al.*, 2020).

Psychiatric disorders can hinder recovery from TBI (Mooney, Speed and Sheppard, 2005; Moore, Terryberry-Spohr and Hope, 2006; Kim *et al.*, 2007; J Horn *et al.*, 2017). Identifying prognostic factors of mental health difficulties after TBI could help aid their prevention, early identification and treatment, improving survivors' outcomes.

Post-traumatic stress disorder (PTSD) is the third most common mental health disorder after TBI, with an estimated prevalence of 17-33% (Ohry, Rattok and Solomon, 1996; Motzkin and Koenigs, 2015). PTSD occurs after traumatic events. It is characterised by re-experiencing symptoms (e.g., flashbacks, nightmares), avoidance of reminders of the event, and persistent hypervigilance and awareness of threat (American Psychiatric Association, 2013).

A systematic review by Gill et al. (2014) investigated psychological and psychosocial factors associated with PTSD after TBI. They identified associations between post-TBI PTSD and variables such as: certain psychological processes (e.g., coping and attribution styles), psychosocial variables (e.g., impaired roles), acute stress disorder and comorbid depression and anxiety. They also noted that certain factors associated with PTSD in the general population were not associated with PTSD in TBI populations, including: marital status, litigation, employment status after TBI and educational level (Gill, Mullin and Simpson, 2014). However, the directions of identified relationships were unclear since all factors associated with PTSD after TBI were examined, not just predictive factors.

A systematic review and meta-analysis by Cnossen et al. (2017) specifically investigated predictors of PTSD after TBI. They found that shorter post-traumatic amnesia (PTA), memory of the traumatic event, and early post-traumatic symptoms were associated with increased risk of PTSD after TBI (Cnossen *et al.*, 2017). Another systematic review by Scholten et al. (2016) investigated risk factors of anxiety disorders (including, but not limited to PTSD) after TBI. They found that female gender, unemployment, and pre-TBI psychiatric history were associated with an increased risk of post-TBI anxiety. However, they did not conduct any meta-analyses.

Both of these reviews only included studies which used "gold standard" structured diagnostic interviews to measure PTSD. This decision was made due to some evidence that self-report measures can over- or under-estimate the incidence of psychiatric disorders after TBI due to confounding symptoms of the injury (Moore, Terryberry-Spohr and Hope, 2006). However, other research does suggest that self-report measures can have validity as screening instruments in TBI populations (Dahm, Wong and Ponsford, 2013; von Steinbuechel *et al.*, 2021). They also have some benefits over structured diagnostic interviews, in that they are less resource- and time-intensive to administer. They are therefore commonly used in clinical practice and research. Providing that the limitations of self-report measures are taken into consideration, conducting a meta-analytic review of studies utilising self-report measures to assess PTSD could expand on previous research and provide a broader overview of potential predictors of post-TBI PTSD.

The aim of this systematic review and meta-analysis is therefore to examine univariable predictors and multivariable models of self-reported PTSD symptoms following TBI.

2. Methods

A comprehensive literature search was conducted until August 2021. The search strategy (see Appendix A) was developed in consultation with a specialist librarian. The following databases were searched: MEDLINE, EMBASE, PsycINFO, Web of Science, Cochrane

Library and Google Scholar. Reference lists and citation indices of relevant papers were also searched. Only studies published in the English language were included. No date restrictions were applied.

2.1. Study selection

Studies were selected that examined univariable predictors or multivariable models of self-reported PTSD symptoms after TBI. Study eligibility was determined using the inclusion and exclusion criteria below.

2.1.1. *Participants*

The participants were civilian adults (aged 16 years or older) who sustained a TBI. TBI was defined as "an alteration in brain function or other evidence of brain pathology, caused by an external force" (Menon *et al.*, 2010). Patients with any severity of TBI were included (mild, moderate and severe). Military patients were excluded due to the fact that there are significant differences between civilian and military TBI patient populations (Taber, Warden and Hurley, 2006; Cernak *et al.*, 2011; Cnossen *et al.*, 2017).

2.1.2. *Outcome measurement*

When the protocol for the current review was initially devised, it aimed to include studies utilising any validated self-report measure of post-TBI anxiety or PTSD symptoms. However, during the study selection process the protocol was amended, narrowing the inclusion criteria to only include studies measuring post-TBI PTSD symptoms using the PTSD Checklist for DSM-5 (PCL-5) (Bovin *et al.*, 2016) or the PTSD Checklist for DSM-IV – Civilian version (PCL-C) (Weathers *et al.*, 2003). This decision was made due to too many papers meeting the eligibility criteria being returned by the original search strategy; it would not have been practically feasible to include all of them. Studies which only used structured diagnostic

interviews to diagnose PTSD were excluded, as these have been previously reviewed (Cnossen *et al.*, 2017).

2.1.3. Predictors

Studies were selected that investigated at least one predictor or multivariable model of self-reported PTSD after TBI. To be included, they needed to report baseline differences in predictors (e.g., means and standard deviations of continuous predictors, or counts for categorical predictors). They could also have reported descriptive statistics (e.g., statistics produced by a t-test, chi-square test, p-values). If they reported a multivariable model, they needed to provide relevant statistics (e.g., odds ratios, measures of goodness-of-fit).

Predictors must have preceded the measurement of PTSD – either by being measured before the PTSD self-report measure was completed (in prospective studies), or by clearly preceding the outcome measurement (e.g., variables such as age, gender). Multivariable models are defined as models incorporating two or more predictors of post-TBI PTSD symptoms.

2.1.4. Study design

Prospective cohort, cross-sectional, retrospective cohort and case-control studies were all included.

2.2. Data extraction and assessment of risk of bias

Eligibility assessment was performed unblinded and in a standardised manner by one reviewer. Uncertainties were resolved by consensus with two supervisors.

Citations were screened by the reviewer on the basis of titles and abstracts. They were then screened based on full texts. Studies which did not meet the eligibility criteria were excluded. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Moher *et al.*, 2009) was used to document the study selection process.

A data extraction form was developed based on the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) Checklist (Moons *et al.*, 2014). The CHARMS Checklist requires extraction of information relating to: participants, outcomes to be predicted, candidate predictors, sample size, missing data, model development, model performance, model evaluation, results and interpretation (Moons *et al.*, 2014).

Information about univariable associations between predictors and self-reported PTSD was collected. This included means and standard deviations for continuous predictors, and counts for categorical predictors. If available, univariable and multivariable statistics and effect measurements were also extracted. The extraction form was pilot-tested on five randomly-selected included studies. Eight authors were contacted for further information via email and online research profiles, but none responded.

The Quality in Prognostic Studies (QUIPS) risk-of-bias tool, which has been recommended by the Cochrane Prognosis Methods groups (Hayden *et al.*, 2013), was used to assess risk of bias in the included studies. It involves rating risk of bias in the following domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting (Hayden *et al.*, 2013). Domains were rated as “low risk”, “moderate risk” or “high risk” of bias. A domain was rated as “low risk” of bias if all items in it were rated as “low risk” of bias. Domains were rated as “moderate risk” of bias if they included at least one or up to 50% of items rated as high risk of bias or unknown risk of bias. Domains were rated as “high risk” of bias if over 50% of items in them were rated as high or unknown risk of bias (Cnossen *et al.*, 2017).

2.3. Data synthesis

Meta-analyses were performed on univariable predictors of PTSD symptoms. Predictors were included in the meta-analysis if relevant univariable data were available in at least two studies. If a study measured a predictor differently to the other studies (e.g., defined it using

different categories), then it was excluded from the meta-analysis. Studies with a high risk of bias in at least two QUIPS domains (other than study confounding, since meta-analyses were only performed on univariable associations) were excluded from meta-analyses. Studies were also excluded from meta-analyses if they had a sample size of 20 or less. If studies assessed predictors of PTSD symptoms at multiple time points, data from the time point closest to that used in other studies were included.

Meta-analyses were performed using Review Manager (RevMan) version 5.4.1 (The Cochrane Collaboration, 2020). All tests were two-sided, with a significance threshold of 0.05. The Mantel-Haenszel statistic was calculated for categorical predictors (Cochrane, 2002). Inverse variance was used to analyse continuous predictors. Random effect models were used for all analyses, as heterogeneity was expected in study samples and methodologies (e.g., follow-up periods, inclusion and exclusion criteria, study design, how measurements were made). For continuous predictors, pooled mean differences (pMD) were reported. For categorical predictors, pooled odds ratios (pOR) were reported. Confidence intervals for both types of pooled statistics were also provided. The I^2 statistic was used to measure heterogeneity. An I^2 statistic greater than or equal to 50% was considered an indication of substantial heterogeneity, in line with Cochrane guidance (Cochrane, 2002). In cases of high heterogeneity, pooled results should be interpreted with caution (Cochrane, 2002).

Two sensitivity analyses were performed to explore the degree to which the main findings were robust. One a priori sensitivity analysis examined the effect of study design (prospective versus non-prospective). Another sensitivity analysis was conducted post-hoc to explore the effect of excluding Bombardier et al's (2006) study which examined predictors of screening positive for PTSD at any of their six, monthly follow-ups (compared to all other studies which examined predictors for PTSD scores at each time-point separately).

Predictors that were reported in one or more studies, but were not eligible for inclusion in the meta-analyses, are described in the narrative synthesis. Multivariable models of PTSD symptoms are also narratively described.

2.4. Multiple publications

Where there were multiple papers analysing data from the same cohort, one main paper was selected. Papers which included multivariable analyses, had the largest sample size, and studied the largest number of predictors were prioritised. If any relevant results were not available from the prioritised paper, the authors were contacted to request them. If they were not provided, data were extracted from the next most suitable paper from the same study. Only data relating to new predictors were extracted from the study's remaining papers.

3. Results

3.1. Study selection

A total of 14,356 citations were returned by the electronic search strategy (see Figure 1**,** below). 6158 duplicate records were removed. The remaining 8198 records were screened based on title and abstract. 7,350 were excluded. The remaining 848 were screened based on full-texts.

225 full-texts were screened, and 161 of these were excluded before a change was made to the review's inclusion criteria. After discussion with supervisors, the decision was made to restrict the inclusion criteria further to only studies utilising the PCL-5 or PCL-C to measure PTSD symptoms (rather than any validated self-report measure of PTSD or anxiety, which had been the previous plan).

Up until this change in eligibility criteria, the most common reasons for full-text exclusion included: the study not exploring predictors of anxiety or PTSD (n = 72), not measuring anxiety or PTSD using a validated self-report measure (n = 31), not using a specific anxiety measure (n = 30), having a non-TBI population (or it not being possible to distinguish findings between TBI vs non-TBI participants) (n = 15). Others reasons for exclusion included: participants being too young (or it not being possible to distinguish findings between participants aged 16+ versus under 16) (N = 10), and the study having a

military TBI population (or mixed civilian and military TBI populations where it was not possible to distinguish findings between the groups) (n = 3).

The remaining 623 full-texts were then screened according to the new eligibility criteria. Studies previously included based on full-text screening (64 papers) were re-screened to re-assess their eligibility according to the new criteria.

669 of these full-texts were excluded, resulting in 19 papers being included. The most common reasons for exclusion in this step were: the study not using the PCL-5 or PCL-C to measure PTSD (n = 598); non-TBI population (or having a mixed trauma population where it was not possible to distinguish between TBI vs non-TBI patient findings) (n = 30); participants being under 16 years of age (or below and above 16 years old, with no age breakdown provided) (n = 21). Other exclusion reasons included: the paper being a review article (n = 7), an intervention study (n = 1), a case study (n = 1), based on a military TBI population (or mixed military and civilian TBI population with no way to distinguish findings between the groups) (n = 11), measures being completed by proxy (n = 1) and the study not being available in English (n = 1).

An additional two eligible studies were identified through searching the references and citation indices of relevant papers.

The final sample of 19 included papers included 10 different studies. There were multiple papers published analysing data from the same prospective cohort studies – including six analysing TRACK-TBI pilot study data (Dams-O'Connor *et al.*, 2013; Haarbauer-Krupa *et al.*, 2017; Winkler *et al.*, 2017; Yue *et al.*, 2018, 2019, 2020), two analysing TRACK-TBI full study data (Stein *et al.*, 2019, 2021), three analysing CENTER-TBI study data (Mikolić *et al.*, 2021; van der Vlegel *et al.*, 2021; Van Praag *et al.*, 2022), and two analysing data from a cross-sectional study based at a trauma centre in Birmingham, UK (Bown *et al.*, 2019; Qureshi *et al.*, 2019). Of these 19 included papers, 9 were included in the meta-analyses of univariate predictors.

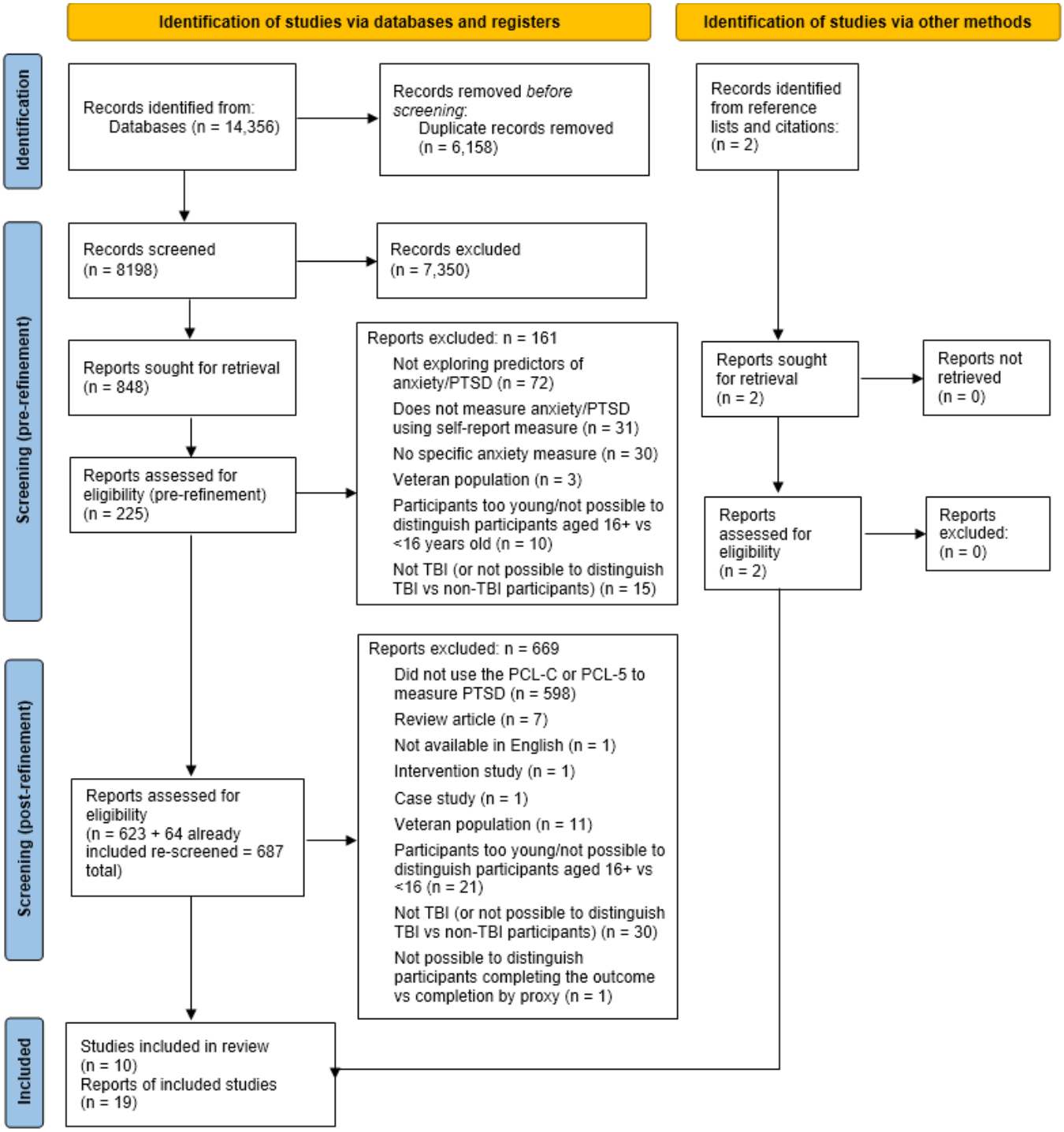

Figure 1. PRISMA flowchart of the study selection process (Moher *et al.*, 2009) PTSD = Post-Traumatic Stress Disorder. PCL-5 = PTSD Checklist for the DSM-5. PCL-C = PTSD Checklist for DSM-IV – Civilian Version. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; TBI = Traumatic Brain Injury.

3.2. Study characteristics

The characteristics of included papers are summarised in Table 2, below. Of the 10 different studies included, the majority (n = 6) were prospective cohort studies (Bai et al. 2019; Bombardier et al. 2006; CENTRE TBI study; McCauley et al. 2013, TRACK-TBI full study and the TRACK-TBI pilot study). However, the only relevant results from Bai et al's (2019) study were collected at a single time-point so it can be considered cross-sectional for the purposes of this review. Three other studies had cross-sectional designs (Grant, 2021; Stillman et al. 2020; and the study analysed by Bown et al. (2019) and Qureshi et al. (2019). One study had a retrospective case-control design (Terry *et al.*, 2018).

Studies were published between 2006 and 2022. The majority of studies were conducted in the United States (US) (n = 6) (Bombardier et al. 2006; Grant, 2021; McCauley et al. 2013; Stillman et al. 2020; TRACK-TBI full study; TRACK-TBI pilot study). The remaining were conducted in Europe and Israel (n = 1) (CENTER-TBI study), the UK (n = 1) (the study analysed by Bown et al. (2019) and Qureshi et al. (2019)), Canada (n = 1) (Terry et al. 2018) and China (n = 1) (Bai et al. 2019).

Patients were most often recruited from level 1 trauma centres (n = 7) (Bombardier et al. 2006; CENTER-TBI study; Grant, 2021; McCauley et al. 2013; TRACK-TBI full study; TRACK-TBI pilot and the study by Bown et al. (2019) and Qureshi et al. (2019)). Two studies recruited participants from specialist concussion outpatient clinics (Terry et al. 2018; Stillman et al. 2013), and one from a local emergency department (Bai et al. 2019).

The TRACK-TBI pilot study recruited participants with all severities of TBI. The six papers analysing TRACK-TBI pilot data limited their inclusion criteria to: participants with any severity of TBI (n = 2; Dams-O'Connor et al., 2013; Yue et al., 2018); participants with "non-devastating" TBI (n = 1; Yue et al., 2020); mTBI (n = 2; Haarbauer-Krupa et al., 2017; Yue et al., 2019) and uncomplicated mTBI (n = 1; Winkler *et al.*, 2017). Both papers from the TRACK-TBI full study analysed data from participants with mTBI only (Stein *et al.*, 2019, 2021). Two papers from the CENTER-TBI study included participants with any

severity of TBI (Mikolić *et al.*, 2021; Van Praag *et al.*, 2022), whilst the other included only those with mTBI (van der Vlegel *et al.*, 2021). Out of the remaining 8 papers, one recruited participants with any severity of TBI (Grant, 2021), one recruited participants with complicated mTBI or moderate or severe TBI (Bombardier *et al.*, 2006) and five recruited only mTBI patients (McCauley *et al.*, 2013; Terry *et al.*, 2018; Bai *et al.*, 2019; Bown *et al.*, 2019; Qureshi *et al.*, 2019; Stillman *et al.*, 2020)

The 19 included papers had an average of 538 participants (ranging from 41 to 4195). The majority of studies recruited predominantly White, male patients. 12 papers included a multivariable model to predict PTSD. Most predictors were measured during visits to the emergency department. Most studies used the PCL-C to assess PTSD symptoms (n = 8) the remainder used the PCL-5 (n = 2) (Terry et al. 2018; TRACK-TBI full study). Most papers only analysed PTSD outcomes 6 months after TBI (Dams-O'Connor *et al.*, 2013; Haarbauer-Krupa *et al.*, 2017; Winkler *et al.*, 2017; Yue *et al.*, 2018, 2019, 2020; Mikolić *et al.*, 2021; van der Vlegel *et al.*, 2021; Van Praag *et al.*, 2022) (range: within 24 hours to 55 months after injury). 14 papers analysed PTSD outcomes at a single time point only. All studies analysed each time point independently, except in Bombardier et al.'s (2006) study, where PTSD outcomes were measured for each participant monthly until 6 months post-injury. Bombardier et al. (2006) explored predictors of screening positive for PTSD at any of these time points.

Study	Study design, setting	Study population	Inclusion and exclusion criteria	Patient characteristics	Sample size	Predictors	PTSD measure	Outcome timing	Relevant statistical analyses performed
Dams-O'Connor et al., 2013 (TRACK-TBI pilot study)	Multi-centre prospective cohort 2010 - 2012	Sampling method: Convenience TBI severity: mild, moderate or severe Location: One of 3 level 1 trauma centres in the USA	Inclusion criteria: - Presented to eligible trauma centre ED within 24 of head injury - Head injury sufficient to necessitate non-contrast CT using the ACEP/CDC evidence-based joint practice guidelines - Able to provide informed consent independently or through proxy - Aged over 16 Exclusion criteria: - People who do not speak English - Pregnant people - People in legal custody - People in the process of psychiatric evaluation - Contraindications to MRI	Sex: 71.5% male Age: mean: 43.3 years, SD: 18.5 Severity: 82% mild (GCS 13-15), 5% moderate (GCS: 9-12), 13% severe (GCS 8 or below) Mechanism of injury: 21.8% assault	586	Previous TBI with LOC Confounders adjusted for: - Age (years) - Education (years) - Race (Caucasian/non-Caucasian) - Admission GCS - Length of hospital stay (days) - LOC for the current injury (present/absent) - CT scan (positive/negative)	PCL-C (in-person) Continuous total score	6 months post-TBI	Univariate: None reported Multivariate: Hierarchical multiple regression (results not reported)
Haarbauer-Krupa et al., 2017 (TRACK-TBI	Multi-centre prospective cohort 2010 - 2012	Sampling method: Convenience TBI severity: mild	Inclusion criteria: - Presented to eligible trauma centre ED within 24 of head injury sufficient to necessitate non-contrast CT using the ACEP/CDC	Sex: 69.3% male Age: mean: 42.9 years, SD: 17.8	280	Age (years; continuous) Gender (male/female) Race (Caucasian/non-Caucasian) Marital status (single/married/separated or	PCL-C (in-person) Categorical. Cut-off: DSM-IV criteria	6 months post-TBI	Univariate: - Wilcoxon Mann-Whitney U - Chi-squared tests - Fisher's

pilot study)		Location: One of 3 level 1 trauma centres in the USA	evidence-based joint practice guideline - Aged over 16 - Had completed the PCL-C measure at 6-months - Mild TBI (GCS score 13-15) Exclusion criteria: - Non-English speakers - Pregnant people - People in legal custody - Under medically-evaluated psychiatric hold at the time of enrolment	Years of education: mean 14.4 (SD: 2.9) Race: 81.8% Caucasian ED GCS on admission: 13: 2.9% 14: 20% 15: 77.1% Mechanism of injury: 15.4% assault		divorced/widowed/other or unknown) Centre Prior psychiatric history (yes/no) Military service history (yes/no) Mechanism of injury (MVA [driver/passenger]/MVA [motorcyclist]/MVA [pedestrian/cyclist] ED toxicology screen (positive/negative) ED GCS (13/14/15) ED disposition (ED discharge/hospital admission/intensive care unit admission) ISS (continuous) Overall injury severity (ISS <16/ ISS >=16)	75/280 PTSD+ (26.8% screened positive at 6m)		Exact - Univariable logistic regressions Multivariate: - Logistic regression with stepwise forward procedure
Winkler et al., 2017 (TRACK-TBI pilot study)	Multi-centre prospective cohort 2010 - 2012	Sampling method: Convenience TBI severity: Uncomplicated mTBI (GCS of 13 or more; LOC < 30 minutes; PTA < 24 hours; no skull fracture or intracranial pathology)	Inclusion criteria: - Patients presenting to one of the three Level I trauma centres with external force trauma to the head and clinically indicated head CT scan within 24h of injury - Aged 16 and over - GCS of 13 or more - LOC < 30 mins - PTA < 24h - No skull fracture or acute intracranial pathology (defined as the absence of	Age: mean: 40 years old Sex: 60% male Race: African American (14%), Asian (7%), mixed race (7%), American Indian/Native Alaskan (2%), Hawaiian/Pacific Islander (2%)	93	Predictor: COMT genotype (Met^{158} carriers vs Val^{158}/Val^{158} homozygotes) Confounders adjusted for: Pre-existing psychiatric disorder (present/absent) Illicit drug use history (present/absent)	PCL-C Categorical. Cut-off: DSM-IV criteria	6 months post-TBI	Univariate: - Chi-squared - Univariable logistic regression Multivariate: - Multivariable logistic regression including Nagelkerke pseudo-R-square

		Location: One of 3 level 1 trauma centres in the USA	intraparenchymal contusions or haemorrhage, axonal injury, ventricular haemorrhage, epidural haematoma, acute subdural haematoma or traumatic subarachnoid haemorrhage) on non-contrasted head CT - No polytrauma as defined by an AIS score >1 in any extracranial body region Exclusion criteria: - Pregnancy - Comorbid life-threatening disease - Incarceration - Serious psychiatric and neurologic disorders that would interfere with outcome assessment - Non-English speakers - Patients who reported pre-injury PTSD or schizophrenia - Patients with previous cerebrovascular accidents, brain tumour and baseline developmental delay	Pre-injury psychiatric history: 39% had one or more psychiatric conditions Pre-injury substance abuse: 76.3% Mechanisms of injury: Assault: 15.1% ED arrival GCS: 13: 1.1% 14: 18.3% 15: 80.6%					

Yue et al., 2018 (TRACK-TBI pilot study)	Multi-centre prospective cohort 2010 - 2012	Sampling method: Convenience TBI severity: Mild, moderate and severe Location: One of 3 level 1 trauma centres in the USA	Inclusion criteria: - External force trauma to the head - Presentation to one of the three trauma centres - Clinically-indicated head CT scan within 24 hours of injury - Aged 18 or over - ED admission GCS score of 13-15 - Recorded pre-injury employment status (not retired, student or on disability payment) - Complete 6 month outcomes Exclusion criteria: - Pregnancy - Ongoing life-threatening disease - Police custody - Involuntary psychiatric hold - Non-English speakers - People with a history of a cerebrovascular accident, CNS tumour, spinal cord or vertebral injury, learning disability and/or developmental delay	Age: 39.8±15.4-years Sex: 73.5% male Race: 74.7% Caucasian Education level: Below high school: 6.8% High school/GED: 55.6% College degree or above: 37.7% Mechanism of injury: 14.2% assault ED GCS =15: 73.5% <15: 26.5%	162	Predictor: Pre-injury employment status (employed vs non-employed) Confounders adjusted for: Age (years) Highest education level (below high school/high school/high school diploma or GED/college degree or above) Race (Caucasian/African-American/other) Pre-injury psychiatric disorder (present/absent) Pre-injury headache/migraine (present/absent) LOC (yes/no/unknown) PTA (yes/no/unknown) ED GCS (=15/<15) Intracranial lesion on CT (present/absent) Polytrauma (AIS >2 in any extracranial region)	PCL-C (in-person) Continuous total score	6 months post-TBI	Univariate: ANOVA Multivariate: Multiple linear regression
Yue et al., 2019 (TRACK-TBI	Multi-centre prospective cohort	Sampling method: Convenience	Inclusion criteria: - Aged 18-39 - Acute external force trauma to the head - Presenting to an	Age: 26.9±6.1 years Sex: 71% male	100	Predictors: Age (categories: 18-29, 30-39) Sex	PCL-C (in-person)	6 months post-TBI	Univariate: None Multivariate: Multiple linear

pilot study)	2010 - 2012	TBI severity: mild Location: One of 3 level 1 trauma centres in the USA	enrolling centre - Triage to a clinically indicated CT scan within 24 hours of injury - Complete 6-month outcome measures - Emergency department admission GCS score of 13-15 - Loss of consciousness <30 minutes - Marshall CT score <5 to include those without the need for surgical decompression and/or large intracranial mass lesions Exclusion criteria - Pregnancy - Ongoing life-threatening disease - Police custody - Involuntary psychiatric hold - Non-English speakers	Race: 72% Caucasian Mechanism of injury: 22% MVA or motorcycle crash 14% pedestrians vs auto 41% falls 21% assaults 2% other ED GCS 15 (78%)		Confounders adjusted for: Race (African American/ other) Education (years) Psychiatric history (yes/no) Mechanism of injury (assault/non-assault) LOC (none/<30mins/unknown GCS (=15/<15) Acute intracranial lesion of CT (yes/no) Polytrauma (AIS score >1 in any extracranial region)	Categorical. Cut-off: >=36		regression with Benjamin-Hochberg correction
Yue et al., 2020 (TRACK-TBI pilot study)	Multi-centre prospective cohort 2010 - 2012	Sampling method: Convenience TBI severity: "Not devastating" (Marshall CT score 1-3	Inclusion criteria - Aged 16 or older - Acute external force trauma to the head - Presenting to an enrolling centre - Triage to a clinically indicated CT scan	Age: mean: 41.4 (SD: 17.6) Sex: 68.4% male Race: 87.2% Caucasian	133	Predictors: ED toxicology screen (positive/negative) Confounders adjusted for: Age (years) Sex (male/female) Education (years)	PCL-C (in-person) Categorical. Cut-off: (DSM-IV criteria)	6 months post-TBI	Univariate: - Chi-squared Multivariate: - Multivariable logistic regression

		and no neurosurgery or insertion of neuromonitoring device) Location: One of 3 level 1 trauma centres in the USA	within 24 hours of injury - Received a urine toxicology test at the ED - Marshall CT score 1-3 Exclusion criteria - Pregnant people - Ongoing life-threatening disease - Police custody - Involuntary psychiatric hold - Non-English speakers - People who underwent neurosurgery or insertion of a neuromonitoring device	Years of education: mean: 13.9, SD: 3.10 Psychiatric history: 6.8% ED GCS: <15: 53.4% =15: 45.1% Mechanism of injury: 11.3% assault		Race (Caucasian vs. non-Caucasian) Psychiatric history (yes/no) Historical substance use (yes/no) ED GCS (15/<15) CT intracranial findings (positive/negative) Polytrauma (AIS =3+/AIS<3)	13.5% had positive PCL-C screen		
Stein et al., 2019 (TRACK-TBI full study)	Multi-centre prospective cohort 2014 - 2016	Sampling method: Non-consecutive sampling TBI severity: Mild (ED GCS: 13-15) Location: 11 academic level 1 trauma centres in the US	Inclusion criteria - Presenting to one of the eligible trauma centres within 24 hours of injury following evaluation in the ED for TBI - ED GCS scores of 13-15 on arrival - Received a CT scan as per order of the evaluating clinician - Fluent in English or Spanish Exclusion criteria: - Significant multiple trauma	Age: mean: 40.5 years (SD: 17.2 years) Gender: 65.1% men Race: 77.2% White Ethnicity: 21.4% Hispanic Education Mean 13.6 years (SD: 2.9)	1155	Predictors: Age (years) Sex (male/female) Race (African-American/non-African-American) Hispanic (yes/no) Employment status at baseline (employed or retired or student vs. unemployed) Insurance (uninsured/Medicaid/Medicare/employment or private insured) Education (years) Care pathway (ED discharge/hospital	PCL-5 Continuous total scores used in some analyses Score of 33 or more used to indicate probable PTSD in others Total PCL-5 was pro-	2 weeks post-TBI 3 months post-TBI 6 months post-TBI 12 months post-TBI	Univariate analyses: None relevant Multivariate analyses: - Weights-adjusted multivariable logistic regression at 3m, 6, and 12-months post-TBI Statistical significance determined

			- Penetrating TBI - Prisoners - Patients in custody - Pregnancy - People in the ED for psychiatric assessment - Major debilitating mental (e.g., schizophrenia, bipolar disorder) or neurological disorders (e.g., stroke, dementia) - Any other disorder that would interfere with follow-up or informed consent 230 trauma controls were recruited using identical inclusion and exclusion criteria except none judged to have probable TBI	<u>Psychiatric history:</u> 21% <u>Mechanism of injury:</u> 6.1% assault		admission no ICU/hospital admission with ICU) Injury cause (motor vehicle/fall/other non-intentional injury/violence or assault) LOC (present/absent) PTA (present/absent) CT intracranial injury (yes/no) Psychiatric history (yes/no) Prior TBI (yes/no)	rated if less than 25% of items were missing		with Wald X^2 tests - Longitudinal linear mixed-effects model
Stein et al., 2021 (TRACK-TBI full study)	Multi-centre prospective cohort Feb 2014 – Aug 2018	<u>Sampling method:</u> Non-consecutive sampling <u>TBI severity:</u> Mild (ED GCS: 13-15) <u>Location:</u> 11 academic level 1 trauma centres in the US	<u>Inclusion criteria:</u> - Aged 17 or over - GCS ED arrival scores 13-15 - PCL-5 outcome measures collected at both 3 months and 6 months post-injury - MRI volumetrics measures analysed from a research-acquired 3D T1-weighted MRI scanner at 2 weeks post-TBI	<u>Age:</u> Mean: 38.7 years (SD: 16.1 years) <u>Sex:</u> 66.5% male <u>Race:</u> 73.9% White, 18.2% Black, 7.9% other <u>Years of education:</u> mean: 14.1	421	<u>Predictors:</u> Age (years) Education (years) Care pathway (ED discharge/hospital admission no ICU/hospital admission with ICU) Sex (male/female) Race (White/Black/other) Ethnicity (Hispanic/non-Hispanic) Injury cause (RTA/incidental fall/violence or	PCL-5 Categorical. Cut-off: >=33	3 months post-TBI 6 months post-TBI	<u>Univariate:</u> Not specified <u>Bivariate:</u> - Logistic regression - Benjamin-Hochberg's method to correct for multiple testing <u>Dimension reduction:</u> - PCA on MRI

			Exclusion criteria: - Penetrating TBI - Significant polytrauma that would interfere with follow-up - Prisoners or patients in custody - Pregnancy - Patients on psychiatric hold - Non-English or non-Spanish speakers - Contraindications to MRI - Major debilitating mental (e.g., schizophrenia, bipolar disorder) or neurological (e.g., stroke, dementia) conditions - Any other disorder that would interfere with follow-up or provision of informed consent	years (SD: 2.73 years) Psychiatric history: 17.6% positive Mechanism of injury: 5.5% assault		assault/other) Psychiatric history (yes/no) Prior TBI (yes/no) CT abnormalities (yes/no) MRI abnormalities (yes/no) Bivariate analyses: Insula MRI volume Hippocampus MRI volume Amygdala MRI volume Superior frontal cortex MRI volume Rostral anterior cingulate cortex MRI volume Caudal anterior cingulate cortex MRI volume Medial orbitofrontal cortex MRI volume Lateral orbitofrontal cortex MRI volume *All adjusted for intracranial volume* Multivariate analysis PC1 (capturing 73.8% of the variance in the regional volumes of the insula, superior frontal cortex, and rostral and caudal anterior cingulate cortices)			brain area volumes Multivariable regression: - Logistic regression

						Controlled for: Male gender, ref: female Black race, ref: White/other Hispanic ethnicity, ref: non-Hispanic) Years of education Any psychiatric history, ref: none Any prior TBI, ref: none Violent injury cause, ref: accidental PCL-5 total score at week 2			
Mikolić et al., 2021 (CENTER-TBI core study)	Multi-centre prospective cohort December 2014 – December 2017	<u>Sampling method:</u> Non-consecutive (maximum caps per centre to prevent over-representation, recruitment strategies decided locally) <u>TBI severity:</u> Mild (baseline GCS score 13-15), and moderate/severe (baseline GCS score 3-12)	<u>Inclusion criteria:</u> - Clinical diagnosis of TBI - Presented to a study centre within 24 hours of injury either to the ER, admission ward or ICU - Had an indication for CT scanning - Provided informed consent <u>Exclusion criteria:</u> - Severe pre-existing neurological disorder that could confound outcome assessments	<u>Sex:</u> 67.3% male <u>Pre-injury psychiatric history:</u> 13.8% <u>Mechanism of injury:</u> 6.7% assault <u>GCS baseline:</u> 3-8: 22.9% 9-13: 8.8% 13: 4.6% 14: 11.8% 15: 51.9%	4195	<u>Predictors:</u> Age Sex (male/female) <u>Confounders adjusted for:</u> Age (years) Baseline GCS score Pupillary reactivity Hypotension and hypoxia before arrival/at admission CT abnormalities (CT Marshall Classification) traumatic subarachnoid haemorrhage Epidural haematoma Injury severity score Pre-injury medical situation (ASA PS classification) Pre-injury psychiatric disorder	PCL-5 Cut-off: >-33 used in most analyses Continuous PCL-5 total scores used in one multivariate analysis	6 months post-TBI	<u>Univariate analyses:</u> - Mann-Whitney U - Univariable mixed effect regression <u>Multivariate analyses:</u> - Multivariable ordinal mixed effects regression (imputed data included) - Complete case only mixed effects regression - Linear mixed effect regression

		Location: 63 academic hospitals, mostly in urban areas in North and Western Europe and Israel				Cause of injury (fall/motor vehicle accident/violence/other)			
van der Vlegel et al., 2021 (CENTER-TBI core study)	Multi-centre prospective cohort December 2014 – December 2017	Sampling method: Non-consecutive (maximum caps per centre to prevent over-representation, recruitment strategies decided locally) TBI severity: Mild (GCS score 13-15) Location: 63 academic hospitals, mostly in urban areas in North and Western Europe and Israel	Inclusion criteria: - Aged 16 and over - GCS score 13-15 at baseline - Completed the RPQ at 6m follow-up - Completed the PCL-5 at 6m follow-up - Clinical diagnosis of TBI - Indication for CT scanning - Presentation to a participating centre within 24 of TBI Exclusion criteria: - Pre-existing neurological disorder (e.g., cerebrovascular accident, transient ischaemic attacks and epilepsy) which could confound outcome assessments	Age: median: 53.0 (IQR: 35.0-66.0) Sex: 63.4% male Level of education: 12.9% primary, 28.9% secondary, 18.6% post-high school training, 30.2% college/university Pre-injury psychiatric condition: 12.1%	1566	Predictors: Age (years) Sex (male/female) Highest level of education (primary/secondary/post-high school training/college or university/NA) Baseline employment (full-time employed/part-time employed/unemployed/student homemaker/retired/NA) Care pathway (ED/hospital ward/ICU) Pre-injury psychiatric condition (yes/no/NA) ISS (continuous) Variables controlled for in multivariate analyses: Age (continuous) Sex (male/female) Educational level Psychiatric history ISS (continuous)	PCL-5 Categorical. Cut-off >-33 9.8% met threshold for PTSD	6 months post-TBI	Univariate: Chi-square tests Kruskall-Wallis tests Multivariate: None relevant No adjustment for multiple comparisons

Van Praag et al., 2022 (CENTER-TBI core study)	Multi-centre prospective cohort December 2014 – December 2017	Sampling method: Non-consecutive (maximum caps per centre to prevent over-representation, recruitment strategies decided locally) TBI severity: Any Location: 63 academic hospitals, mostly in urban areas in North and Western Europe and Israel	Inclusion criteria: - Clinician diagnosis of TBI defined by the treating physician - Indication for a CT scan Seen in an affiliated study centre within 24 hours of the injury - Aged over 15 years - 6-month post-TBI score >3 on the Glasgow Outcome Scale – Extended Exclusion criteria: - Severe pre-existing neurological disorder	Sex: 68.3% male GCS score at baseline: 3-8: 13.1% 9-12: 7.2% 13-15: 77.1% Mechanism of injury: 4.2% assault Pre-TBI psychiatric history: 10.9%	1134 complete cases 2863 meeting inclusion criteria	Univariate predictors: Age (years; continuous) Sex (male/female) Educational level (primary school or less/secondary school or high school/post high school training/college or university) Marital status (never been married/marris or living together or common law/ divorced or separated or widowed or other) GCS (mild/moderate/severe) Cause of injury (RTA/incidental fall/violence or assault or act of mass violence/suicide attempt/other) Care pathway (emergency room/admitted to hospital/ICU) Pre-TBI psychiatric history (yes/no) Type of pre-TBI psychiatric disorder (anxiety/depression/sleep disorder/substance abuse /schizophrenia/other) Variables included in multivariate analyses:	PCL-5 Continuous total score in some analyses Categorical in other analyses (cut off: items with a score of 2 or higher in at least: one item in the intrusion and avoidance clusters, two or more in negative alterations in mood and cognition, and two or more arousal symptoms)	6 months post-TBI	Univariate: - Chi-squared tests - Mann Whitney U test Multivariate: - Multiple logistic regression (complete cases) -Multiple logistic regression (sensitivity analysis on imputed data) - Multiple linear regression (sensitivity analysis)

						Age (years) Sex (male/female) Educational level History of psychiatric disorders: GCS			
Bombardier et al., 2006	Prospective cohort May 2001 – January 2003	Sampling method: Consecutive TBI severity: complicated mTBI (GCS >=12 and CT abnormality), moderate (GCS 9-12) or severe (<=8) Location: Single Level 1 trauma centre in Seattle, USA	Inclusion criteria: - Hospitalised patients who sustained definite TBI as defined by radiological evidence of acute brain abnormality or lowest GCS score <= 12 within 24 hours of admission - Residing in King, Pierce, Kitsap or Snohomish counties - 18 years old or over - Speaking English Exclusion criteria: - Uncomplicated mild TBI (GCS 13-15 and no CT abnormality) - Homelessness - Incarceration - History of schizophrenia - Participation in an investigational drug study	Age: mean: 43 years old (SD: 18.6 years) Sex: 7&% male Race: 92% Caucasian, 6% African-American, 2% Asian-American Mechanism of injury: MVA (49%) Falls (32%), Assault (7%), Other (12%) GCS: >12: 44% 9-12: 30% <=8: 27%	141	Predictors: Gender (male/female) No high school diploma or GED (yes/no) Recall feeling terrified or helpless (PCL-C item) (yes/no) Toxicology positive for stimulant drugs (yes/no) Assaulted (yes/no) History of anxiety or depression (yes/no) Coma severity (GCS: 13-15/9-12/3-8)	PCL-C (administered via phone) Categorical. Cut off: DSM-IV criteria 11.3% met symptoms criteria at least once in those 6 months	Monthly up until 6 months post-TBI	Univariate: - T tests - Fisher's Exact tests Multivariate: None relevant
McCauley et al., 2013	Prospective cohort Time period: unknown	Sampling method: Consecutive TBI severity: mTBI (GCS	Inclusion criteria: - Documented/verified head injury - Aged 18-50 - Presented, treated and released from the	Characteristics of mTBI participants: Age: mean: 30.6 years (SD:	75 (including 29 OI controls and 46	Predictors: Age (years) Gender (male/female) Level of education (years) Group injury status	PCL-C Continuous total scores	Baseline (within 24 hours of injury) 1-week	Univariate: None relevant Multivariate: Multiple linear regressions

		13-15, LOC < 30 mins, PTA < 24 hours and no trauma-related abnormalities on CT scan) <u>Location:</u> Two level 1 trauma centres in Houston, US	ED within 24 hours of injury - Fluent in English or Spanish - GCS 13-15, LOC < 30 minutes, PTA < 24 hours, no trauma-related abnormalities on CT scan - For orthopaedic controls: injury to extremities or pelvis with an AIS score < 3 in any defined body region and no evidence of head injury	9.6) <u>Gender:</u> female: male ratio = 6:23 <u>Education:</u> mean: 13.3 years (SD: 2.9 years) <u>Race:</u> 26% African-American 4% Asian 33% European American 35% Hispanic 2% other <u>Mechanism of injury</u> 5.3% assault 4% Auto-pedestrian 2.7% blow to head 17.3% fall 30.7% MVA 1.3% sports	mTBI patients)	(mTBI/orthopaedic injury) Resilience (Connor-Davidson Resilience Scale total score) Pre-injury mood (Centre for Epidemiologic Studies Depression Scale total score)		post-injury 1-month post-injury	
Terry, Iverson, Panenka, Colantonio, & Silverberg, 2018	Multi-centre case control study March 2015 – February 2017	<u>Sampling method:</u> Consecutive <u>TBI severity:</u> mTBI <u>Location:</u> 4 outpatient	<u>Inclusion criteria:</u> - Aged 18-65 years old - Sustained a mTBI in the past 6 months - Fluent in English - Employed prior to injury - GCS score of 13-15 after 30 minutes post-	<u>Age:</u> Mean: 41.2 years (SD: 11.7 years) <u>Sex:</u> 46.1% male <u>Education level:</u>	102	<u>Predictor:</u> Workplace vs non-workplace TBI	PCL-5 Continuous total scores <u>Mean PCl-5 score:</u> 29.2 (SD: 17.0)	Initial visit a mean of 12 weeks post-injury (range 2-26 weeks post-mTBI)	<u>Univariate analyses:</u> ANCOVA <u>Multivariate analyses:</u> None

		clinics specialising in mTBI/concussion rehabilitation in Vancouver, Canada. Two treat workers compensation claimants, the other two are publicly-funded centres treating non-work-related injuries	injury or later upon presentation for health care - One or more of the following: confusion or disorientation; LOC for <=30 minutes, PTA < 24 hours and. or other transient neurological abnormalities e.g., focal signs, seizure, and intracranial lesion not requiring surgery. - Presentation not due to drugs, alcohol, medications, or other causes <u>Exclusion criteria:</u> None stated	High school or lower: 30.5% <u>Pre-injury mental health treatment:</u> 52% <u>Mechanism of injury:</u> 4.9% assault					
Bai et al., 2019	Prospective cohort (though data relevant to this study only collected at one time point therefore regarded as cross-sectional) <u>Time period:</u> unknown	<u>Sampling method:</u> Consecutive <u>TBI severity:</u> mTBI (GCS score 13-15 at ED, one or more of the following: LOC < 30 mins, PTA <- 24 hours, other transient neurological abnormalities (e.g., focal	<u>Inclusion criteria:</u> - GCS score 13-15 at ED - One or more of any of the following: LOC < 30 mins, PTA <= 24 hours; transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery - Within week of mTBI onset - Aged 18 and over - Agreement to communicate by telephone or email and	<u>Age:</u> mean: 38.15 years (SD: 11.9 years) <u>Sex:</u> 61.0% male <u>Education:</u> mean: 8.3 years (SD: 3.8 years) <u>GCS:</u> =15: 100%	41 (but inconsistently reported in the paper)	<u>Predictor:</u> Gender (male/female)	PCL-C Continuous total scores	Within 7 days of injury	<u>Univariate:</u> None relevant, but reported mean and standard deviation of PCL-C scores in male and female group <u>Multivariate analysis:</u> None reported

		signs, seizure and intracranial lesion not requiring surgery) Location: Single ED in China	to return to hospital for follow-up Exclusion criteria: - History of a previous brain injury, neurological disease, long-standing psychiatric condition - Concurrent substance or alcohol use - A structural abnormality on neuroimaging (CT and MRI) - Intubation and/or presence of a skull fracture and administration of sedatives - The manifestation of mTBI due to medications by other injuries (e.g., systemic injuries, facial injuries, or spinal cord injury) - Other problems (psychological trauma, language barrier or co-existing medical conditions) - Caused by penetrating craniocerebral injury						
Bown et al., 2019	Cross-sectional August 2013 –	Sampling method: Consecutive	Inclusion criteria: - Recruited patients attending the trauma centre TBI clinic for a	Gender 77.7% male	202	Predictors (univariate): Age (continuous) Time in hospital (continuous) Time in ICU	PCL-C Continuous	Median: 5.1 months post-TBI	Univariate: - Kruskal-Wallis - Mann-Whitney U

	February 2016 Overlapping data with Qureshi et al. 2019 (below).	<u>TBI severity:</u> Mild (GCS on admission: 13-15), moderate (GCS: 9-12), and severe (GCS: 3-8) <u>Location:</u> Single major level 1 urban trauma centre in Birmingham, UK	follow-up appointment <u>Exclusion criteria:</u> - If it was not possible to ascertain the cause of the injury - People who were injured in combat - Patients without TBI	<u>Age:</u> Mean: 43.58 years, SD: 20.37 years <u>Race:</u> 83.7% White <u>GCS scores:</u> 3-8: 19.8% 9-12: 11.4% 13-15: 63.9% <u>Mechanism of injury:</u> 21% assault, 40% falls, 33% road traffic collisions, 6% other causes		(continuous) Assault mechanism of injury (yes/no) Mechanism of injury (assault/RTAs/falls or other causes) <u>Predictor (multivariate):</u> Mechanism of injury (assault vs non-assault) *Controlling for:* Age (continuous) Ethnicity (White/Asian/other) Extracranial trauma (yes/no) Also provides access to full dataset online	And conducted analyses using different cur offs (36+/44+/50+)	(IQR: 3.6-7.7)	- Chi-squared - Correlation analyses <u>Multivariate:</u> - Multiple linear regression
Qureshi et al., 2019	Cross-sectional December 2013 – February 2016 Overlapping data with Bown et al. 2019 (above).	<u>Sampling method:</u> Consecutive <u>TBI severity:</u> Mild, moderate and severe – based on Marshall CT score and best GCS rating (13-15: mild; 9-12: moderate; 3-8: severe)	<u>Inclusion criteria:</u> - Patients attending the outpatient trauma centre TBI clinic <u>Exclusion criteria:</u> - Data required for the analysis unavailable - Attendance due to non-traumatic pathology - Chronic subdural haematoma - Declining to provide informed consent	<u>Age:</u> median: 38 years (IQR: 32 years) <u>Gender:</u> 78% male <u>Ethnicity:</u> 77% White 4% African Caribbean 11% Asian 5% mixed 5% other	171	<u>Predictors:</u> Marshall CT grade (I, II, III, IV and V-VI) GCS (13-15/9-12/3-8) *Confounders adjusted for:* Sex (male/female) Age (continuous) Quality of life (QOLIBRI) (continuous) Concussion symptoms (RPQ; continuous) Depression symptoms (PHQ-9; continuous)	PCL-C Mean PTSD score 34.46 (SD: 18.12)	Not stated – just stated that administered during follow-up appointment at the TBI clinic	<u>Univariate:</u> None <u>Multivariate:</u> Two-level hierarchical regression

		Location: Single major level 1 urban trauma centre in Birmingham, UK							
Stillman, Madigan, Torres, Swan, & Alexander, 2020	Cross-sectional January 2012 - December 2015	Sampling method: Consecutive TBI severity: mTBI (GCS 13 or more, LOC<=30 mins and confusion <=12 hours after injury or CT abnormalities) Location: Single concussion speciality clinic within an academic urban hospital in the US	Inclusion criteria: - Referred for focused neuropsychological evaluation at the concussion specialist clinic Exclusion criteria: - More acute patients (seen by neurology earlier than 2 weeks) - Patients seen by neurology or neuropsychology more than 6 months post-injury - TBI more severe than concussion, based on documented GCS < 13 on initial evaluation after injury or reported LOC > 30 min or confusion > 12 hours (AAN 1997 Guidelines) - Significant acute neuroimaging findings (e.g., widespread subarachnoid haemorrhage, intraventricular haemorrhage, or any haemorrhagic	Age: mean: 41.4 years (SD: 12.9 years) Sex: 36% male Education: mean: 15.97 (SD: 2.3) Mechanism of injury: MVA (35%), falls (24%), assault (12%), walking into an object (6%), falling object (4%), miscellaneous (19%). Prior psychiatric illness: 57% Injury severity: Grade 0-1: 65% Grade 2-4 (35%)	100	Predictors: Prior psychiatric history (yes/no) Prior concussion (yes/no) Age (continuous) Gender (male/female) Concussion severity (categorical – based on AAN 1997 criteria regarding injury severity).	PCL-C Categorical. Cut-off >50	Average 51.4 days post-injury	Univariate: Spearman's correlations Multivariate: None relevant

			contusions), - Minor, localised subarachnoid haemorrhage or petechial haemorrhage was not an exclusion - Non-credible neuropsychological performance on the Test of Memory Malingering (poor reliable digit span, forced choice recognition, or standalone performance validity measure						
Grant, 2021	Cross-sectional Time period: unknown	<u>Sampling method:</u> Not available <u>TBI severity:</u> Mild, moderate and severe Mild: normal structural imaging, LOC <30 minutes, PTA < 24 hours, initial GCS 13-15) Moderate: normal or abnormal structural	<u>Inclusion criteria:</u> - Providing medical records or consent to release medical records related to their history of TBI - Evaluated and treated at an urban mid-western level 1 trauma centre <u>Exclusion criteria:</u> - Females - Involved in litigation - Evidence of poor effort (score <45 on the Test of Memory Malingering Trial 2 or Retention Trials) - Incomplete Test of Memory Malingering - Failing the Word	<u>Age:</u> mean; 34.05 years (SD: 9.22 years) <u>TBI severity:</u> Mild: 48.3% Moderate: 19.0% Severe: 29.3% <u>Ethnicity:</u> not reported for civilian TBI sample specifically so unknown. Overall sample was majority White/Caucasian (81%)	58 civilians	<u>Predictors:</u> Level of education (years) Premorbid intelligence (WTAR) – corrected for age, gender, ethnicity and education Occupational attainment (Hollingshead classification)	PCL-C Categorical. Cut-off of >=40	Mean 55 months after injury in the civilian group	<u>Univariate:</u> Pearson correlations <u>Multivariate:</u> None relevant

		imaging, LOC 30 minutes – 24 hours, PTA from 1-7 days, GCS 9-12 Severe: normal or abnormal structural imaging, LOC > 24 hours, PTA > 7 days, initial GCS score <9 <u>Location:</u> Single mid-western Level 1 trauma centre in the US	Memory Test but not meeting the genuine Memory Impairment Profile. - People with less than 11 years of education (to match the military group)	<u>Mechanism of injury:</u> MVA: 44.8% Fall: 13.8% Assault: 6.9% Sports: 1.7% Other: 3.4%					

Table 1. Study characteristics of the 19 included papers (from 10 studies). AAN = American Academy of Neurology; ACEP = American College of Emergency Physicians; AIS = Abbreviated Injury Scale; ASA PS = Association Society of Anaesthesiologists Physical Status; CDC = Centers for Disease Control and Prevention; CENTER-TBI = Collaborative European Neurotrauma Effectiveness Research; CT = Computed Tomography; DSM = Diagnostic and Statistical Manual; ED = Emergency Department; GCS = Glasgow Coma Scale; ICU = Intensive Care Unit; IQR = Interquartile Range; ISS = Injury Severity Scale; LOC = Loss of Consciousness; MRI = Magnetic Resonance Imaging; mTBI = Mild Traumatic Brain Injury; MVA = Motor Vehicle Accident; NA = Not Applicable; PC1 = Principal Component 1; PCA = Principal Components Analysis; PCL-5 = PTSD Checklist for DSM-5; PCL-C = PTSD Checklist for DSM-IV – Civilian Version; PTA = Post-Traumatic Amnesia; PTSD = Post-Traumatic Stress Disorder; RPQ = Rivermead Post-Concussion Symptoms Questionnaire; SD = Standard Deviation; TBI = Traumatic Brain injury; TRACK-TBI = Transforming Research and Clinical Knowledge in Traumatic Brain Injury; US = United States; WTAR = Wechsler Test of Adult Reading.

3.3. Risk of bias in the included studies

Risk of bias assessments were conducted using the QUIPS tool (Hayden *et al.*, 2013). Outcomes are presented in Table 2**,** below. Studies were rated in relation to the data and analyses relevant to the current review question. Four studies (Bombardier *et al.*, 2006; Bai *et al.*, 2019; Stillman *et al.*, 2020; Grant, 2021) were rated as high risk of study confounding, due to only assessing the effects of predictors in univariate analyses. Because the meta-analyses were planned for univariable data only, a 'high' risk of bias rating in the study confounding domain was not a factor in deciding whether to exclude a study from the meta-analyses.

The majority of papers (n = 13) had a moderate risk of bias in the 'study participation' domain. This was often due to studies not reporting study participation rates. Three studies did not state study recruitment periods (McCauley *et al.*, 2013; Bai *et al.*, 2019; Grant, 2021). The majority of papers (n = 10) had high risk of attrition bias. This was due to there often being high rates of drop-out (>33.3%), and lack of information provided about reasons for drop-out, methods used to try to contact participants, or differences in key characteristics between dropouts and retained participants. Four papers (Bai *et al.*, 2019; Bown *et al.*, 2019; Qureshi *et al.*, 2019; Grant, 2021) were not assessed for risk of bias in the study attrition domain due to having cross-sectional designs.

The majority of included papers (n = 16) had low risk of bias ratings in the 'predictor factor measurement' domain, and all had low risk of bias rating in the 'outcome measurement' domain. One paper received a high risk of bias rating in the 'statistical analysis and reporting' domain (Dams-O'Connor *et al.*, 2013) due to not reporting the results of their multivariable analysis. They were contacted to request this information, but no response was received. Nine of the other papers had 'moderate' risk of bias rating in this domain (Bombardier *et al.*, 2006; Haarbauer-Krupa *et al.*, 2017; Winkler *et al.*, 2017; Yue *et al.*, 2018, 2020; Stillman *et al.*, 2020; van der Vlegel *et al.*, 2021; Van Praag *et al.*, 2022). Reasons for this included: failure to correct for multiple statistical comparisons, not explaining the rationale for confounder selection, low numbers of events-per-variable in

some multivariate analyses and failure to report multivariate model summary statistics (e.g., R^2, adjusted-R^2, other measures of model performance). Haarbauer-Krupa et al. (2017) used a forward stepwise selection procedure in their multivariate analysis, which is associated with an increased risk of statistical overfitting (Smith, 2018).

No studies had a ‘high’ risk of bias rating in two domains other than ‘study confounding’ and so no studies were excluded from meta-analyses on the basis of risk of bias assessments.

Study	Study participation	Study attrition	Predictor factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Terry et al., 2018	Moderate	Moderate	Low	Low	Low	Low
Yue et al., 2020	Moderate	High	Low	Low	Low	Moderate
Winkler et al., 2017	Moderate	Low	Low	Low	Low	Moderate
Dams-O'Connor et al., 2013	Moderate	High	Low	Low	Moderate	High
Yue et al., 2018	Moderate	High	Low	Low	Low	Moderate
Stein et al., 2019	Moderate	Moderate	Low	Low	Low	Low
Haarbauer-Krupa et al., 2017	Moderate	High	Low	Low	Low	Moderate
Stillman et al., 2020	Low	Low	Moderate	Low	High	Moderate
Stein et al., 2021	Low	Moderate	Low	Low	Low	Low
Bai et al., 2019	Moderate	N/A	Low	Low	High	Low
Yue et al., 2019	Low	High	Low	Low	Low	Low
Mikolić et al., 2021	Moderate	High	Low	Low	Low	Moderate
van der Vlegel et al., 2021	Moderate	High	Low	Low	Low	Moderate
Van Praag et al., 2022	Low	Low	Low	Low	Low	Moderate
Bombardier et al., 2006	Low	High	Low	Low	High	Moderate
Bown et al., 2019	Low	N/A	Moderate	Low	Moderate	Low
Qureshi et al., 2019	Moderate	N/A	Moderate	Low	Low	Low
McCauley et al., 2013	Moderate	High	Low	Low	Low	Low
Grant, 2021	Moderate	N/A	Low	Low	High	Low

Table 2. Risk of bias assessment according to the Quality in Prognostic Studies tool. N/A = Not applicable. The 'study attrition' domain was not rated for cross-sectional studies.

3.4. Meta-analyses of univariable predictors

The included studies investigated a total of 32 different univariable predictors of PTSD. 12 predictors were excluded from meta-analyses as they were assessed in only one study. Consequently, 20 predictors were included in the meta-analyses (see Table 3, below).

Predictor	**Number of participants (number of studies)**	**Pooled effect size meta-analysis odds ratio (95% CI) (unless specified otherwise)**	**Heterogeneity (I^2)**
Age (years; MD [95% CI])	831 (3)	-3.47 (-7.12, 0.19)	46%
Male gender (vs female)	5205 (6)	0.99 (0.69, 1.41)	58%***
Non-Caucasian race (vs Caucasian)	840 (3)	1.78 (1.21, 2.62)**	0%
Level of education (High school diploma or above vs lower)	1541 (2)	0.50 (0.17, 1.43)	64%***
Years of education (years; MD [95% CI])	701 (2)	-1.43 (-1.93, -0.94)**	0%
Employed at the time of injury (vs. unemployed)	1641 (2)	0.60 (0.13, 2.76)	94%***
Married marital status	1366 (2)	0.65 (0.38, 1.10)	56%***
Pre-TBI psychiatric history	2384 (4)	2.95 (2.25, 3.89)**	0%
Positive toxicology screen	389 (2)	3.40 (1.45, 7.95)**	0%
ED GCS = 15 (vs <15)	391 (2)	0.53 (0.17, 1.66)	82%***
ED GCS 13-15 (vs <13)	1218 (2)	0.68 (0.29, 1.56)	43%
ED GCS 9-12 (vs < 9 or > 12)	1218 (2)	1.26 (0.72, 2.18)	0%
ED GCS < 9 (vs > 8)	1218 (2)	1.17 (0.66, 2.08)	18%
CT intracranial lesion	697 (2)	0.63 (0.39, 1.01)	23%
Hospital admission duration (days; MD [95% CI]	1688 (2)	-1.36 (-4.48, 1.76)	48%
ED discharge (versus hospital or ICU admission)	2378 (3)	0.97 (0.64,1.46)	56%***
ICU admission (vs ED discharge or hospital admission without ICU)	2390 (4)	0.96 (0.73, 1.28)	0%
ICU length of stay (days; MD [95% CI])	1689 (2)	1.61 (-1.57, 4.79)	80%***
Assault mechanism of injury (vs non-assault)	2084 (5)	3.44 (2.37, 5.00)**	7%
RTA mechanism of injury (vs non-RTA)	1960 (4)	1.10 (0.56, 2.17)	85%***

Table 3. Results of meta-analyses of univariable predictors of self-reported PTSD symptoms after TBI. CI = Confidence Interval; ED = Emergency Department; ICU = Intensive Care Unit; pMD = Pooled Mean Difference; pOR = Pooled Odds Ratio; RTA = Road Traffic Accident. ** = $p < 0.05$. *** = High heterogeneity ($I^2 > 50\%$).

Predictors significantly associated with higher PTSD symptoms included: non-Caucasian race (vs Caucasian) (pOR = 1.78, 95% CI: 1.21, 2.62; I^2 = 0%; 3 studies), pre-TBI psychiatric history (pOR = 2.95; 95% CI: 2.25, 3.89; I^2 = 0; 4 studies), positive toxicology screen on admission (pOR = 3.40; 95% CI: 1.45 to 7.95; I^2 = 0%; 2 studies), and assault mechanism of injury (pOR = 3.44; 95% CI: 2.37 to 5.00; I^2 = 7%; 5 studies). A greater number of years of education was significantly associated with decreased PTSD symptoms (pMD = -1.43; 95% CI: -1.93, -0.94; I^2 = 0%; 2 studies). None of the other predictors were significantly associated with self-reported PTSD.

There was high heterogeneity (I^2 > 50%) in 8 of the meta-analyses, including: gender, level of education (categorical), employment status, marital status, emergency department (ED) Glasgow Coma Scale (GCS) score (15 vs <15), ED discharge (vs hospital or intensive care unit (ICU) admission), ICU length of stay and road traffic accident (RTA) mechanism of injury. However, there was low heterogeneity in each of the significant meta-analyses.

3.4.1. Sensitivity analyses

Sensitivity analyses revealed that there were no changes to the significance of any associations between predictors and self-reported PTSD symptoms when only prospective cohort studies were included (excluding cross-sectional and retrospective designs). Post-hoc sensitivity analyses also showed that there were no changes to the significance of any associations when Bombardier et al's (2006) study was excluded (due to it predicting above-threshold PTSD scores at any of the study's six follow-up time points, compared to every other study which predicted self-reported PTSD scores at each time point separately). The results of the sensitivity analyses are presented in Appendices E and F.

3.5. Narrative synthesis of univariable predictors

A narrative synthesis is presented below for univariate data from papers not included in the meta-analyses (a summary is provided in Table 4, below). This includes other papers from studies already included in the meta-analyses.

3.5.1. Demographic variables

Van Praag et al. (2022) found that age was significantly lower in participants screening positive for PTSD, in contrast to the non-significant results of the meta-analysis.

Three additional papers reported univariate data for the association between gender and PTSD symptoms – these findings were mixed. Stillman et al. (2020) found a significant correlation between sex and PTSD symptoms. Van der Vlegel et al. (2021) and van Praag et al. (2022) found no significant association. These mixed results are consistent with the mixed results from papers included in the meta-analysis for gender.

Grant et al. (2021) conducted correlation analyses and found no significant associations between years of education and PTSD symptoms, in contrast to the results of the meta-analysis. Grant et al's (2021) cross-sectional study also found no significant association between employment status and PTSD symptoms after TBI, consistent with the results of the meta-analysis.

Winkler et al's (2017) reported significantly higher odds of PTSD symptoms in African-American participants compared to Caucasian participants, consistent with the results of the meta-analysis. Stein et al. (2021) reported no significant association between Hispanic ethnicity and PTSD symptoms.

Stillman et al. (2020) and van Praag et al. (2022) found that psychiatric history was significantly correlated with PTSD symptoms, consistent with the results of the meta-analysis. Van Praag et al. (2022) found no significant differences in the rates of different types of pre-TBI psychiatric disorders (anxiety, depression, substance abuse, sleep disorder, schizophrenia, 'other') between participants screening positive for PTSD at 6-months and those not.

Some of the studies in the narrative synthesis investigated predictors that were not included in the meta-analyses. A significant association was found between increased PTSD symptoms and a history of substance use (vs none) (Winkler *et al.*, 2017), and no military service (Haarbauer-Krupa *et al.*, 2017).

3.5.2. Injury-related and clinical variables

Terry et al. (2018) found that TBIs sustained in the workplace were associated with significantly higher levels of PTSD symptoms than non-workplace TBIs.

Yue et al (2020) reported that participants with a positive toxicology screen on admission had significantly higher PTSD symptoms at follow-up. This is consistent with the results the meta-analysis.

Bombardier et al. (2006) reported no significant association between GCS category and PTSD symptoms, consistent with the results of the meta-analyses. Van Praag et al. (2022) reported significant associations between PTSD and care pathway (ED admission/hospital admission/ICU admission) and highest level of education (primary school or less/secondary or high school/post-high school training/college or university).

One paper each reported non-significant associations between PTSD symptoms and injury severity score at baseline (Haarbauer-Krupa *et al.*, 2017), presence of any abnormality on MRI scans (Stein *et al.*, 2021), or premorbid intelligence measured using the Wechsler Test of Adult Reading (WTAR) (Grant, 2021). Significant associations were found between PTSD symptoms and the COMT Met^{158} polymorphism (vs the $Val^{158}Val^{158}$-polymorphism) (Winkler *et al.*, 2017), recalling feeling terrified or helpless at the time of injury (Bombardier *et al.*, 2006), and Marshall CT grade (Bown *et al.*, 2019).

Variable (total number of papers reporting on this variable)	Study	Results
Demographic variables		
Age (years; continuous) (4)	Van Praag et al., 2022 (CENTER-TBI)	PTSD+ group: median: 43, IQR: 28-55 PTSD- group: median: 49, IWR: 30-61 Mann-Whitney U test p = 0.009 (significant difference)
Gender (6)	Stillman et al., 2020	Reported results of Spearman's correlations: Rho = 0.26, p = 0.01
	van der Vlegel et al., 2021 (CENTER-TBI) *	PTSD+ group: 96/153 male (62.7%) PTSD- group: 897/1413 male (63.5%) Non-significant association (manually calculated)
	Van Praag et al., 2022 (CENTER-TBI)*	PTSD+ group: 102/154 male (66.7%) PTSD- group: 673/981 male (68.6%) Non-significant association (p = 0.63)
Race (Caucasian vs non-Caucasian) (4)	Winkler et al., 2017* (TRACK-TBI pilot)	African-American vs Caucasian OR = 3.89 (95% CI: 1.13 – 13.35) Significantly higher odds of PTSD in African-American group
Hispanic ethnicity (1)	Stein et al., 2021 (TRACK-TBI full study)	Hispanic ethnicity vs non-Hispanic p = 0.73 (PTSD at 3 months) p = 0.86 (PTSD at 6 months) No significant association at either time point
Post-injury employment status (1)	Grant, 2021	Reported Pearson correlations between Occupation (measured using Hollingshead classification) and PCL-C scores r = -0.305, p > 0.05 Non-significant association between employment status and PTSD symptoms
Highest level of education (categorical) (3)	Van Praag et al., 2022 (CENTER-TBI)*	Primary school or less PTSD+ group: 22/154 (15.6%) PTSD- group: 100/981 (11.1%) Secondary school/high school PTSD+: 56/153 (39.7%) PTSD-: 273/981 (30.3%) Post-high school training PTSD+: 25/153 (17.7%) PTSD-: 191/981 (21.2%) College/university: PTSD+: 38/153 (27%) PTSD-: 191/981 (27.4%) Missing PTSD+: 12/153 PTSD-: 80/981 Overall chi-squared p value = 0.019*
Years of education (3)	Grant, 2021	Reported Pearson's correlation between years of education and PCL-C scores r = -0.39, p > 0.05

		Non-significant association between years of education and PTSD symptoms
Psychiatric history (5)	Stillman et al., 2020	Reported Spearman's correlations between psychiatric history and PCL-C scores Rho = 0.26, p = 0.01 Significant positive association between psychiatric history and PTSD symptoms
	Van Praag et al., 2022 (CENTER-TBI)*	Previous psychiatric disorder PTSD+: 29/153 (19.1%) PTSD- 95/981 (9.8%) No previous psychiatric disorder PTSD+: 123/153 (80.9%) PTSD-: 879/981 (90.2%) Missing: PTSD+: 1/153 PTSD-: 7/981 Chi-squared p value = 0.001 (significant)
Type of pre-TBI psychiatric disorder (1)	Van Praag et al., 2022 (CENTER-TBI)	Anxiety: PTSD+: 7/153 (4.6%) PTSD-: 27/981 (2.8%) p = 0.65 (non-significant) Depression: PTSD+: 17/153 (11.1%) PTSD-: 51/981 (5.2%) p = 0.64 (non-significant) Substance abuse: PTSD+: 3/153 (2%) PTSD-: 11/981 (1.1%) p = 0.85 (non-significant) Sleep disorder: PTSD+: 3/153 (2%) PTSD-: 15/981 (1.5%) p = 0.47 (non-significant) Schizophrenia: PTSD+: 2/153 (1.3%) PTSD-: 2/981 (0.2%) p = 0.20 (non-significant) Other: PTSD+: 7/153 (4.6%) PTSD-: 14/981 (1.4%) p = 0.24 (non-significant)
History of substance use (1)	Winkler et al., 2017 (TRACK-TBI pilot)	Univariate logistic regression Present current substance use (ref: no current substance use): OR = 3.44 (1.26 - 9.38), p = 0.016, Nagelkerke pseudo-R2 = 8.6%
Military service history (1)	Haarbauer-Krupa et al., 2017 (TRACK-TBI pilot)	People with a military service history in the PTSD+ group: 4/75 (5.3%) People with military service history in the PTSD- group: 31/205 (15.1%)

		p = 0.039 The PTSD group contained a significantly lower proportion of participants with a military history
Injury-related and clinical variables		
Workplace vs non-workplace TBI (1)	Terry et al., 2018	F(1,98) = 4.04, p = 0.047 PTSD scores significantly higher in the workplace TBI group
Toxicology screen on admission vs. negative (3)	Yue et al 2020 (TRACK-TBI pilot)*	PTSD in positive toxicology screen group: 40.0% PTSD in negative toxicology screen group: 15.9% p = 0.023
Care pathway (4 papers overall examine ED admission, 5 examine ICU admission)	Van Praag et al., 2022 (CENTER-TBI)*	<u>Emergency room</u> PTSD+: 25/153 (16.3%) PTSD-: 244/981 (24.9%) <u>Admitted to hospital</u> PTSD+: 60/153 (39.2%) PTSD-: 366/981 (36.3%) <u>Intensive care unit</u> PTSD+: 68/153 (44.4%) PTSD-: 371/981 (37.8%) Chi-squared test p value = 0.058 (non-significant)
ED GCS (3)	Bombardier et al., 2006	PTSD+ in GCS 13-15 group: 5/54 (9.26%) PTSD+ in GCS 9-12 group: 3/27 (11.1%) PTSD+ in GCS 3-8 group: 6/33 (18.2%) Chi-squared p-value = 0.3
COMT gene Met^{158} allele (1)	Winkler et al., 2017 (TRACK-TBI pilot)	COMT genotype (Met^{158} carriers vs Val^{158}/Val^{158} homozygotes) univariable logistic analysis Met^{158-} carrier (ref: $val^{158}Val^{158}$): OR = 0.25 (0.09-0.69), p= 0.006, Nagelkerke pseudo-R2 = 11.0% Met^{158} COMT allele significantly associated with increased risk of PTSD
Injury severity score (1)	Haarbauer-Krupa et al., 2017 (TRACK-TBI pilot)	Mean ISS in PTSD+ group: 7.3 ± 8.5 Mean ISS in PTSD- group: 9.8 ± 10.4 Mann-Whitney U test p value: 0.062 Non-significant association between ISS and PTSD symptoms
Any MRI abnormality (1)	Stein et al., 2021 (TRACK-TBI full study)	<u>PTSD at 6 months post-TBI:</u> Number of people in PTSD group with MRI abnormalities: 26/75 (37.1%) Number of people in PTSD group without MRI abnormalities: 44/75 (62.9%) Number of people in PTSD- group with MRI abnormalities: 161/351 (45.9%) Number of people in PTSD- group with no MRI abnormalities: 190/351 (62.9%) p = 0.19 (non-significant association) <u>PTSD at 3 months post-TBI:</u> Number of people in PTSD group with MRI abnormalities: 33/77 (42.9%)

		Number of people in PTSD group without MRI abnormalities: 44/77 (57.1%) Number of people in PTSD- group with MRI abnormalities: 154/344 (44.8%) Number of people in PTSD- group with no MRI abnormalities: 190/344 (55.2%) p = 0.80 (non-significant association)
Recall feeling terrified or helpless (PCL-5 item) (1)	Bombardier et al., 2006	Number who recalled feeling terrified or helpless at time of TBI who were PTSD+ in first 6 months after TBI: 5/15 (33.3%) Number of people who did not recall feeling terrified at time of TBI who were PTSD+ in the first 6 months after TBI: 9/109 = 8.26% Fisher's exact test p-value = 0.01 Significantly higher risk of PTSD in those recalling feeling terrified or helpless at time of injury
Marshall CT grade (1)	Bown et al., 2019	p = 0.031
WTAR (measure of pre-morbid IQ) (1)	Grant, 2021	Spearman's correlations reported: r = -0.065, p > 0.05 No significant association between WTAR score and PCL-C symptoms

Table 4. Narrative summary of findings from papers not included in the meta-analyses. '*' = another paper from the same study was included in the meta-analysis for that predictor. CENTER-TBI = Collaborative European Neurotrauma Effectiveness Research; CT = Computed Tomography; ED = Emergency Department; GCS = Glasgow Coma Scale; MRI = Magnetic Resonance Imaging; OR = Odds Ratio; PCL-5 = PTSD Checklist for DSM-5; PCL-C = PTSD Checklist for PCL-IV – Civilian Version; PTSD = Post-Traumatic Stress Disorder; TRACK-TBI = Transforming Research and Clinical Knowledge in Traumatic Brain Injury; WTAR = Wechsler Test of Adult Reading.

3.6. Narrative synthesis of multivariable models

12 papers, from five different studies, used a multivariable model to predict PTSD (see Table 5, below). A total of 41 multivariate models were reported across the papers. The majority of papers reported only one multivariate model (n = 7). Five papers reported multiple multivariate models – ranging from 3 (McCauley *et al.*, 2013) to 17 (Stein *et al.*, 2021). The average number of participants included in multivariate models was 563.7. The sample size was not reported for 1 model (Stein *et al.*, 2019). The average number of predictors across all models was 9.6.

The majority of models (26/41) utilised multivariate logistic regression analyses. This included Haarbauer-Krupa et al's (2017) multivariable binary logistic regression model which involved a stepwise forward feature selection procedure. The remaining multivariable models included: 10 multiple linear regression analyses (McCauley *et al.*, 2013; Yue *et al.*, 2018, 2019; Bown *et al.*, 2019; Stein *et al.*, 2019; Mikolić *et al.*, 2021), four weights-adjusted multivariable logistic regression analyses (Stein *et al.*, 2019), and one hierarchical linear regression analysis (Qureshi *et al.*, 2019). Only four studies made statistical corrections for multiple comparisons (Yue *et al.*, 2019, 2020; Stein *et al.*, 2021; Van Praag *et al*., 2022).

Only three papers reported imputing missing data (Stein *et al.*, 2019; Mikolić *et al.*, 2021; Van Praag *et al.*, 2022). Stein et al. (2019) pro-rated PCL-C total scores if less than 25% of individual items were missing, and developed propensity weights using generalised boosted regression models to account for missing data at follow-up visits. In contrast, Mikolić et al. (2021) and Van Praag et al. (2022) imputed missing values in potential confounders based on an imputation model with all baseline characteristics, outcomes and auxiliary variables. In both papers, sensitivity analyses were performed by conducting multivariate analyses on both complete cases only and on the imputed data. In the remaining papers, missing data was just excluded from analyses.

In studies utilising multivariate logistic regression or weights-adjusted multivariate logistic regression analyses, the average number of events-per-variable (excluding the

model in Stein et al. (2019) in which the sample size and number of cases was not reported) was 17.1 (ranging from 1.8 (Yue *et al.*, 2020) to 38.5 (Stein *et al.*, 2021)). In studies performing multiple linear regression or hierarchical linear regression analyses, the average number of participants per predictor was 46.6 (ranging from 10 (Yue *et al.*, 2019) to 130 (Mikolić *et al.*, 2021)).

Summary statistics were only provided for 7 of the models. Three papers reported the overall significance of the multivariable models (McCauley *et al.*, 2013; Winkler *et al.*, 2017; Qureshi *et al.*, 2019) – all were statistically significant ($p < 0.05$). McCauley *et al*. (2013) reported R^2 and adjusted-R^2 values for each of their models predicting PTSD scores at 24 hours, 1-week and 1-month post-TBI. The R^2 and adjusted-R^2 values decreased as time since injury increased, with R^2 values decreasing from 0.47 to 0.28, and adjusted-R^2 values decreasing from 0.43 to 0.22. Winkler *et al.* (2017) and Van Praag *et al*. (2002) reported Nagelkerke R^2 values of 29.5 and 0.058-0.081, respectively. Haarbauer-Krupa *et al.* (2017) utilised the Hosmer and Lemeshow chi-square statistic (11.081; $p = 0.135$) as a measure of goodness-of-fit instead. Haarbauer-Krupa et al's (2017) paper was the only paper in which model performance was evaluated - reporting a c-statistic of 0.713 (95% CI: 0.642, 0.895; $p < 0.001$). None of the models were internally or externally validated.

Study	Measurement of PTSD outcome	Timing of PTSD measurement	Number of participants in multivariable analysis	Number of cases (if applicable)	Number of candidate predictors	Selection of predictors	Statistical model	Summary statistics	Final predictors in model
Winkler et al. 2017 (TRACK-TBI pilot)	PCL-C (categorical – DSM-IV criteria used as threshold)	6 months post-TBI	93	26.5%	3	Consistent predictors cited in the literature COMT polymorphism = hypothesised predictor	1 x multivariate binary logistic regression	Overall model Nagelkerke pseudo-R^2 = 29.5% Overall model p value = 8.1 x 10^{-5*}	**COMT Met^{158}** (ref: Val^{158}Val^{158}) OR = 0.32 (95% CI: 0.11-0.97), p = 0.044* **Pre-existing psychiatric disorder** (ref: none) OR = 5.17 (95% CI: 1.80-14.89), p = 0.002* **Substance abuse** (ref: none) B = 1.88 (95% CI: 0.60-5.88), p = 0.281
Haarbauer-Krupa et al. 2017 (TRACK-TBI pilot)	PCL-C (categorical – DSM-IV criteria used as threshold)	6 months post-TBI	280	26.8%	Initially: 5 Final model: 3	Candidate predictors selected from the literature and clinical knowledge Two predictors (Caucasian race & married marital status) dropped in the final model derived by step-wise forward procedure; p-entry	1 x multivariate binary logistic regression	Overall model significance: p < 0.001* c-statistic: 0.713 (95% CI: 0.642-0.895; p < 0.001) Hosmer and Lemeshow chi-square statistic = 11.081; p = 0.135	**Education** (per year): B = -0.13, OR = 0.88 (95% CI: 0.79 – 0.98), p = 0.021* **Prior psychiatric history** Ref: None B = 0.94, OR = 2.56 (95% CI: 1.42-4.61), p = 0.002* **Mechanism of assault** Ref: Non-assault mechanism of injury B = 1.28, OR = 3.59 (95% CI: 1.69-7.63), p = 0.001*

						≤0.25; *p*-remain ≤0.15)			
Yue et al., 2018 (TRACK-TBI pilot)	PCL-C (continuous total scores)	6 months post-TBI	162	N/A	11	Validated predictors for outcome after mTBI in the literature	1 x multivariable linear regression	Not reported	**Unemployed at baseline (ref: employed):** B = 5.99 (95% CI: 0.76, 11.22), p = 0.025* **Age** (per-year): B = 0.01 (95% CI: -0.13, 0.14), p = 0.934 **Race** (ref: Caucasian): African-American/African: B = 8.57 (95% CI: 0.92, 16.21), p = 0.028. Other races: B = 4.28 (-1.78, 10.34), p = 0.165. Overall p for race = 0.053 **Education level** (ref: college or above) High school diploma/GED: B = 1.05 (95% CI: -3.64, 5.74), p = 0.659 Below HS: B = 10.21 (95% CI: 1.37, 19.04), p = 0.024* Overall p value for education level: 0.073 **Pre-injury headache/migraine** (ref: none). B = 5.25 (95% CI: -1.13, 11.62), p = 0.106 **Pre-injury psychiatric history** (ref: none) B = 6.52 (95% CI: 1.65, 11.39), p = 0.009* **LOC** (ref: no) Unknown: B = 3.43 (95% CI: -6.84, 13.70), p = 0.510 Yes: B = -0.56 (95% CI: -5.85, 4.73), p = 0.835 Overall p value for LOC: p = 0.702 **PTA** (ref: no) Yes: B = 0.48 (95% CI: -4.52, 5.49), p = 0.849 Unknown: B = 3.39 (95% CI: -5.87,

									12.65), p = 0.471 Overall p value for PTA = 0.762 **ED GCS** (ref: =15) <15: B = 1.13 (95% CI: -3.59, 5.84), p = 0.637 **CT intracranial lesion** (ref: negative): B = 0.85 (95% CI: -4.10,5.80), p = 0.735 **Polytrauma** (ref: no): B = 1.94 (95% CI: -4.52 – 8.39), p = 0.554
Yue, Levin et al. 2019 (TRACK-TBI pilot)	PCL-C (continuous total scores)	6 months post-TBI	100	N/A	10	Validated predictors for outcome after mTBI in the literature	Multivariable linear regression	Not reported	**Age group * sex** Ref: 30-39 years * female 18-29 years * male: B = -19.80 (95% CI: -30.07, -9.33), p < 0.001* 18-29 years * female: B = -19.55 (95% CI: -30.64, -8.47), p = 0.001* 30-39 years * male: B = -15.49 (95% CI: -26.54, -4.45), p = 0.007* Age group p value < 0.001* Sex p value = 0.021* Overall p value 0.022* **Race** Ref: African-American/African Caucasian: B = -5.16 (95% CI: -14.52, 4.19), p = 0.276 Other races: B = 1.68 (95% CI: -8.93, 12.29), p = 0.754 Overall p value = 0.097 **Education** (years) Per-year: B = -1.79 (95% CI: -2.93, -0.66), p = 0.002* **Pre-injury psychiatric history** Ref: No Yes: B = 8.37 (95% CI: 2.34, 14.41), p = 0.007* **Mechanism of assault** Ref: No

									Yes: B = 10.45 (95% CI: 3.313, 17.77), p = 0.006* **LOC duration** Ref: Unknown None: B = 1.33 (95% CI: -6.57 9.23), p = 0.738 <30 min: B = -0.20 (95% CI: -6.83, 6.44), p = 0.954 Overall p-value: 0.896 **ED GCS** Ref: <15 =15: B = -6.39 95% CI: -13.40, 0.62), p = 0.074 **CT intracranial lesion** Ref: No Yes: B = -2.19 (95% CI: -8.57, 4.19), p = 0.496 **Polytrauma** Ref: No Yes: B = -4.10 (95% CI: -12.14, 3.94), p = 0.313
Yue et al. 2020 (TRACK-TBI pilot)	PCL-C (categorical - scored according to DSM-IV criteria)	6 months post-TBI	83	18	10	Method not stated	1 x multivariable logistic regression	Not reported	**Positive ED urine toxicology screen** (ref: negative screen): mOR = 8.24 (95% CI: 1.35 – 50.27), p = 0.022* **Age** (per-year): mOR = 0.99 (95% CI: 0.99-1.04), p = 0.784 **Female sex** (ref: male): mOR = 1.05 (95% CI: 0.23-4.71), p = 0.952 **Education (per-year):** mOR = 0.73 (95% CI: 0.53-0.99), p = 0.047* **Non-Caucasian race** (ref: Caucasian): mOR = 1.50 (95% CI: 0.17 – 13.65), p = 0.717 **Previous psychiatric history** (ref: none): mOR = 2.20 (95% CI: 0.44-11.14), p = 0.340

									Previous substance use (ref: none): mOR = 0.44 (95% CI: 0.05-4.51), p = 0.447 **ED GCS** < 15 (ref: = 15): mOR = 1.02 (95% CI: 0.23-4.51), p = 0.978 **CT intracranial finding** (ref: none): mOR = 2.33 (95% CI: 0.36-15.14), p = 0.375 **Polytrauma** (ref: none): mOR = 1.05 (95% CI: 0.16-6.72), p = 0.961
Stein et al. 2019 (TRACK TBI full study)	PCL-5 (total score >32 indicative of PTSD)	2 weeks post-TBI 3 months post-TBI 6 months post-TBI 12 months post-TBI	3 months multivariate model: 704 6 months multivariate model: 671 12 months: 619	3 months: 18.7% 6 months: 19.2% 12 months: 17.2%	Up to 14 in each multivariable model	Not stated	5 x multivariate analyses, including: 4 x weights-adjusted multivariable logistic regression models with design-based Wald X^2 tests 1 x linear mixed effects model fit with PCL-5 total score as the dependent variable. Fixed effects: visit, demographic, injury and pre-injury factors listed. Random effects	None reported	<u>PTSD at 3 months model:</u> **Age** (years)**:** AOR = 1.00 (95% CI: 0.99,1.01), X^2 = 0.06, p = 0.80 **Sex** (ref: female) Male: AOR = 0.57 (95% CI: 0.37, 0.89), X^2 = 6.25, p = 0.01 **Race** (ref: Non-African American) African American: AOR = 2.98 (95% CI: 1.76-5.03), X^2 = 16.59, p < 0.0005* **Hispanic** (ref: no) Yes: AOR: 2.04 (95% CI: 1.10, 3.78) **Years of education:** AOR = 0.91 (95% CI: 0.84, 0.98), X^2 = 6.70, p = 0.01 **Patient type** (ref: ED discharge) Hospital admit no ICU: AOR = 0.73 (95% CI: 0.45, 1.17), Hospital admit with ICU: AOR = 1.26 (95% CI: 0.67, 2.37) Overall X^2 = 3.90, overall p value = 0.14 **Injury cause** (ref: MVA/fall/other non-intentional injury) Violence/assault: AOR = 4.07 (95% CI: 1.94, 8.54), X^2 = 13.79, p < 0.0005* **LOC** (ref: No) Yes: AOR = 1.49 (95% CI: 0.80-2.76), X^2 = 1.60, p = 0.21

							include random intercept Note: for all multivariate models, a 2-sided p-value < 0.005 considered significant (corrected for multiple analyses) .		**PTA** (ref: No) Yes: AOR = 1.01 (95% CI: 0.61, 1.67), X^2 = 0.00, p = 0.97 **CT intracranial injury** (ref: No) Yes: AOR = 0.59 (95% CI: 0.34, 1.01), X^2 = 3.66, p = 0.06 **Psychiatric history** (ref: None) Yes: AOR = 3.32 (95% CI: 2.04, 5.41), X^2 = 23.19, p < 0.0005* **Prior TBI** (ref: No) Yes: AOR = 1.62 (95% CI: 1.04, 2.52), X^2 = 4.50, p = 0.03 <u>PTSD at 6 months model:</u> **Age** (years)**:** AOR = 1.00 (95% CI: 0.98, 1.01), X^2 = 0.26, p = 0.61 **Sex** (ref: female) Male: AOR = 0.60 (95% CI: 0.38, 0.96), X^2 = 4.64, p = 0.03 **Race** (ref: Not Black) Black: AOR = 5.11 (95% CI: 2.89, 9.05), X^2 = 31.28, p < 0.001* **Hispanic** (ref: no) Yes: AOR = 1.95 (95% CI: 0.98, 3.88), X^2 = 3.63, p = 0.06 **Years of education:** AOR = 0.89 (95% CI: 0.82, 0.97), X^2 = 7.86, p = 0.005 **Patient type** (ref: ED discharge) Hospital admit no ICU: AOR = 1.39 (95% CI: 0.83, 2.33) Hospital admit with ICU: AOR = 1.68 (95% CI: 0.83, 3.37) Overall X^2 = 2.45 Overall p value = 0.29 **Injury cause** (ref: MVA/fall/other non-intentional injury)

									Violence/assault: AOR = 3.43 (95% CI: 1.56, 7.54), X^2 = 9.4, p = 0.002* **LOC** (ref: No) Yes: AOR = 0.73 (95% CI: 0.38, 1.42), X^2 = 0.85, p = 0.36 **PTA** (ref: No) Yes: AOR = 0.88 (95% CI: 0.50, 1.54), X^2 = 0.21, p = 0.65 **CT intracranial injury** (ref: No) Yes: AOR = 0.65 (95% CI: 0.37, 1.16), X^2 = 2.14, p = 0.14 **Psychiatric history** (ref: None) Yes: AOR = 3.57 (95% CI: 2.09, 6.09), X^2 = 21.64, p < 0.001* **Prior TBI** (ref: No) Yes: AOR = 1.63 (95% CI: 1.02, 2.60), X^2 = 4.16, p = 0.04 <u>PTSD at 12 months model:</u> **Age** (years)**:** AOR = 1.00 (95% CI: 0.96, 1.01), X^2 = 0.51, p = 0.48 **Sex** (ref: female) Male: AOR = 0.64 (95% CI: 0.37, 1.09), X^2 = 2.92, p = 0.09 **Race** (ref: Non-African American) African American: AOR = 2.97 (95% CI: 1.64, 5.37), X^2 = 12.87, p < 0.0005* **Hispanic** (ref: no) Yes: AOR = 1.54 (95% CI: 0.74, 3.22), X^2 = 1.31, p = 0.25 **Years of education:** AOR = 0.85 (95% CI: 0.78, 0.93), X^2 = 14.03, p < 0.0005* **Patient type** (ref: ED discharge) Hospital admit no ICU: AOR = 0.72 (95% CI: 0.31, 1.29) Hospital admit with ICU: AOR = 1.04

									(95% CI: 0.52, 2.09) Overall X^2 = 1.91 Overall p value = 0.38 **Injury cause** (ref: MVA/fall/other non-intentional injury) Violence/assault: AOR = 4.00 (95% CI: 1.79, 8.97), X^2 = 11.38, p = 0.001* **LOC** (ref: No) Yes: AOR = 1.38 (95% CI: 0.67, 2.82), X^2 = 0.76, p = 0.38 **PTA** (ref: No) Yes: AOR = 1.18 (95% CI: 0.64, 2.20), X^2 = 0.28, p = 0.60 **CT intracranial injury** (ref: No) Yes: AOR = 0.90 (95% CI: 0.50, 1.61), X^2 0.13, p = 0.72 **Psychiatric history** (ref: None) Yes: AOR = 3.23 (95% CI: 1.82, 5.73), X^2 = 16.15, p < 0.0005* **Prior TBI** (ref: No) Yes: AOR = 2.13 (95% CI: 1.29, 3.52), X^2 = 8.77, p = 0.003* <u>Longitudinal model to assess risk factors on PCL-5 total score over time:</u> **Visit** (ref: Month 3) Month 6: Coefficient: -0.93 (95% CI: -1.94, 0.09), p = 0.07 Month 12: Coefficient = -1.34 (95% CI: -2.38, -0.30), p = 0.01 **Age** (years) Coefficient = -0.05 (95% CI: -0.11, 0.01), p = 0.12 **Sex – male vs female** Coefficient = -3.80 (95% CI: -5.90, -1.70), p < 0.001*

									Race – African American vs non-African American Coefficient: 8.67 (95% CI: 6.01, 11.33), p < 0.001* **Hispanic – yes vs no** Coefficient: 3.95 (95% CI: 1.16, 6.74), p = 0.006 **Years of education** Coefficient = -0.67 (95% CI: -1.03, -0.31), p < 0.001* **Patient type (ref: ED discharge)** Hospital admit no ICU: Coefficient: -0.38 (95% CI: -2.66, 1.91), p = 0.75 Hospital admit with ICU: Coefficient = 0.95 (95% CI: -2.00, 3.90), p = 0.53 **Injury cause – violence vs non-intentional injury** Coefficient: 11.21 (95% CI: 7.14, 15.28), p < 0.001* **LOC – yes vs no** Coefficient = 0.95 (95% CI: -1.83, 3.74), p = 0.50 **PTA – yes vs no** Coefficient = 0.13 (95% CI: -2.32, 2.57), p = 0.92 **CT intracranial injury – yes vs no** Coefficient = -1.84 (95% CI: -4.27, 0.60), p = 0.14 **Psychiatric history – yes vs no** Coefficient = 8.86 (95% CI: 6.44, 11.28), p < 0.001* **Prior TBI – yes vs no** Coefficient: 4.49 (95% CI: 2.37, 6.62), p < 0.001*

									<u>Sensitivity analysis for 6-month PTSD outcome with additional SES predictors:</u> **Age** (years) AOR = 0.99 (95% CI: 0.97, 1.01), X^2 = 1.36, p = 0.24 **Sex** (ref: Female) Male: AOR = 0.64 (95% CI: 0.40, 1.03), X^2 = 3.32, p = 0.07 **Race** (ref: Non-African American) African American: AOR = 4.32 (95% CI: 2.33, 8.01), X^2 = 21.48, p < 0.005* **Hispanic** (ref: No) Yes: AOR = 2.00 (95% CI: 0.99, 4.02), X^2 = 3.74, p = 0.05 **Employment** (ref: employed/retired/student) Unemployed: AOR = 1.11 (95% CI: 0.55, 2.22), X^2 = 0.08, p = 0.78 **Insurance** (ref: Uninsured) Medicaid: AOR = 1.44 (95% CI: 0.66, 3.13), Medicare: AOR = 1.55 (95% CI: 0.49, 4.95) Employment/private insured: AOR = 0.80 (95% CI: 0.42, 1.52) Overall X^2 = 4.36, overall p = 0.36 **Years of education** AOR = 0.91 (95% CI: 0.84, 1.00), X^2 = 3.89, p = 0.05 **Patient type** (red: ED discharge) Hospital admit no ICU: AOR = 1.34 (95% CI: 0.79, 2.26) Hospital admit with ICU: AOR = 1.66 (95% CI: 0.82, 3.34), Overall X^2 = 2.17, p = 0.34

									Injury cause (ref: MVA/fall/other non-intentional injury) Violence/assault: AOR = 3.14 (95% CI: 1.43, 6.89), X^2 = 8.09, p = 0.003* **LOC** (ref: No) Yes: AOR = 0.81 (95% CI: 0.42, 1.59), X^2 = 0.37, p = 0.55 **PTA** (ref: No) Yes: AOR = 0.95 (95% CI: 0.53, 1.68), X^2 = 0.04, p = 0.85 **CT intracranial injury** (ref: No) Yes: AOR = 0.70 (95% CI: 0.40, 1.22), X^2 = 1.61, p = 0.21 **Psychiatric history** (ref: No) Yes: AOR = 3.29 (95% CI: 1.93, 5.62), X^2 = 19.10, p < 0.0005* **Prior TBI** (ref: No) Yes: AOR = 1.55 (95% CI: 0.96, 2.49), X^2 = 3.25, p = 0.07
Stein et al. 2021 (TRACK TBI full study)	PCL-5 (categorical – total score > 32 indicating probable PTSD)	3 months post-TBI	n = 421 in first 16 multivariate models n = 405 in final logistic regression model)	PTSD at 3 months post-injury: 77/421	18 in total (10 in final model)	Established risk factors for post-TBI PTSD	8 x bivariate logistic regression models 8 x multivariable logistic regression models (with Benjamin-Hochberg-corrected p-values) 1 x multivariate logistic	None reported	<u>Bivariate models exploring associations between adjusted brain region of interest volumes (standardised) for intracranial volume and 3-month PTSD:</u> **Insula:** OR = 0.66 (95% CI: 0.47, 0.94), p = 0.020* **Hippocampus:** OR = 1.16 (95% CI: 0.85, 1.59), p = 0.36 **Amygdala:** OR = 1.12 (95% CI: 0.82, 1.54), p = 0.47 **Superior frontal cortex:** OR = 0.70 (95% CI: 0.51, 0.96), p = 0.026* **Rostral anterior cingulate cortex:** OR = 0.70 (95% CI: 0.50, 0.96), p = 0.028* **Caudal anterior cingulate cortex:** OR = 0.78 (95% CI: 0.57, 1.05), p = 0.10

							regression model (no correction)		**Medial orbitofrontal cortex:** OR = 0.87 (95% CI: 0.64, 1.19), p = 0.38 **Lateral orbitofrontal cortex:** OR = 0.86 (95% CI: 0.64, 1.16), p = 0.32 <u>Multivariable models exploring associations between brain regions of interest and PTSD at 3 months, adjusted for:</u> intracranial volume, sex, race, ethnicity, years of education, history of psychiatric illness, prior TBI, injury cause and 2-week PTSD symptom score **Insula:** OR = 0.66 (95% CI: 0.41, 1.06), p = 0.084, BH-adjusted p value: 0.168 **Hippocampus:** OR = 1.09 (95% CI: 0.71, 1.67), p-value = 0.70, BH-adjusted p-value: 0.70 **Amygdala:** OR = 0.82 (95% CI: 0.53, 1.25), p = 0.35, BH-adjusted p value = 0.40 **Superior frontal cortex:** OR = 0.53 (95% CI: 0.34, 0.84), p = 0.019, BH-adjusted p value: 0.036* **Rostral anterior cingulate cortex:** OR = 0.58 (95% CI: 0.37, 0.92), p = 0.019, BH-adjusted p value: 0.051 **Caudal anterior cingulate cortex:** OR = 0.57 (95% CI: 0.37, 0.87), p = 0.009, BH-adjusted p-value: 0.036* **Medial orbitofrontal cortex:** OR = 0.82 (95% CI: 0.54, 1.24), p = 0.35, BH-adjusted p-value: 0.40 **Lateral orbitofrontal cortex:** OR = 0.78 (95% CI: 0.52, 1.18), p = 0.24, BH-adjusted p-value: 0.39

									<u>Multivariable logistic regression model predicting PTSD at 3 months:</u> **PC1** (principal component explaining 73.8% of the variance in the regional volumes of the insula, superior frontal cortex, and rostral and caudal anterior cingulate) OR = 0.65 (95% CI: 0.49, 0.87), X^2 = 8.75, p = 0.003* **Intracranial volume (standardised)** OR = 2.03 (95% CI: 1.19, 3.48), X^2 = 6.67, p = 0.01* **Male** (ref: Female) OR = 0.72 (95% CI: 0.31, 1.68), X^2 = 0.58, p = 0.45 **Black** (ref: White/other) OR = 1.05 (95% CI: 0.42, 2.63), X^2 = 0.01, p = 0.92 **Hispanic** (ref: Non-Hispanic) OR = 1.31 (95% CI: 0.50, 3.38), X^2 = 0.30, p = 0.58 **Years of education** OR = 0.96 (95% CI: 0.84, 1.10), X^2 = 0.31, p = 0.58 **Any psychiatric history** (ref: None) OR = 1.89 (95% CI: 0.84, 4.28), X^2 = 2.34, p = 0.13 **Any prior TBI** (ref: None) OR = 1.63 (95% CI: 0.81, 3.28), X^2 = 1.90, p = 0.17 **Violent injury cause** (ref: Accidental) OR = 1.40 (95% CI: 0.39, 5.10), X^2 = 0.26, p = 0.61 **PCL-5 total score at Week 2** OR = 1.09 (95% CI: 1.07, 1.12), X^2 = 65.54, p < 0.001*

									<u>Multivariable logistic regression model predicting PTSD at 6 months:</u> **PC1** (principal component explaining 73.8% of the variance in the regional volumes of the insula, superior frontal cortex, and rostral and caudal anterior cingulate) OR = 0.86 (95% CI: 0.65, 1.13), X^2 = 1.20, p = 0.27 **Intracranial volume (standardised)** OR = 1.10 (95% CI: 0.65, 1.84), X^2 = 0.12, p = 0.73 **Male** (ref: Female) OR = 0.97 (95% CI: 0.42, 2.26), X^2 = 0.00, p = 0.95 **Black** (ref: White/other) OR = 1.96 (95% CI: 0.82, 4.67), X^2 = 2.27, p = 0.13 **Hispanic** (ref: Non-Hispanic) OR = 1.06 (95% CI: 0.40, 2.84), X^2 = 0.01, p = 0.91 **Years of education** OR = 0.89 (95% CI: 0.77, 1.02), X^2 = 2.76, p = 0.10 **Any psychiatric history** (ref: None) OR = 2.08 (95% CI: 0.91, 4.75), X^2 = 3.02, p = 0.08 **Any prior TBI** (ref: None) OR = 1.36 (95% CI: 0.67, 2.74), X^2 = 0.72, p = 0.40 **Violent injury cause** (ref: Accidental) OR = 1.56 (95% CI: 0.45, 5.47), X^2 = 0.49, p = 0.49

									PCL-5 total score at Week 2 OR = 1.08 (95% CI: 1.06, 1.10), X^2 = 56.48, p < 0.0005*
Mikolić *et al.*, 2021 (CENTER-TBI study)	PCL-5 (categorical – total score >32)	6 months post-TBI	<u>In models on imputed data:</u> Mild TBI multivariate analyses: n = 1569 Moderate/severe multivariate analyses: n = 485 <u>In complete case models:</u> Mild TBI: n = 1281 Moderate/severe TBI: n = 368	<u>In models on imputed data:</u> Number of cases in mild TBI group = 153 (9.8%) Number of cases in moderate/severe TBI group models: 44 (9.1%) <u>In complete case models:</u> Cases in mild TBI group: n = 135 Cases in moderate/severe TBI group: n =	12	Included important predictors of outcome in TBI and factors associated with sex/gender in the literature	6 x multivariate models in total, including: 2 x multivariable ordinal mixed effects regressions (with imputed data) 2 x mixed effects regression analysis (complete cases only) 2 x multiple linear regression <u>Note:</u> All multivariate analyses conducted separately for participants with mild vs moderate/severe TBI	None reported	<u>Note:</u> all multivariate analyses reported below were adjusted for: Age Baseline GCS score Pupillary reactivity Hypotension and hypoxia before arrival/at admission Marshall Classification Traumatic subarachnoid haemorrhage Epidural haematoma ISS Pre-injury medical situation (ASA PS classification) Pre-injury psychiatric disorder Cause of injury <u>Multivariate ordinal mixed effects regression analyses (imputed data):</u> **Mild TBI:** Gender (ref: Male) Female: AOR = 1.1 (95% CI: 0.7-1.6), p value: 0.68 n = 1569 **Moderate/severe TBI** Gender (ref: Male) Female: AOR = 1.5 (95% CI: 0.7-3.3), p = 0.28 n = 485 <u>Complete case mixed effects regression analyses:</u> **Mild TBI:** Gender (ref: Male)

				36					Female: OR = 1.1 (95% CI: 0.7-1.6), p = 0.78 n = 1281 **Moderate/severe TBI:** Gender (ref: Male) Female: OR = 1.1 (96% CI: 1.0 – 5.7), p = 0.047* n = 368 <u>Linear mixed effect multiple regression analyses</u> **Mild TBI** Gender: (ref: Male) Female: beta = 1.88; p = 0.007* n = 1569 **Moderate/severe TBI** Gender (ref: Male) Female: 2.01; p = 0.15 n = 485
Van Praag et al., 2022 (CENTER-TBI study)	PCL-5 continuous total score in the multiple linear regression analysis PCL-5 (categorial – DSM-5 criteria) in the multivariate logistic regression analyses	6 months post-TBI	1134 (complete case analyses) 2863 (sensitivity analysis with imputed data)	153/1134 complete cases	9	Not stated	1x Multivariate logistic regression (original data only) – significance level < 0.01 1 x Multiple logistic regression (sensitivity analysis) – significance level p < 0.01	<u>Logistic regression</u> Nagelkerke R^2 = 0.081 <u>Multiple linear regression:</u> Nagelkerke R^2 = 0.058 <u>Multiple linear regression (sensitivity analysis of imputed data):</u>	<u>Logistic regression of covariates associated with probable PTSD</u> **Age** (years; continuous) B = -0.026, standard error: 0.006, OR = 0.97, 95% CI: 0.91, 0.99, p < 0.001*, VIF = 1.30 **Sex** (ref: Female) Male: B = 0.30, standard error: 0.20, OR = 1.34, 95% CI: 0.91, 1.98, p = 0.14, VIF = 1.07-1.08 **Educational level** (ref: College/University) Primary school of less: B = 0.13, standard error: 0.31, OR = 1.13, 95% CI: 0.62, 2.08, p = 0.69 Secondary school/high school: B = 0.23, standard error: 0.24, OR = 1.25, 95% CI: 0.78, 2.00, p = 0.34

							1 x Multiple linear regression (sensitivity analysis of imputed data) – significance level p < 0.01	Nagelkerke R^2 = 0.074 VIF = VIF range of the original and 5 imputed datasets	Post-high school training: B = -0.012, standard error = 0.27, OR = 0.99, 95% CI: (0.58, 1.69), p = 0.97 VIF = 1.16-1.19 **Psychiatric history** (ref: absent) Present: B = 0.79, standard error = 0.24, OR = 2.20, 95% CI: 1.37, 3.53, p = 0.001*, VIF = 1.01 **GCS:** B = 0.030, standard error: 0.026, OR = 1.03, 95% CI: 0.98, 1.09, p = 0.25, VIF = 1.09 **Trail Making Test (B-A)** B = 0.30, standard error = 0.085, OR = 1.35, 95% CI: 1.14, 1.60, p < 0.001*, VIF = 1.22-1.25 **RAVLT-delayed recall** B = -0.30, standard error = 0.10, OR = 0.74, 95% CI: 0.61, 0.91, p = 0.004*, VIF = 1.36-1.41 <u>Multivariate logistic regression – sensitivity analysis of imputed data (full cohort)</u> **Age** (years; continuous) B = -0.026, standard error = 0.004, OR = 0.97, 95% CI: 0.96, 0.99, p < 0.001* , VIF = 1.30 **Sex** (ref: Female) Male: B = 0.26, standard error = 0.16, OR = 1.29, 95% CI: 0.96, 1.94, p = 0.13, VIF = 1.07-1.08 **Educational level** (ref: College/University) Primary school or less: B = 0.32, standard error = 0.43, OR = 1.38, 95% CI: 0.85,

									2.41, p = 0.48 Secondary school/high school: B = 0.29, standard error = 0.26, OR = 1.33, 95% CI: 0.83, 1.99, p = 0.29 Post high school training: B = 0.29, standard error = 0.30, OR = 1.30, 95% CI: 0.71, 2.32, p = 0.41 **Psychiatric history** (ref: Absent) Present: B = 0.71, standard error = 0.29, OR = 2.03, 95% CI: 1.52, 2.93, p = 0.041, VIF = 1.01 **GCS** B = 0.038, standard error = 0.021, OR = 1.04, 95% CI: 0.99, 1.07, p = 0.083, VIF = 1.09 **Trail Making Test (B-A)** B = 0.25, standard error = 0.065, OR = 1.28, 95% CI: 1.13, 1.50, p < 0.001*, VIF = 1.22-1.25 **RAVLT Delayed recall** B = -0.22, standard error = 0.085, OR = 0.80, 95% CI: 0.65, 0.99, p = 0.013, VIF = 1.36-1.41 <u>Multiple linear regression of covariates associated with PTSD symptoms (sensitivity analysis)</u> **Age** (years; continuous) B = -0.13, standard error = 0.025, p = 0.003*, VIF = 1.30 **Sex** (ref: Female) B = 1.99, standard error = 0.87, p = 0.001*, VIF = 1.08-1.08 **Educational level** (ref: College/University) Primary school or less: B = 1.30, standard

									error = 1.41, p = 0.022 Secondary school/high school: B = 2.01, standard error = 1.02, p = 0.060 Post high school training: B = 1.08, standard error = 1.10, p = 0.026 VIF = 1.16-1.19 **Psychiatric history** (ref: Absent) Present: B = 6.04, standard error = 1.25, p = 0.006*, VIF = 1.01 **GCS** B = 0.019, standard error = 0.12, p = 0.004*, VIF = 1.09 **Trail Making Test (B-A)** B = 2.08, standard error = 0.43, p = 0.003*, VIF = 1.22-1.25 **RAVLT-delayed recall** B = -0.69, standard error = 0.46, p = 0.002*, VIF = 1.36-1.41
Bown et al. 2019 (overlaps with Qureshi et al's study)	PCL-C continuous total score	Median 5.1 months post-TBI (IQR: 3.6-7.7)	144	N/A	4	Variables controlled for were significantly different (or borderline) between assault and non-assault groups	1 x multiple linear regression	None reported	**Assault (ref: Non-assault)** B = 5.200, standard error: 3.925 p value: 0.188 Adjusted for age, ethnicity and the incidence of extracranial trauma
Qureshi et al. 2019 (overlaps with Bown et	PCL-C continuous total score	Not stated	127	Dependent on diagnostic threshold used, between 20.6%	First level of the hierarchical linear regression: 5	Variables controlled for were potential confounding factors	1 x hierarchical linear regression (including two levels)	<u>First level:</u> F(5,121)=35.59, p < 0.01, accounting for 57.9% of the variance in PTSD severity	<u>Level 1:</u> **Sex (male/female):** Coefficient beta: -0.10; B = -0.47 (95% CI: -6.22, 5.28) B standard error: 2.90; p > 0.05 **Age (years): C**oefficient beta: -0.03; B = -0.03 (95% CI: -0.16, 0.10); B standard error: 0.06; p > 0.05

al's study)				and 31.6%	Second level: 7			<u>Second level:</u> F(7,119) = 27.06, p < 0.05.	**QoL**: Coefficient beta: 0.13; B = 0.15 (95% CI: -0.07, 0.36); B standard error = 0.11; p > 0.05 **Concussion symptoms**: Coefficient beta: 0.23; B = 0.28 (95% CI: -0.06, 0.62); B standard error: 0.17; p > 0.05 **Depression symptoms:** Coefficient beta: 0.23; B = 1.57 (95% CI: 0.97, 2.17); B standard error: 0.30; p < 0.05* <u>Levell 2:</u> **Sex (male/female):** Coefficient beta: -0.01; B = -0.51 (95% CI: -6.13, 5.11); B standard error: 2.84; p > 0.05 **Age (years): C**oefficient beta: -0.03; B = -0.03 (0.16, 0.09); B standard error: 0.06; p > 0.05 **QoL**: Coefficient beta: 0.13; B = 0.15 (95% CI: -0.07, 0.36); B standard error = 0.11; p > 0.05 **Concussion symptoms**: Coefficient beta: 0.18; B = 0.22 (95% CI: -0.12, 0.56); B standard error: 0.17; p > 0.05 **Depression symptoms:** Coefficient beta: 0.69; B = 1.67 (95% CI: 1.08, 2.26); B standard error: 0.30; p < 0.05* **GCS (mild/moderate/severe):** Coefficient beta = -0.08; B = -1.86 (95% CI: -4.67, 0.96); B standard error: 1.42; p > 0.05 **Marshall grade:** Coefficient beta: -0.12; B = -1.73 (95% CI: -3.45, 0.01); B standard error: 0.87; p value < 0.05*

McCauley et al. 2013	PCL-C continuous total score	Within 24 hours of injury 1-week post-injury 1-month post-injury	75 (46 mTBI and 29 OI controls)	N/A	5	Predictors selected based on their demonstrated increased risk (either in the general population or post-TBI) for developing acute stress disorder, PTSD and/or PCS	3 x multiple linear regressions	<u>Within 24 hours of injury model:</u> $F(5,68) = 12.10$, $p < 0.001$*; $R^2 = 0.47$; adjusted $R^2 = 0.43$ <u>1 week post-TBI model:</u> $F(5,65) = 8.10$, $p < 0.0001$*; $R^2 = 0.38$; adjusted $R^2 = 0.34$ <u>1 month post-TBI model:</u> $F(5,55) = 4.31$, $p < 0.003$*; $R^2 = 0.28$; adjusted $R^2 = 0.22$	<u>PTSD symptoms within 24 hours of injury multivariate model:</u> **Age at injury (years):** B = -0.11; B standard error: 0.11; t = -1.05; Beta coefficient = -0.18; p > 0.07 **Gender (ref: female)**: B = 1.47; B standard error: 2.25; t = 0.65; Beta coefficient = 0.06; p > 0.07 **Group (ref = OI controls):** B = 6.65; B standard error: 2.0; t = 3.32; Beta coefficient = 0.30; p < 0.001* **CES-D:** B = 0.86; B standard error: 0.14; t = 6.02; Beta coefficient: 0.63; p < 0.0001* **CD-RISC:** B = 0.07; B standard error: 0.06; t = 1.2; Beta coefficient = 0.13; p > 0.05 <u>PTSD symptoms one week after TBI multivariate model:</u> **Age at injury (years):** B = -0.17; B standard error: 0.15; t = -1.13; Beta coefficient = -0.11; p > 0.07 **Gender (ref: female)**: B = 6.2; B standard error: 3.14; t = 1.97; Beta coefficient = 0.19; p < 0.07 **Group (ref: OI controls):** B = 8.03; B standard error: 2.86; t = 2.81; Beta coefficient = 0.29; p < 0.01* **CES-D:** B = 0.96; B standard error: 0.2; t = 4.75; Beta coefficient: 0.56; p < 0.0001* **CD-RISC:** B = 0.15; B standard error: 0.08; t = 1.86; Beta coefficient = 0.21; p < 0.07

									<u>PTSD symptoms one month after TBI multivariate model:</u> **Age at injury (years):** B = -0.23; B standard error: 0.18; t = -1.28; Beta coefficient = -0.15; p > 0.07 **Gender (ref: female):** B = 3.71; B standard error: 3.63; t = 1.02; Beta coefficient = 0.12; p > 0.07 **Group (ref: OI controls):** B = 7.72; B standard error: 3.31; t = 2.34; Beta coefficient = 0.27; p < 0.05* **CES-D:** B = 0.86; B standard error: 0.24; t = 3.62; Beta coefficient: 0.48; p < 0.001* **CD-RISC:** B = 0.2; B standard error: 0.1; t = 2.13; Beta coefficient = 0.28; p < 0.05*

Table 5. Multivariable models of post-traumatic stress disorder after traumatic brain injury. * = statistically significant results. AOR = Adjusted Odds Ratio; CD-RISC = Connor-Davidson Resilience Scale; CES-D = Centre for Epidemiologic Studies Depression Scale; CT = Computed Tomography; DSM = Diagnostic and Statistical Manual of Mental Disorders; ED = Emergency Department; GCS = Glasgow Coma Scale; ICU = Intensive Care Unit; ISS = Injury Severity Scale; N/A = Not Applicable; LOC = Loss of Consciousness; mOR = Multivariate Odds Ratio; MVA = Motor Vehicle Accident; OI = Orthopaedic Injury; OR = Odds Ratio; PCL-5 = PTSD Checklist for DSM-5; PCL-C = PTSD Checklist for DSM-IV – Civilian Version; PCS = Post-Concussive Symptoms; PTA = Post-Traumatic Amnesia; PTSD = Post-Traumatic Stress Disorder; QoL = Quality of Life; RAVLT = Rey Auditory Verbal Learning Test; RTA = Road Traffic Accident; TBI = Traumatic Brain Injury; TRACK-TBI = Transforming Research and Clinical Practice in Traumatic Brain Injury; VIF = Variance Inflation Factor.

4. Discussion

This systematic review provides an overview of univariable predictors and multivariable models of self-reported PTSD after TBI. 19 papers from 10 different studies were included, published over the last 16 years. Meta-analyses of univariable predictors found that higher self-reported PTSD symptoms were significantly associated with non-Caucasian race, pre-TBI psychiatric history, positive toxicology screen on admission and an assault mechanism of injury. Lower self-reported PTSD symptoms were significantly associated with more years of education.

4.1. Significant predictors identified in this review

4.1.1. Race/ethnicity

The finding that non-Caucasian race is associated with increased risk of PTSD symptoms after TBI is consistent with previous research showing worse mental health outcomes for ethnic minority groups with and without TBI (Borowsky *et al.*, 2000; Shafi *et al.*, 2007; Staudenmayer *et al.*, 2007; Stockdale *et al.*, 2008; Barger, Donoho and Wayment, 2009; Sander *et al.*, 2009; Arango-Lasprilla *et al.*, 2011, 2012).

This association could be due to black and minority ethnic groups facing increased racial/ethnic discrimination, and so greater stress and adversity, increasing their risk of mental health difficulties (Smedley, Stith and Nelson, 2003; Ayalon and Gum, 2011; Perrin *et al.*, 2014). Black and minority ethnic groups may also face more barriers to accessing support, including: stigma, language gaps, distrust of services and healthcare professionals (e.g., due to previous experiences of institutional racism), lack of diversity in mental health professionals, and inequalities in access to services (Anugwom, 2021). Furthermore, there can be cultural differences in how distress is experienced and understood, in health-seeking behaviours, in the roles of social support systems, and in beliefs about causes and alleviators of distress (Perrin *et al.*, 2014). In Western countries, the approach to recovery in

healthcare services is very Eurocentric. This may not be well-suited to the needs and preferences of diverse communities (Anugwom, 2021). All of these factors could contribute to the observed associations between race/ethnicity and post-TBI PTSD symptoms.

Actions that could be taken to help improve outcomes for TBI patients from black and minority ethnic groups could include: taking action to reduce racial and ethnic inequalities, reducing stigma, providing training for healthcare staff to better understand and meet the needs of diverse patients, increasing representation of black and minority ethnic groups within healthcare professions, more constructive working with voluntary and community sector organisations and faith groups, making services more accessible and less stigmatising, and engaging in co-production with marginalised groups during service development, policy-making and commissioning decision-making (Bignall *et al.*, 2019).

4.1.2. Mechanism of injury

An assault mechanism of injury was found to be significantly associated with increased risk of post-TBI PTSD symptoms. Assault is a particularly intrusive intentional form of injury (Bown *et al.*, 2019). This finding is therefore consistent with previous research showing that intentional injuries are associated with an increased risk of adverse mental health outcomes compared to non-intentional injuries (Ozer *et al.*, 2003; Alarcon *et al.*, 2012). Screening for mechanism of injury at the time of admission may therefore help to identify individuals at higher risk of experiencing post-TBI PTSD symptoms.

4.1.3. Pre-TBI psychiatric history

Pre-TBI psychiatric history was significantly associated with increased risk of PTSD symptoms. The direction of this effect was consistent across all studies included in the meta-analysis. Whilst it is inconsistent with Cnossen et al's (2017) meta-analysis, which did not find a statistically significant association between pre-TBI psychiatric history and post-TBI PTSD assessed using structured clinical interviews, it is consistent with literature exploring

predictors of PTSD more generally (Brewin, Andrews and Valentine, 2000; Ozer *et al.*, 2003; DiGangi *et al.*, 2013). There is limited research exploring whether associations vary according to type of pre-injury psychiatric disorder (Van Praag *et al.*, 2022). However, the findings indicate that screening for the presence of any pre-TBI psychiatric history on admission could help to identify TBI patients at increased risk of PTSD.

4.1.4. Toxicology screen on admission

A positive toxicology screen on admission, indicating active substance use at the time of injury, was a significant predictor of higher post-TBI PTSD symptoms. A possible mechanism underpinning this association could be trauma responses being sensitised by substances.

There is evidence that cocaine enhances amygdala functioning in humans (Semple *et al.*, 2000) and intensifies fear conditioning in animals (Borowski and Kokkinidis, 1994). This may result in trauma memories being triggered more easily (Bombardier *et al.*, 2006). This suggests that toxicology screening could be an important part of TBI assessment.

Detecting acute intoxication could help to prevent neurologic exams being confounded by unrecognised intoxication, and provide an opportunity to offer appropriate intervention (e.g., counselling, treatment, onward referral to outpatient services) (Yue *et al.*, 2020). This could help to break negative long-term health cycles (Yue *et al.*, 2020).

4.1.5. Years of education

A greater number of years of education was significantly associated with lower self-reported PTSD symptoms after TBI in the meta-analysis. However, there was no significant association between categorical level of education (high school qualification and above versus lower) in the meta-analysis. This disparity may be due to the fact that dichotomising variables leads to information being lost, reducing statistical power (Altman and Royston, 2006).

Education is commonly used as an indicator of socioeconomic status. It may be that lower educational attainment negatively impacts employment status, contributing to lower income, and so higher levels of deprivation. However, this association could be bidirectional; mental health difficulties could contribute to reduced educational attainment, decreased income and so more economic difficulties (Wilson & Finch, 2021). Even sub-diagnostic PTSD is associated with lost wages, use of temporary workers, sick time and increased cost (Judd *et al.*, 1996; Richmond *et al.*, 2011). However, research suggests that the main direction is from economic difficulties to mental health difficulties (Weich and Lewis, 1998; Wang, Schmitz and Dewa, 2010; Kosidou *et al.*, 2011; Molarius and Granström, 2018).

4.1.6. Persistence of associations in multivariate models

Each of the significant predictors in the current review remained significant in some multivariate models, but not in others. This may be due to different confounding variables being controlled for in different multivariate models, and also due to differences in methodology, study populations, and changes in associations over time. Future research could further investigate factors moderating these associations.

4.2. Comparison with previous reviews

Cnossen et al. (2017) performed a systematic review and meta-analysis of predictors of diagnosed PTSD after TBI. They identified shorter PTA, memory of the traumatic event, and early post-injury symptoms as predictors of PTSD after TBI. These variables could not be explored in the current review's meta-analyses due to inadequate numbers of studies investigating them.

Whilst pre-TBI psychiatric history and years of education were significantly associated with post-TBI PTSD in the current review, these associations were non-significant in Cnossen et al's (2017) review. The current review also identified significant

predictors not investigated in Cnossen et al's (2017) review, including: race, assault mechanism of injury and toxicology screen on admission.

Discrepancies in the findings between the results of the current meta-analytic review and Cnossen *et al's* (2017) could be due to methodological differences in the included studies. One of the key differences is that the current review only included studies assessing PTSD using self-report measures, whereas Cnossen *et al.* (2017) only included studies where PTSD was diagnosed using structured diagnostic interviews. The accuracy of self-report measures for assessing PTSD symptoms in TBI patients has sometimes been criticised. This is due to overlap in symptoms between TBI and PTSD making differential diagnosis difficult (e.g., sleep problems, irritability, concentration difficulties) and some TBI patients experiencing impairments in self-awareness, attention and memory (Moore, Terryberry-Spohr and Hope, 2006; Prigatano and Sherer, 2020) affecting the accuracy of self-report measure completion. Despite this, there is evidence that self-report measures are valid screening tools for PTSD in TBI populations, and they are commonly used in clinical practice and research (Whelan-Goodinson, Ponsford and Schönberger, 2009; Dahm, Wong and Ponsford, 2013; Geier *et al.*, 2019; van Praag *et al.*, 2020; von Steinbuechel *et al.*, 2021).

Discrepancies in findings between the current meta-analyses and those of Cnossen et al. (2017) could also be due to other methodological differences between the studies included in the reviews, such as in inclusion and exclusion criteria, study design, follow-up periods, TBI severity, participant characteristics and statistical methods.

4.3. Strengths and limitations

Systematic reviews and meta-analyses can help to establish the consistency of scientific findings and whether they can be generalised across populations – they are therefore very helpful when findings in the literature are mixed, as they are for predictors of PTSD after TBI.

A strength of the current review is that a protocol for the systematic review and meta-analysis was developed prospectively. Specifying the methods a priori helps to reduce the risk of biased post-hoc methodological decisions. Registering the protocol with PROSPERO also helps to reduce the risk of duplicate reviews, increase transparency when updating systematic reviews, and decrease the risk of publication bias (Greco *et al.*, 2013). The methodology set out in this prospective protocol was adhered to as far as possible. Any deviations have been explained with a clear rationale (e.g., refinement of the inclusion and exclusion criteria to narrow the scope of the review, to make it more practically manageable to complete within the time-frame).

Study selection can be linked to multiple types of bias which can influence the interpretation of findings, including: time-lag bias, citation bias and publication bias (Cochrane, 2002; Greco *et al.*, 2013). Actions taken to ensure maximal completeness of the review included: searching multiple databases, searching grey literature, employing "backward snowballing" by scanning references of retrieved articles and relevant reviews, examining supplementary materials, and requesting additional data from study authors where relevant. Prominent researchers could have also been contacted to enquire about any additional unpublished studies they are aware of. Publication bias can be examined by creating funnel plots and conducting file-drawer or trim-and-fill analyses to identify and correct for asymmetry in them (Duval and Tweedie, 2000; Taylor and Tweedie, 2000; Cochrane, 2002; Rosenberg, 2005). Such analyses can only be conducted when there are at least 10 studies in the meta-analysis (Cochrane, 2002), therefore it was not possible in the current review.

A criticism of risk of bias assessments is that judgements can be subjective and reviewers can be influenced by features of studies such as the prestige of the author and journal (Stegenga, 2011). To reduce the risk of this, the QUIPS tool was used to conduct risk of bias assessments (Hayden *et al.*, 2013). Likewise, the CHARMS tool was used for data extraction (Moons *et al.*, 2014). These are both structured, Cochrane-recommended tools. They help to increase the transparency and reproducibility of these processes (Greco *et al.*,

2013). Had time provided, enlisting multiple independent, blinded reviewers to complete the study selection, data extraction and risk of bias assessments (and evaluating inter-rater reliability and resolving any discrepancies between reviewers) could have also helped to further ensure the accuracy of these procedures (Cochrane, 2002).

Many predictors identified in the literature only had univariate data available from one study, and so could not be meta-analysed. Furthermore, the majority of meta-analysed predictors were examined in only two studies, and in six meta-analyses (for gender, level of education (categorical), employment status at the time of injury, ED GCS, ED discharge (vs hospital or ICU admission) and ICU length of stay) there was high heterogeneity ($I^2 > 50\%$).

Ideally, sources of heterogeneity would be explored and their impact quantified using statistical methods such as weighted meta-regression or ANOVA (Harrison, 2011; Greco *et al.*, 2013). Unfortunately, the number of included studies was insufficient to do this. However, sensitivity analyses did confirm that the findings were robust to the exclusion of cross-sectional and retrospective study designs, and the exclusion of Bombardier et al's (2006) study, which examined predictors of above-threshold PTSD symptoms at any of the monthly follow-up points during the first six months after injury (in contrast to other studies which examined predictors of PTSD symptoms at each time point separately). Also, random effect meta-analyses were conducted to account for some expected heterogeneity between studies, though this cannot account for it completely.

The results of the meta-analyses must also be interpreted with caution because significant associations may have been confounded by other variables (since only univariate predictors were meta-analysed). Likewise, non-significant associations may have become significant after controlling for confounders. If a certain core set of confounding variables were consistently controlled for in multivariate analyses across different studies, this would facilitate comparisons of multivariate results.

The conclusions of a meta-analysis depend on the quality of the included studies (Harrison, 2011). The risk of bias assessments revealed that the majority of included papers had a moderate risk of bias in the 'study participation' domain – often due to not specifying

study participation rates. Likewise, the majority of papers had moderate-high risk of bias in the 'study attrition' domain – often due to high drop-out rates (>33.3%), lack of information about reasons for drop-out or significant differences in key characteristics between drop-outs and those who were retained in the study. In terms of statistical analysis and reporting, most papers did not make any corrections for multiple comparisons (increasing the risk of type I errors) or account for missing data (e.g., using imputation methods). In some papers, the number of events-per-variable or cases-per-predictor in multivariate analyses was under 10, increasing the risk of statistical overfitting, limiting the generalisability of their findings (Tabachnick and Fidell, 2001). The majority of studies conducting multivariate analyses did not evaluate the multivariate models (e.g., by providing measures of goodness-of-fit or model performance, or validating the model). This makes it challenging to assess the likely real-world clinical utility of these predictive models.

Most of the included studies were conducted in European countries and the US, and recruited majority male, Caucasian participants. Therefore, the findings of this review may not be generalisable to more diverse populations and TBI patients in other countries, regions and services. Indeed, there is considerable variation in healthcare systems both between and within countries (e.g., in terms of funding, accessibility, and facilities and resources available) which could contribute to variation in associations (Papanicolas *et al.*, 2019).

4.4. Directions for future research

Further research is needed to confirm the relevance of these predictors of self-reported PTSD symptoms after TBI. Defining categorical variables with more levels (e.g., multiple categories of racial/ethnic groups, or mechanisms of injury) instead of dichotomising predictors could provide more information about their relation to post-TBI PTSD symptoms.

Future research could also examine predictors of post-TBI PTSD that appear promising, but have only been examined in one study to-date (e.g., workplace versus non-workplace TBI, COMT polymorphisms, previous TBI, and volumes of brain regions of

interest). It could also examine new candidate predictors, identified based on the current knowledge about the aetiology of psychiatric disorders (Cnossen *et al.*, 2017). Research examining predictors of post-TBI PTSD should explore how associations change over time (including over longer follow-up periods) and the factors moderating these relationships.

To achieve this, more prospective cohort studies in more geographically diverse locations and with larger and more demographically diverse samples are needed. Increased standardisation in methodology across prospective studies (e.g., in follow-up periods, measures used, confounders controlled for in multivariate analyses) could facilitate comparisons between studies. Future research should ensure that participants lost to follow-up are described and compared to those retained. Future studies should also consider blinding predictor and outcome measurement, and could try to account for missing data where appropriate (e.g., through multiple imputation). Analyses should be sufficiently powered, corrections should be made for multiple statistical comparisons (where appropriate), and measures of multivariate model goodness-of-fit and performance should be reported to aid assessment of their prognostic utility.

This quantitative research could be complemented by qualitative approaches investigating the perspectives of key stakeholders, including TBI patients, family members, carers, clinicians and policy-makers. It could explore their views on risk and protective factors for post-TBI psychiatric disorders, underpinning mechanisms and moderating factors.

5. Conclusions

The findings of this meta-analytic review suggest that self-reported PTSD symptoms after TBI are associated with: non-Caucasian race, assault mechanism of injury, pre-TBI psychiatric history, positive toxicology screen on admission and fewer years of education. Multivariate models predicting post-TBI PTSD symptoms currently have significant limitations. Further research is needed to confirm associations found in this review, to identify further predictors, and understand factors moderating these associations. This could

facilitate the development of multivariable models to predict post-TBI PTSD in clinical practice. This would aid the early detection, prevention and treatment of PTSD in TBI survivors.

6. Additional information

6.1. Registration and protocol

This review was registered on PROSPERO. Registration number: CRD42021281045. It can be accessed at: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=281045

6.2. Contributors

JG is the main author and conducted all aspects of the review. NK and DF provided supervision throughout.

6.3. Funding

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6.4. Competing interests

None declared.

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Part 2: Empirical paper

Association between Marshall computed tomography grade and anxiety, depression and post-traumatic stress disorder one-year after moderate-severe traumatic brain injury

Abstract

Background: Traumatic brain injury (TBI) is associated with deleterious outcomes, including depression, anxiety and post-traumatic stress disorder (PTSD). This study aims to examine the relationship between Marshall computed tomography (CT) classification grade – a measure of brain injury severity – and self-reported depression, anxiety and PTSD symptoms 12-months after moderate-severe TBI.

Methods: This study analyses data from the prospective, longitudinal, international BIOmarkers of AXonal injury after TBI (BIO-AX-TBI) study. TBI patients aged 18-80, with a moderate-severe TBI according to the Mayo classification, were recruited prospectively across eight European trauma centres. This analysis includes participants recruited between November 2017 – July 2019. Marshall CT grade was measured in the emergency department (ED) at baseline, and psychiatric outcomes were measured at 12-months post-injury using the PTSD Checklist for DSM-5 (PCL-5) and the Hospital Anxiety and Depression Scale (HADS) self-report measures.

Results: In total, 75 participants were included in the current analysis. No statistically significant associations were found between Marshall CT grade and PCL-5 or HADS scores at 12-months in univariate or multivariate analyses ($p > 0.05$). In the multivariate models, there were also no significant associations between confounders (gender, employment status at the time of injury, mechanism of injury (assault vs. accidental), Glasgow Coma Scale score, loss of consciousness or post-traumatic amnesia) and 12-month HADS or PCL-5 scores.

Conclusions: The lack of significant associations between Marshall CT grade and 12-month psychiatric outcomes in this study warrants further investigation in larger and more diverse TBI patient samples. Future research could explore moderators of relationships between predictors and psychiatric outcomes after TBI, and examine the predictive utility of other neuroimaging features (e.g., finer structural abnormalities, and changes in brain

connectivity). Developing a more comprehensive understanding of biopsychosocial factors associated with post-TBI psychiatric disorders could help to improve prognostication and outcomes for TBI survivors.

1. Introduction

Traumatic brain injury (TBI), defined as “an alteration in brain function, or other evidence of brain pathology, caused by an external force” (Menon *et al.*, 2010), is a leading cause of mortality and disability (Maas *et al.*, 2017). TBI is associated with a range of deleterious outcomes, including physical disability, cognitive impairment, functional impairment and mental health difficulties (Rabinowitz and Levin, 2014; Devi *et al.*, 2020).

Mental health difficulties can interfere with rehabilitation and hinder recovery from TBI (Kim *et al.*, 2007), and are associated with high direct and indirect costs (Walker *et al.*, 2003; Humphreys *et al.*, 2013; Scholten *et al.*, 2014). Identifying factors associated with post-TBI mental health difficulties could aid their early identification, prevention and treatment.

Depression is the most common mental health difficulty reported after TBI, with prevalence rates of 25-52% in the first year post-TBI (Fann, Hart and Schomer, 2009). Anxiety disorders are the second most common, with 37% of people experiencing clinically significant levels of anxiety after TBI (Osborn, Mathias and Fairweather-Schmidt, 2016a). Post-traumatic stress disorder (PTSD) is the third most common mental health disorder after TBI, with a prevalence of 17-33% (Ohry, Rattok and Solomon, 1996; Motzkin and Koenigs, 2015).

The development and maintenance of these psychiatric disorders is multifactorial (Belmaker and Agam, 2008). Various genetic, developmental, demographic, behavioural and psychosocial factors appear to influence post-TBI psychiatric outcomes (Jorge *et al.*, 2004; Juengst, Kumar and Wagner, 2017).

1.1. Factors associated with post-TBI depression

A systematic review and meta-analysis by Cnossen et al. (2017) attempted to synthesise the literature on predictors of post-TBI depression diagnosed using structured diagnostic interviews. It identified predictive factors including female gender, pre-injury depression,

post-injury unemployment and lower brain volume, all of which increase the risk of major depression after TBI.

Additional factors in the literature linked to an increased risk of depression after TBI include: pre-injury substance use, income status and susceptibility to high stress (Juengst, Kumar and Wagner, 2017; Yeo, 2021), post-injury fatigue and sleep disturbance (Rao *et al.*, 2013; Schönberger, Herrberg and Ponsford, 2014; Beaulieu-Bonneau and Ouellet, 2017; Juengst, Kumar and Wagner, 2017), and unemployment and adjustment difficulties (Fann, Hart and Schomer, 2009; Jorge and Arciniegas, 2014).

There is mixed evidence regarding the link between TBI severity and post-TBI depression. Some studies suggest that increased TBI severity is associated with increased risk of post-TBI depression (Deb *et al.*, 1999; Huang, Spiga and Koo, 2005) and others decreased risk (Van Reekum *et al.*, 1996; Hudak *et al.*, 2012; Siponkoski *et al.*, 2014). There is also research suggesting that TBI severity has no link with post-TBI depression (Seel *et al.*, 2003; Dikmen *et al.*, 2004; Malec, Testa, *et al.*, 2007; Bombardier *et al.*, 2010). Indeed, studies examining the effects of demographic and injury-related variables such as injury severity, gender, ethnicity, age, injury aetiology, and level of social support often yield inconsistent and contradictory results (Rosenthal, Christensen and Ross, 1998; Singh *et al.*, 2017).

There is also some evidence for associations between certain biological factors and post-TBI depression, including: pre-frontal and basal ganglia damage (Fann, Hart and Schomer, 2009; Jorge and Arciniegas, 2014; Cnossen *et al.*, 2017; Yeo, 2021), increasing severity of brain injury abnormality examined using the “overall appearance” approach (Wardlaw, Easton and Statham, 2002; Singh *et al.*, 2017), disruption to serotonergic and adrenergic pathways in the brain (Schwarzbold *et al.*, 2008), pro-inflammatory cytokine dysregulation (Juengst *et al.*, 2015; Failla *et al.*, 2016; Devoto *et al.*, 2017; Juengst, Kumar and Wagner, 2017; Bodnar, Morganti and Bachstetter, 2018), and various disturbances in connectivity between different brain regions (Kaiser *et al.*, 2015; Moreno-López *et al.*, 2016; Van Der Horn *et al.*, 2017). Some research has also explored whether genetic

polymorphisms predict post-traumatic depression (Chan *et al.*, 2009; Fakhoury *et al.*, 2020). However, more research is needed.

1.2. Factors associated with post-TBI anxiety

Scholten et al's (2016) systematic review identified that diagnosed anxiety disorders after TBI are associated with female gender, unemployment and a pre-TBI psychiatric history (Scholten *et al.*, 2016). There is some evidence for an inverse relationship between TBI severity and post-TBI anxiety (Osborn, Mathias and Fairweather-Schmidt, 2016a). In the wider literature, there is also evidence for potential links between anxiety disorders and environmental factors (e.g., stressful life events, lack of social support, reduced participation in active and leisure activities), psychological factors (e.g., passive emotion-focused coping styles, lower levels of resilience), and biological factors (e.g., diffuse axonal injury, neuroendocrine abnormalities, altered neurotransmitter levels, and hypothalamic-pituitary-adrenal axis dysfunction) (Osborn, 2016).

1.3. Factors associated with post-TBI PTSD

Research suggests that the risk of PTSD is greatest in the first year after TBI (Van Praag *et al.*, 2019). A systematic review by Gill et al. (2014) examined psychological and psychosocial factors associated with post-TBI PTSD. Variables significantly associated with post-TBI PTSD included: certain psychological processes (e.g., coping styles and attribution) and psychosocial variables (e.g., role impairment), acute stress disorder and comorbid depression and anxiety (Gill, Mullin and Simpson, 2014). They also noted that certain factors associated with PTSD in the general population were not associated with PTSD in TBI populations, including: marital status, litigation, employment status after TBI and educational level (Gill, Mullin and Simpson, 2014). However, the directions of identified relationships were unclear since all factors associated with PTSD after TBI were examined, not just predictive factors.

Cnossen et al's (2016) systematic review and meta-analysis did specifically examine predictors of post-TBI PTSD. The significant predictors they identified included: shorter post-traumatic amnesia (PTA), early post-traumatic symptoms, and memory of the traumatic event.

1.4. The current study

As summarised above, there is some evidence that TBI severity is associated with post-TBI psychiatric outcomes. One measure of TBI severity is the Marshall CT Classification (Marshall *et al.*, 1991), which categorises brain injuries based on CT imaging characteristics.

In the Marshall CT classification, there are six different grades, each based on degree of basal cistern compression and midline shift, and the presence or absence of one or more surgical mass lesions. The classification is commonly used in clinical practice and research. There is some evidence that it can help to predict some outcomes after TBI, including functional outcomes measured using the Glasgow Outcome Scale (GOS), neuropsychological outcomes and mortality (Ono *et al.*, 2001; Maas *et al.*, 2007; Zhu, Wang and Liu, 2009).

No studies have yet explored associations between Marshall CT grade and depression or anxiety symptoms after TBI. Two papers analysing data from the same study at a UK trauma centre reported that higher Marshall CT grades were associated with lower scores on the PTSD Checklist for DSM-5 (PCL-5) (Bovin *et al.*, 2016; Bown *et al.*, 2019; Qureshi *et al.*, 2019). They suggested that more severe injuries (indicated by higher Marshall CT grades) may result in more peri-traumatic amnesia, protecting against PTSD (Bryant *et al.*, 2009; Bown *et al.*, 2019). However, it is difficult to draw conclusions about causality since this was a cross-sectional study based at a single centre.

The current study aims to build on these findings by conducting multivariate analyses to explore associations between Marshall CT grade and scores on self-report measures of anxiety, depression and PTSD symptoms 12-months after moderate-severe TBI. It also aims

to conduct exploratory analyses of univariate associations between Marshall CT grade and outcomes, demographic, clinical and injury-related characteristics.

2. Methods

2.1. Study design

The study population consisted of patients from the BIOmarkers of Axonal injury after Traumatic Brain Injury (BIO-AX-TBI) study (Graham *et al.*, 2020). This is an international, prospective, longitudinal, multi-centre observational study of fluid and neuroimaging biomarkers of axonal injury after moderate-to-severe TBI. It recruited patients with acute moderate-severe TBI, according to the Mayo Classification of injury severity (Malec, Brown, *et al.*, 2007), from eight participating trauma centres across Europe. It followed-up with participants over the course of a year. Assessments were conducted acutely, at 10 days-6 weeks, 6 months and 12 months post-injury (Graham *et al.*, 2020).

2.2. Setting

The current study analyses data collected from participants recruited between 30th November 2017 (when BIO-AX-TBI recruitment started) and July 2019. Patients were recruited from eight trauma centres across Europe. These included: Lausanne University Hospital, Switzerland, University Medical Centre, Ljubljana, Slovenia; St George's and St Mary's Hospitals, London; and Carregi University Hospital, Santa Chiara Hospital, Trento, Italy, and Niguarda Hospital and Policlinico in Milan, Italy (Graham *et al.*, 2020).

2.3. Study procedures

Patients eligible for participation were identified by clinicians and researchers working at participating trauma centres. Patients satisfying the BIO-AX-TBI study's inclusion and exclusion criteria were approached, provided with verbal and written information about the

study and invited to participate. They were given 24 hours to consider whether to participate before being recruited. The aim was to recruit participants promptly after their TBI – ideally within ten days of injury (Graham *et al.*, 2020).

Patients who did not have capacity to provide fully informed consent were assented with permission from their next of kin or personal/nominated consultee, in line with national legislations (Graham *et al.*, 2020). If these participants were later able to provide fully informed consent, they were re-consented. Participants could withdraw or be withdrawn by their legal representative at any point in the study without needing to provide a reason (Graham *et al.*, 2020).

The BIO-AX-TBI study includes a core programme of work. This included blood biomarkers and baseline magnetic resonance imaging (MRI). At selected research sites this was supplemented by longitudinal MRI, advanced imaging techniques and cerebral microdialysis (Graham *et al.*, 2020). This current study does not analyse any MRI, cerebral microdialysis or blood biomarker data.

2.4. Inclusion and exclusion criteria

To be included in the study, participants had to have sustained a moderate-severe TBI (according to the Mayo Classification of Injury Severity) (Malec, Brown, *et al.*, 2007), and be aged 18-80. As per the Mayo classification, moderate-to-severe TBIs were identified by the presence of any of the following features: lowest Glasgow Coma Scale (GCS) score of less than 13 in the first 24 hours after injury; PTA duration of 24 hours or more, loss of consciousness (LOC) of 30 minutes or more, neuroimaging abnormalities (e.g., intracerebral haematoma, subdural haematoma, epidural haematoma, cerebral contusion, haemorrhagic contusion, penetrating TBI (dura penetrated), subarachnoid haemorrhage or brainstem injury), or death due to the TBI (Malec, Brown, *et al.*, 2007; Graham *et al.*, 2020).

Exclusion criteria included: previous significant TBI (requiring hospitalisation), cardiac arrests, moribund patients, previous significant neurological or psychiatric conditions,

previous significant disability from any cause, and inability or unwillingness to participate in the BIO-AX-TBI study (Graham, 2009).

Participants were included in the present analysis if they had been recruited by July 2019, providing time for them to have had their one-year follow-up. To be included, participants also needed to have completed the PCL-5 and/or Hospital Anxiety and Depression Scale (HADS) at 12-months follow-up.

Inclusion criteria	**Exclusion criteria**
Moderate-severe TBI (according to the Mayo classification)	Previous significant TBI (requiring hospitalisation)
Aged 18-80	Moribund patients
	Cardiac arrests
	Prior significant neurological or psychiatric conditions
	Previous significant disability from any cause
	Inability or unwillingness to participate in the study
	For MRI: typical MRI contraindications of ferromagnetic implants in the body, pregnancy, claustrophobia

Table 1. Inclusion and exclusion criteria for the BIO-AX-TBI study. MRI = Magnetic Resonance Imaging; TBI = Traumatic Brain Injury.

2.5. Data collection

2.5.1. Clinical and demographic information

Clinical and demographic information was collected at baseline using an electronic case report form (eCRF) (Graham *et al.*, 2020). This required collection of TBI common data elements (Maas *et al.*, 2010). Clinical and demographic variables measured included:

- Demographic characteristics (e.g., age, gender, ethnicity, study centre, employment status at the time of injury, level of education)
- Number of days hospitalised and number of days admitted to an intensive care unit (ICU)
- Neurosurgical interventions
- Presence of hypoxia and hypotension
- Pupillary response
- Lowest Glasgow Coma Scale (GCS) score in the first 24 hours after injury (Teasdale and Jennett, 1976) (a widely used measure of TBI severity)
- At-scene LOC
- Retrograde amnesia and PTA
- TBI features (e.g., presence of contusions, intracerebral haemorrhages, subdural haematomas, maximum lesion volume)
- Mechanism of injury
- Previous cranial trauma

The independent variable in this study is Marshall CT grade (Marshall *et al.*, 1991), measured at baseline. The criteria for each of the six grades of CT scan abnormalities defined by the Marshall CT classification are shown in Table 2, below.

Marshall CT classification grade	Criteria
I	No visible intracranial pathology seen on the CT scan.
II	Cisterns are present with midline shift of 0-5mm; high or mixed density lesion <25cm^3.
III	Cisterns are compressed/absent with midline shift of 0-5mm; high or mixed density lesion <25cm^3
IV	Midline shift 5mm; high or mixed density lesion <25cm^3
V	High or mixed density lesion >25cm^3; any lesion surgically evacuated
VI	High or mixed density lesion >25cm^3; not surgically evacuated

Table 2. Marshall CT Classification criteria (Marshall *et al.*, 1991). CT = Computed Tomography.

2.5.2. Clinical, cognitive and functional outcome assessments

The outcomes included in the current analysis are listed below. They were all administered at 12-months follow-up. Continuous total scores from each measure were used in the statistical analyses. 12-month follow-ups were conducted face-to-face by appropriately-trained researchers. If face-to-face follow-ups were not possible, attempts to follow-up with participants were made remotely (e.g., through telephone consultation) (Graham *et al.*, 2020).

PTSD Checklist for DSM-5 (PCL-5): The PCL-5 (Weathers *et al.*, 2013) is a self-report questionnaire measuring symptoms of PTSD in the past month according to the Diagnostic and Statistical Manual for Mental Health Disorders 5 (DSM-5) criteria. It consists of 20 items, each rated on a Likert scale ranging from 0 (“Not at all”) to 5 (“Extremely”). The overall score can range from 0-80. Research has shown that cut-off scores of 31-33 are optimal for diagnosing PTSD (Bovin *et al.*, 2016). The PCL-5 demonstrates strong reliability and validity

in psychometric evaluation (Blevins *et al.*, 2015), including in TBI populations (von Steinbuechel *et al.*, 2021).

Hospital Anxiety and Depression Scale (HADS): The HADS (Zigmond and Snaith, 1983) is a 14-item self-report questionnaire consisting of an anxiety subscale (HADS-A) and a depression subscale (HADS-D), each 7 items long. The appraisal period is one week. Items are rated on a scale from 0 to 3. The presence of anxiety and/or depression is usually indicated by a total score of 8 or more on each of these subscales. The HADS is a widely-used measure in TBI research, with research demonstrating it to be a reliable and valid measure of anxiety and depression in this population (Whelan-Goodinson, Ponsford and Schönberger, 2009; Dahm, Wong and Ponsford, 2013; Boxley *et al.*, 2016).

Insomnia Severity Index (ISI): The ISI (Morin *et al.*, 2011) is a 7-item self-report questionnaire that measures symptoms of insomnia during the past two weeks. It assesses: sleep dissatisfaction, sleep onset, maintenance, early morning awakening, degrees of distress, noticeability of the sleep problems by others, and the impact of the sleep problems on functioning. Each item is rated on a scale from 0 to 4. Total ISI scores range from 0-28 with higher scores indicating more severe insomnia. Total raw scores of 0-7 indicate absence of insomnia; 8-14 indicate sub-threshold insomnia, 15-21 clinical insomnia with moderate severity; and 22-28 clinical insomnia with severe severity (Bastien, Vallières and Morin, 2001; Morin *et al.*, 2011; Chen, Yang and Morin, 2015). The ISI has demonstrated excellent psychometric properties (Bastien, Vallières and Morin, 2001; Morin *et al.*, 2011; Kaufmann *et al.*, 2019) and has been used in numerous prior studies in TBI (Wickwire *et al.*, 2022).

Quality of Life after Brain Injury Questionnaire (QOLIBRI): The QOLIBRI (Von Steinbüchel *et al.*, 2010) is a 37-item questionnaire developed to subjectively assess health-related quality of life and cognitive function in people who have experienced TBI. Part A assesses satisfaction levels across the following four domains: ‘Social relationships’ (6 items),

'Autonomy in daily life' (7 items), 'Self-perception' (7 items) and 'Cognition' (7 items). Part B assesses symptom burden and comprises two domains: 'Negative emotions' and 'Physical problems', each 5 items long. Each item is rated on a scale from 0-4, with burden responses (part B) reversed. The scores of the answered questions are averaged and multiplied by 25 to obtain the overall score. Scores range from 0-100. The QOLIBRI is widely used in TBI studies, and research has shown it to be reliable and valid in TBI populations (Steinbüchel *et al.*, 2010; Von Steinbüchel *et al.*, 2010; Born, Amsler and Gross, 2018; von Steinbuechel *et al.*, 2021).

Montreal Cognitive Assessment (MoCA): The MoCA (Nasreddine *et al.*, 2005) is a 30-item measure used to screen for cognitive impairment. The scale ranges from 0 to 30. Scores lower than 27 are indicative of cognitive impairment. Mild cognitive impairment is defined by scores between 18-25. Moderate cognitive impairment corresponds to scores between 10-17 and scores less than 10 indicate severe cognitive impairment. The MoCA has been shown to have good sensitivity and specificity in detecting cognitive impairment (Smith, Gildeh and Holmes, 2007) and good criterion validity (Lam *et al.*, 2013). It has been validated in TBI populations (Wong *et al.*, 2013).

Glasgow Outcome Scale Extended (GOS-E): The GOS-E (Sander, 2002) provides an overall measure of disability. It involves gathering information through a structured interview. It focuses on the following domains: independence, social/community participation, cognition and employability. Scores range from 1 (dead) to 8 (upper good recovery). It is a frequently used measure in outcome studies, and there is considerable research demonstrating its reliability and validity in TBI populations (Wilson, Pettigrew and Teasdale, 1998, 2000; Wilson *et al.*, 2002; Pettigrew, Wilson and Teasdale, 2003; Levin *et al.*, 2004; Lu *et al.*, 2010; Wong *et al.*, 2013; Dikmen *et al.*, 2019).

2.6. Ethical approval

The relevant ethical approvals have been granted by the following ethics committees: in London, by the Camberwell St Giles Research Ethics Committee, in Policlinico (Milan), by the Comitato Etico Milano Area 2; in Niguarda (Milan) by the Comitato Etico Milano Area 3; in Careggi (Florence),by the Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana, Sezione area vasta centro; in Trento, by the Trento Comitato Etico per le Sperimentazioni Cliniche, Azienda Provinciale per I Servizi Sanitari della Provincia autonoma di Trento; in Lausanne by the Commission cantonale d d'éthique de la recherche sur l'être humain; in Ljubljana, by the National Medical Ethics Committee at the Ministry of Health of the Republic of Slovenia (Graham *et al.*, 2020).

2.7. Patient and public involvement

Patients and research participants were involved in the development of the BIO-AX-TBI study via regular participant involvement events at Imperial College London (Graham *et al.*, 2020).

2.8. Statistical analysis

2.8.1. Descriptive statistics and univariate analyses

Descriptive statistics are presented as medians and interquartile ranges for continuous variables and frequencies and percentages for categorical variables.

Mann-Whitney U tests and Chi-squared tests are used to explore differences in demographic and clinical characteristics between participants included in the current analysis, and those who were enrolled in the BIO-AX-TBI study by July 2019 but did not have a completed HADS or PCL-5 measure at 12-months.

All continuous variables involved in univariate analyses violated the assumptions of independent samples t-tests; none were approximately normally distributed as shown by Shapiro Wilk tests ($p < 0.05$). Therefore, group differences in all continuous variables across

the Marshall CT grade categories were explored using non-parametric Kruskal-Wallis tests. Differences in categorical variables between the Marshall CT grades were assessed using Fishers' Exact Tests (since all variables had individual cell counts ≤5).

As there was only one participant with a Marshall CT grade of IV, categories III and IV were combined for all univariate analyses. All univariate analyses were performed on the original (non-imputed) dataset, with pairwise exclusion of missing values to ensure maximal usage of data.

Correlations between continuous outcome measure total scores were assessed using Spearman's rank correlation coefficients, pooled across the multiply imputed datasets.

2.8.2. Multivariate multiple linear regression analyses

Multiple linear regression analyses were performed to predict PCL-5, HADS-A and HADS-D total scores. Marshall CT grade (dichotomised into grades I-III and IV-VI) was the independent variable. Six confounders derived from pre-existing empirical literature were also incorporated. These included: gender (female vs. male), employment status (unemployed/not fit for work/retired vs. employed/student), GCS (3-8 vs. 9-15), mechanism of injury (non-assault vs. assault), PTA (absent vs. suspected/present) and LOC (absent vs. suspected/present). The adjusted mean differences and their 95% confidence intervals (CI) are reported for each independent variable in the multiple regression analyses. A sample size of 75 was considered adequate given seven independent variables, according to the 10:1 rule (Tabachnick and Fidell, 2001).

The multiple linear regression analyses were performed across multiply imputed datasets, in which missing values were imputed based on an imputation model with all demographic, injury and clinical characteristics and all 12-month outcome measures. Statistics were then pooled and reported. The percentage of imputed missing values ranged from 1.3% (PCL-5 items 1, 7, 15 and 16; ISI items 1, 2, 5, 6; intracranial pressure raised ever) to 33.3% (LOC duration).

To check the sensitivity of the results to imputation of missing values, multiple regression analyses were also performed on only the original data (with missing values deleted pairwise).

To check the sensitivity of the results to the inclusion of LOC, PTA and GCS (variables involved in the BIO-AX-TBI study inclusion and exclusion criteria used to select participants into the study) as potential confounders in the multivariate analyses, additional multiple regression sensitivity analyses were performed in which only gender, employment status and mechanism of injury were controlled for. These were performed across the multiply imputed datasets.

Multiple imputation, analyses of descriptive statistics and univariate analyses were conducted in SPSS (version 23) (IBM Corp, 2015). The assumptions of multiple regression analyses were tested in SPSS, whilst the regression analyses themselves were conducted in Stata (version 17) (StataCorp, 2019).

Corrections for multiple comparisons were not made for univariate analyses, as these were exploratory (Armstrong, 2014). The significance threshold for univariate analyses was therefore $p < 0.05$. However, the Bonferroni correction was applied for multiple comparisons in multivariate analyses (54 comparisons across the nine multiple regression analyses) and so significance in multivariate analyses was assessed at $p < 0.000926$ (3 s.f.).

3. Results

3.1. Participant characteristics

Of 311 patients in the BIO-AX-TBI database, 75 adults were included in the current study's analysis. 61 patients had been enrolled after July 2019 (and so had not yet had their 12-month follow-up). Another 16 died before 12-month follow-up (mean of 19.7 days after injury, standard deviation 21.0). Reasons for non-completion of PCL-5 and HADS measures at 12-months for the remaining participants were not documented, but the non-completion was likely due to study drop-out.

Compared to participants enrolled by July 2019 but without a completed 12-months HADS or PCL-5 measure, participants included in the current study had a statistically significantly: higher level of education ($p = 0.024$), higher prevalence of retrograde amnesia ($X^2 = 7.781$; $p = 0.024$), longer PTA duration ($p = 0.03$) and lower GOS-E scores at 12-months ($p < 0.001$), according to a threshold of $\alpha = 0.05$.

In the present study, 70/111 (63.1%) variables had missing values. 72/75 (96.0%) cases had at least one missing value. 463/8325 (5.6%) values overall were missing. These missing values are illustrated in Figure 1, below.

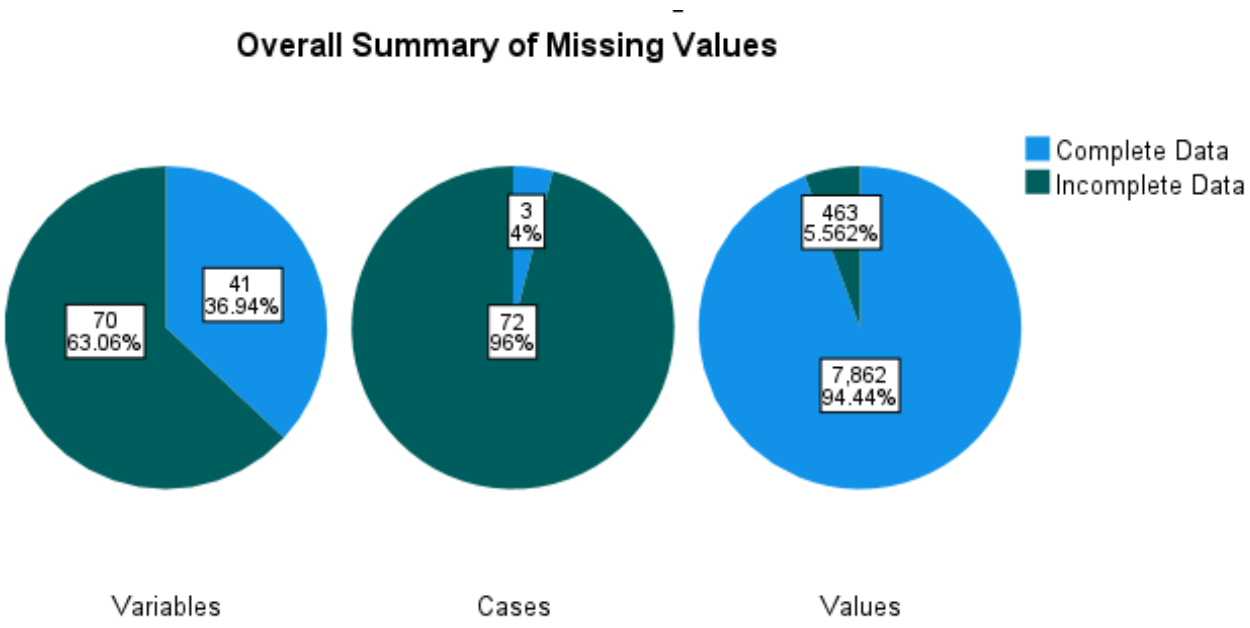

Figure 1. Pie charts (from left to right) showing the overall numbers and percentages of: variables with any missing data, cases with any missing data, and any missing values overall.

12.3% of participants met Marshall grade I criteria, 40.1% grade II, 9.7% grade III, 1.7% grade IV, 12.3% grade V and 23.9% grade VI (see Table 3**,** below). The median age of participants was 43 years old (interquartile range: 30 years), and the majority were male (81.3%) and White (95.7%). At baseline, 63.4% were employed in work, and 40.0% were university educated.

Marshall CT grade	Number of participants (%) (n = 72)*
I	9 (12.3)
II	30 (40.1)
III	6 (9.7)
IV	1 (1.7)
V	9 (12.3)
VI	17 (23.9)

Table 3. Number of participants with each Marshall CT grade in the current study. CT = Computed Tomography. * 3 participants were missing data for Marshall CT grade.

3.2. Univariate analyses

Distributions and group differences in participants' outcomes and demographic, injury-related and clinical characteristics by Marshall CT grade are shown in Table 4, below.

Based on a significance threshold of $p < 0.05$, exploratory univariate analyses showed no significant association between Marshall CT grade and HADS-A, HADS-D or PCL-5 scores. However, statistically significant differences were found between Marshall CT grade and the following variables: study centre ($p < 0.001$), level of education ($p = 0.006$), ICU admission duration ($p < 0.001$), hospital admission duration ($p < 0.001$), GCS score ($p < 0.001$), LOC duration ($p = 0.021$), PTA duration ($p = 0.002$), 12-month GOS-E scores ($p = 0.029$) and the presence of various types of brain pathology including intracerebral haemorrhage ($p = 0.031$), subdural haematoma ($p < 0.001$), epidural haematoma ($p = 0.023$), contusion ($p = 0.040$), and procedures including ICP monitoring ($p < 0.001$) and neurosurgery ($p < 0.001$). All other group differences were non-significant.

Demographic, injury, clinical or outcome variable	Sample size (n = 75) (% of total sample)	Marshall grade I (n = 9)	Marshall grade II (n = 30)	Marshall grade III-IV (n = 7)	Marshall grade V (n = 9)	Marshall grade VI (n = 17)	Test statistic	p-value (2-sided)
Age (years; continuous)	72 (96.0%)	40.0 (27.0)	45.5 (26.0)	24.0 (22.0)	43.0 (8.0)	47.0 (39.0)	3.874	0.423
Gender	72 (96.0%)							0.159
Male		3 (33.3%)	8 (26.7%)	0 (0.0%)	0 (0.0%)	2 (11.8%)		
Female		6 (77.7%)	22 (73.3%)	7 (100.0%)	9 (100.0%)	15 (88.2%)		
Ethnicity	66 (88.0%)							0.421
Asian		0 (0.0%)	1 (3.7%)	0 (0.0%)	1 (16.7%)	0 (0.0%)		
White		9 (100.0%)	26 (96.3%)	7 (100.0%)	5 (83.3%)	17 (100.0%)		
Study centre	75 (100.0%)							< 0.001***
Florence		0 (0.0%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	1 (5.9%)		
Lausanne		1 (11.1%)	7 (23.3%)	3 (42.9%)	1 (11.1%)	2 (11.8%)		
Ljubljana		0 (0.0%)	3 (10.0%)	4 (57.1%)	0 (0.0%)	6 (35.3%)		
London		4 (44.4%)	8 (26.7%)	0 (0.0%)	8 (88.9%)	0 (0.0%)		
Milan		1 (11.1%)	2 (6.7%)	0 (0.0%)	0 (0.05%)	4 (23.5%)		
Niguarda		1 (11.1%)	4 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		
Trento		2 (22.2%)	4 (13.3%)	0 (0.0%)	0 (0.0%)	4 (23.5%)		
Employment status	68 (90.7%)							0.302
In work		8 (88.9%)	16 (57.1%)	4 (66.7%)	8 (88.9%)	8 (50.0%)		
Not fit for work		1 (11.1%)	4 (14.3%)	2 (33.3%)	0 (0.0%)	2 (12.5%)		
Retired		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)		
Student		0 (0.0%)	2 (7.1%)	0 (0.0%)	1 (11.1%)	4 (25.0%)		
Unemployed		0 (0.0%)	6 (21.4%)	0 (0.0%)	0 (0.0%)	1 (6.3%)		
Level of education	53 (70.7%)							0.006**
Primary school		2 (25.0%)	7 (33.3%)	2 (33.3%)	0 (0.0%)	10 (83.3%)		
Secondary school		3 (37.5%)	4 (19.0%)	3 (50.0%)	1 (16.7%)	0 (0.0%)		
University		3 (37.5%)	10 (47.6%)	1 (16.7%)	5 (83.3%)	2 (16.7%)		
Intensive care unit admission duration (days; continuous)	72 (96.0%)	4.0 (4.0)	7.0 (10.0)	23.0 (11.0)	4.0 (4.0)	17.0 (19.0)	21.211	<0.001***

Hospital admission duration (days; continuous)	72 (96.9%)	7.0 (26.0)	17.5 (20.0)	48.0 (113.0)	6.0 (9.0)	27.0 (49.0)	23.035	<0.001***
Mechanism of trauma	72 (96.0%)							0.209
Accidental		9 (100.0%)	28 (93.3%)	7 (100.0%)	7 (77.8%)	17 (100.0%)		
Assault		0 (0.0%)	2 (6.7%)	0 (0.0%)	2 (22.2%)	0 (0.0%)		
RTA type	72 (96.0%)							0.083
Non-RTA		4 (44.4%)	16 (53.3%)	2 (28.6%)	6 (66.7%)	12 (70.6%)		
Bicycle		2 (22.2%)	1 (3.3%)	1 (14.3%)	1 (11.1%)	1 (5.9%)		
Car/van		0 (0.0%)	5 (16.7%)	2 (28.6%)	0 (0.0%)	3 (17.6%)		
Motorbike		3 (33.3%)	3 (10.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)		
Pedestrian		0 (0.0%)	5 (16.7%)	0 (0.0%)	2 (22.2%)	1 (5.9%)		
Other		0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)		
GCS score	50 (66.7%)							< 0.001***
3		0 (0.0%)	2 (10.0%)	2 (40.0%)	0 (0.0%)	0 (0.0%)		
4		0 (0.0%	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		
5		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		
6		0 (0.0%)	1 (5.0%)	1 (20.0%)	0 (0.0%)	0 (0.0%)		
7		2 (25.0%)	2 (10.0%)	0 (0.0%)	0 (0.0%)	5 (50.0%)		
8		0 (0.0%)	2 (10.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)		
9		1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)		
10		0 (0.0%)	0 (0.0%)	2 (40.0%)	0 (0.0%)	1 (10.0%)		
11		0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		
12		0 (0.0%	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)		
13		2 (25.0%)	1 (5.0%)	0 (0.0%)	1 (14.3%)	1 (10.0%)		
14		0 (0.0%)	1 (5.0%)	0 (0.0%)	4 (57.1%)	0 (0.0%)		
15		3 (37.5%)	9 (45.0%)	0 (0.0%)	2 (28.6%)	0 (0.0%)		
LOC	66 (88.0%)							0.175
Absent		0 (0.0%)	5 (17.9%)	0 (0.0%)	0 (0.0%)	2 (12.5%)		
Suspected		2 (28.6%)	6 (21.4%)	0 (0.0%)	4 (50.0%)	1 (6.3%)		
Present		5 (71.4%)	17 (60.7%)	7 (100%)	4 (50.0%)	13 (81.3%)		
LOC duration	48 (64%)							0.021*

No confirmed loss of consciousness		2 (28.6%)	11 (57.9%)	0 (0.0%)	4 (66.7%)	3 (23.1%)		
1-29 minutes		2 (28.6%)	1 (5.3%)	0 (0.0%)	2 (33.3%)	0 (0.0%)		
1-24 hours		1 (14.3%)	2 (10.5%)	1 (33.3%)	0 (0.0%)	2 (15.4%)		
1-7 days		2 (28.6%)	4 (21.1%)	1 (33.3%)	0 (0.0%)	2 (15.4%)		
>7 days		0 (0.0%)	1 (5.3%)	1 (33.3%)	0 (0.0%)	6 (46.2%)		
Retrograde amnesia	61 (81.3%)							0.242
Absent		1 (11.1%)	3 (12.0%)	0 (0.0%)	2 (28.6%)	0 (0.0%)		
Suspected		2 (22.2%)	9 (36.0%)	1 (16.7%)	2 (28.6%)	9 (64.3%)		
Present		6 (66.7%)	14 (52.0%)	5 (83.3%)	3 (42.9%)	5 (35.7%)		
Retrograde amnesia duration	54 (72.0%)							0.645
No confirmed retrograde amnesia		3 (42.9%)	12 (54.5%)	1 (25.0%)	4 (57.1%)	9 (64.3%)		
1-29 minutes		1 (14.3%)	2 (9.1%)	0 (0.0%)	2 (28.6%)	1 (7.1%)		
30-60 minutes		0 (0.0%)	2 (9.1%)	1 (25.0%)	1 (14.3%)	0 (0.0%)		
1-24 hours		0 (0.0%)	2 (9.1%)	0 (0.0%)	0 (0.0%)	1 (7.1%)		
1-7 days		1 (14.3%)	2 (9.1%)	1 (25.0%)	0 (0.0%)	0 (0.0%)		
>7 days		2 (28.6%)	2 (9.1%)	1 (25.0%)	0 (0.0%)	3 (21.4%)		
PTA presence (subacute)	65 (86.7%)							0.211
Absent		0 (0.0%)	4 (15.4%)	0 (0.0%)	3 (33.3%)	0 (0.0%)		
Suspected		3 (37.5%)	10 (38.5%)	1 (14.3%)	2 (22.2%)	8 (53.3%)		
Present		5 (62.5%)	12 (46.2%)	6 (85.7%)	4 (44.4%)	7 (46.7%)		
PTA duration (subacute)	61 (81.3%)							0.002**
No confirmed PTA (subacute)		3 (37.5%)	14 (58.4%)	1 (20.0%)	5 (55.6%)	8 (53.3%)		
1-29 minutes		1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		
1-24 hours		2 (25.0%)	1 (4.2%)	0 (0.0%)	3 (33.3%)	1 (6.7%)		
1-7 days		1 (12.5%)	8 (33.3%)	1 (20.0%)	1 (11.1%)	0 (0.0%)		
>7 days		1 (12.5%)	1 (4.2%)	3 (60.0%)	0 (0.0%)	6 (40.0%)		
Skull fracture	72 (96.0%)							0.421
Absent		6 (66.7%)	15 (50.0%)	4 (57.1%)	4 (44.4%)	5 (29.4%)		
Present		3 (33.3%)	15 (50.0%)	3 (42.9%)	5 (55.6%)	12 (70.6%)		

Intracerebral haemorrhage	72 (96.0%)							0.031*
Absent		9 (100.0%)	28 (93.3%)	4 (57.1%)	9 (100.0%)	13 (76.5%)		
Present		0 (0.0%)	2 (6.7%)	3 (42.9%)	0 (0.0%)	4 (23.5%)		
Epidural haematoma	72 (96.0%)							0.023*
Absent		9 (100.0%)	24 (80.0%)	5 (71.4%)	8 (88.9%)	8 (47.1%)		
Present		0 (0.0%)	6 (20.0%)	2 (28.6%)	1 (11.1%)	9 (52.9%)		
Subdural haematoma	72 (96.0%)							<0.001***
Absent		9 (100.0%)	15 (50.0%)	1 (14.3%)	0 (0.0%)	7 (41.2%)		
Present		0 (0.0%)	15 (50.0%)	6 (85.7%)	9 (100.0%)	10 (58.8%)		
Subarachnoid haemorrhage	72 (96.0%)							0.349
Absent		3 (33.3%)	14 (46.7%)	2 (28.6%)	1 (11.1%)	8 (47.1%)		
Present		6 (66.7%)	16 (53.3%)	5 (71.4%)	8 (88.0%)	9 (52.9%)		
Contusion	72 (96.0%)							0.040*
Absent		49 (100.0%)	16 (53.3%)	4 (57.1%)	6 (66.7%)	7 (41.2%)		
Present		0 (0.0%)	14 (47.8%)	3 (42.9%)	3 (33.3%)	10 (58.8%)		
ICP monitoring performed	72 (96.0%)							<0.001***
Absent		7 (77.8%)	23 (76.7%)	1 (14.3%)	7 (77.8%)	5 (29.4%)		
Present		2 (22.2%)	7 (23.3%)	6 (85.7%)	2 (22.2%)	12 (70.6%)		
ICP raised – ever	72 (96.0%)							0.054
Absent		8 (88.9%)	24 (80.0%)	3 (42.9%)	8 (88.9%)	9 (52.9%)		
Present		1 (11.1%)	6 (20.0%)	4 (57.1%)	1 (11.1%)	8 (47.1%)		
Neurosurgery – any operation	72 (96.0%)							<0.001 ***
Absent		9 (100.0%)	26 (86.7%)	2 (28.6%)	8 (88.9%)	0 (0.0%)		
Present		0 (0.0%)	4 (13.3%)	5 (71.4%)	1 (11.1%)	17 (100.0%)		
Hypoxia	60 (80.0%)							0.431
Absent		8 (100.0%)	20 (80.0%)	3 (60.0%)	6 (85.7%)	13 (86.7%)		
Present		0 (0.0%)	5 (20.0%)	2 (40.0%)	1 (14.3%)	2 (13.3%)		
Hypotension	61 (81.3%)							0.224
Absent		7 (87.5%)	24 (92.3%)	3 (60.0%)	8 (100.0%)	13 (92.9%)		
Present		1 (12.5%)	2 (7.8%)	2 (40.0%)	0 (0.0%)	1 (7.1%)		

Pupils in emergency department	58 (77.3%)							0.070
Bilaterally reactive and/or miotic		7 (100.0%)	23 (95.8%)	5 (100.0%)	6 (100.0%)	11 (68.8%)		
Unilaterally dilated and non-reactive		0 (0.0%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	5 (31.3%)		
Previous cranial trauma	68 (90.7%)							0.625
Absent		9 (100.0%)	27 (96.4%)	6 (100.0%)	8 (100.0%)	14 (82.4%)		
Suspected		0 (0.0%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	2 (11.8%)		
Present		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)		
GOS-E (12m)	68 (90.7%)							0.029*
3		0 (0.0%)	4 (14.3%)	0 (0.0%)	0 (0.0%)	1 (6.3%)		
4		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (18.8%)		
5		1 (11.1%)	5 (17.9%)	0 (0.0%)	0 (0.0%)	3 (18.8%)		
6		0 (0.0%)	6 (21.4%)	3 (42.9%)	2 (25.0%)	3 (18.8%)		
7		1 (11.1%)	9 (32.1%)	1 (14.3%)	2 (25.0%)	5 (31.3%)		
8		7 (77.8%)	4 (14.3%)	3 (42.9%)	4 (50.0%)	1 (6.3%)		
ISI total score (continuous)	66 (88.0%)	9.0 (13.0)	3.0 (8.0)	11.0 (14.0)	3.0 (5.5)	4.5 (8.0)	4.622	0.328
PCL-5 total score (continuous)	63 (84.0%)	9.5 (14.5)	10.0 (16.0)	9.0 (19.5)	11.0 (19.5)	7.5 (20.8)	1.579	0.813
HADS-A total score (continuous)	69 (92.0%)	3.0 (5.0)	5.0 (6.5)	6.0 (3.0)	1.0 (4.0)	6.5 (4.75)	9.077	0.059
HADS-D total score (continuous)	67 (89.3%)	2.0 (4.0)	3.0 (5.0)	4.0 (4.0)	3.0 (5.0)	4.0 (4.5)	7.937	0.094
MOCA – total score (continuous)	61 (81.3%)	28.0 (4.0)	26.0 (4.0)	27.0 (3.0)	28.0 (5.0)	23.0 (10.0)	7.625	0.106
QOLIBRI (12m) (continuous)	57 (76.0%)	83.3 (30.0)	79.2 (25.0)	79.2 (31.0)	75.0 (38.0)	68.8 (20.0)	5.021	0.285

Table 4. Demographic, injury and clinical characteristics and outcome measure scores of 75 patients with moderate-to-severe TBI included in the current analysis. p-values from Fisher's Exact tests are shown for categorical variables. p-values from Kruskal-Wallis tests are shown for continuous variables. GCS = Glasgow Coma Scale; GOS-E: Glasgow Outcome Scale Extended; HADS-A: Hospital Anxiety and Depression Scale – anxiety subscale; HADS-D = Hospital Anxiety and Depression Scale – depression subscale; ICP = intracranial pressure; ISI: Insomnia Severity Index; LOC = loss of consciousness; MoCA = Montreal Cognitive Assessment; PCL-5 = PTSD Checklist for DSM-5; PTA = post-traumatic amnesia; QOLIBRI = Quality of Life After Brain Injury; RTA = road traffic accident. * = $p < 0.05$. ** < $p = 0.01$. *** = $p < 0.001$.

Total scores on all six outcome measures correlated significantly with each other ($p < 0.05$). Age, hospital admission duration and ICU duration did not significantly correlate with any 12-month outcome measure, but they did all have significant positive correlations with each other ($p < 0.05$) (see Table 5, below).

	QOLIBRI total	MoCA total	ISI total	PCL-5 total	HADS-A total	HADS-D total	Age (years)	Hospital duration (days)	ICU duration (days)
MoCA total	r = 0.277* p = 0.024	-	-	-	-	-	-	-	-
ISI total	r = -0.277* p = 0.018	r = -0.084 p = 0.493	-	-	-	-	-	-	-
PCL-5 total	r = -0.464** p < 0.001	r = -0.270* p = 0.023	r = 0.413** p < 0.001	-	-	-	-	-	-
HADS-A total	r = -0.568** p < 0.001	r = -0.188 p = 0.121	r = 0.311** p = 0.007	r = 0.648** p = < 0.001	-	-	-	-	-
HADS-D total	r = 0.532** p < 0.001	r = -0.134 r = 0.268	r = 0.358** p = 0.002	r = 0.459** p < 0.001	r = 0.444** p < 0.001	-	-	-	-
Age (years)	r = -0.182 p = 0.127	r = -0.162 P = 0.178	r = 0.057 p = 0.632	r = -0.044 p = 0.707	r = 0.083 p = 0.481	r = 0.204 p = 0.081	-	-	-
Hospital duration (days)	r = 0.114 p = 0.341	r = -0.127 p = 0.290	r = -0.002 p = 0.988	r = 0.079 p = 0.504	r = 0.078 p = 0.507	r = -0.008 p = 0.945	r = -0.343** p = 0.002	-	-
ICU duration (days)	r = -0.050 p = 0.674	r = -0.156 p = 0.200	r = -0.005 p = 0.966	r = 0.048 p = 0.658	r = 0.021 p = 0.856	r = 0.131 p = 0.265	r = -0.245* p = 0.034	r = 0.656** p < 0.001	-

Table 5. Correlations between outcome measure scores and continuous demographic and clinical variables**.** r represents Spearman's correlation coefficients. HADS-A: Hospital Anxiety and Depression Scale – anxiety subscale; HADS-D = Hospital Anxiety and Depression Scale – depression subscale; ISI: Insomnia Severity Index; MoCA = Montreal Cognitive Assessment; PCL-5 = PTSD Checklist for DSM-5; QOLIBRI = Quality of Life After Brain Injury. * = $p < 0.05$; *** = $p < 0.001$.

3.3. Multivariate analyses

Multiple linear regression analyses were conducted on the multiply imputed datasets with the aim of predicting PCL-5, HADS-A and HADS-D total scores.

3.3.1. Assumption testing

Homoscedasticity

Whilst there was homoscedasticity in the HADS-A regression analysis, there was evidence of heteroscedasticity in the HADS-D and PCL-5 analyses. Therefore, square root transformations were applied to HADS-D and PCL-5 total scores and multiple regressions were run on these transformed variables. This resulted in homoscedasticity as assessed by visual inspection of a plot of studentized residuals versus unstandardised predicted values.

From this point onward, all assumption testing and multivariate analyses results are therefore reported on multiple regression analyses predicting HADS-A total scores, square root transformed HADS-D total scores (sqrt(HADS-D total scores)) and square root transformed PCL-5 total scores (sqrt(PCL-5 total scores)).

Linearity

There was linearity in all multiple regressions, as assessed by plots of studentized residuals against the predicted values.

Independence of residuals

There was independence of residuals in all analyses, as assessed by Durbin-Watson statistics between 1.5-2.5 on all of the regression models on all of the datasets.

Multicollinearity

There was no evidence of multicollinearity in any of the analyses, as assessed by all Pearson correlations between independent variables in each analysis <0.7 and all tolerance values >0.1.

Outliers, leverage and highly influential points

There were no studentized deleted residuals greater than ±3 standard deviations in any of the multiple regression analyses. There were 15, 16, and 17 leverage values greater than 0.2 in the HADS-A, sqrt(HADS-D) and sqrt(PCL-5) multiple regression analyses, respectively. However, none had values for Cook's distance above 1 and so none were highly influential points, therefore they were retained in the analyses.

In the HADS-A, sqrt(HADS-D) and sqrt(PCL-5) multiple regression sensitivity analyses where only gender, employment status and mechanism of injury were controlled for, there were one, two and zero studentized residuals greater than ±3 standard deviations, respectively. There were also four leverage values greater than 0.2 in each of these regression analyses. However, none had Cook's distance values above 1 and so none were highly influential points, therefore they were retained in the analyses.

Normality

The assumption of normality was met in all of the regression analyses, as assessed by visual inspection of histograms of regression standardized residuals and normal P-P plots.

3.3.2. Results of multiple regression analyses

The multiple regression model did not statistically significantly predict sqrt(PCL-5 total scores). The pooled statistics were: $F(7, 64.6) = 0.72$, $p = 0.6585$, mean $R^2 = 0.0831$, mean adjusted $R^{2=} = -0.0127$. Marshall CT grade did not add statistically significantly to the prediction, and neither did the other six confounders included ($p > 0.000926$). See Table 6, below, for a summary of these results.

Sqrt(PCL-5 total scores)	*B*	95% CI for *B*		*SE B*	*p*	β	R^2	△*R2*
		LL	UL					
Model							0.0831	-0.0127
Marshall CT grade	0.061	-0.870	0.991	0.464	0.896	0.017		
Gender	-0.071	-1.258	1.115	0.594	0.905	-0.016		
Employment status	-0.250	-1.248	0.747	0.499	0.618	-0.065		
LOC	0.913	-0.526	2.352	0.720	0.209	0.166		
PTA	-0.929	-0.509	2.368	0.720	0.201	0.167		
GCS	-0.062	-1.120	0.996	0.525	0.907	-0.016		
Assault mechanism	1.273	-0.685	3.232	0.981	0.199	0.165		
Constant	1.929	-0.284	4.142	1.105	0.086			

Table 6. Results of the multiple linear regression model predicting square root transformed PCL-5 total scores. *B* = unstandardized regression coefficient; CI = confidence interval; *LL* = lower limit; *UL* = upper limit; *SE B* = standard error of the coefficient; β = standardized coefficient; R^2 = coefficient of determination; △*R2* = adjusted R^2

The regression model did not statistically significantly predict HADS-A total scores. The pooled statistics were F(7, 64.7) = 0.49, p = 0.8378, mean R^2 = 0.0596, mean adjusted R^2 = -0.0387. None of the seven independent variables added statistically significantly to the prediction (p > 0.000926). See Table 7, below, for a summary of these results.

HADS-A total scores	*B*	95% CI for *B*		*SE B*	*p*	β	R^2	∆*R2*
		LL	UL					
Model							0.0596	-0.0387
Marshall CT grade	-0.149	-2.076	1.779	0.963	0.878	-0.019		
Gender	-1.731	-4.262	0.800	1.267	0.177	-0.185		
Employment status	0.470	-1.649	2.589	1.060	0.659	0.058		
LOC	0.205	-2.833	3.242	1.519	0.893	0.017		
PTA	0.448	-2.604	3.500	1.526	0.880	0.037		
GCS	-0.740	-2.831	1.351	1.042	0.481	-0.098		
Mechanism	-1.504	-5.852	2.843	2.172	0.491	-0.094		
Constant	6.271	1.764	10.779	2.255	0.007			

Table 7. Results of the multiple linear regression model predicting HADS-A total scores.
Note. B = unstandardized regression coefficient; CI = confidence interval; *LL* = lower limit; *UL* = upper limit; *SE B* = standard error of the coefficient; β = standardized coefficient; R^2 = coefficient of determination; ∆*R2* = adjusted R^2

The regression model also did not significantly predict square root transformed HADS-D total scores, $F(7, 64) = 0.22$, $p = 0.9783$, mean $R^2 = 0.0419$, mean adjusted $R^2 = -0.0582$. None of the seven independent variables added statistically significantly to the model ($p > 0.000926$). See Table 8, below, for a summary of these results.

Sqrt(HADS-D total scores)	*B*	95% CI for *B*		*SE B*	β	*p*	R^2	$\Delta R2$
		LL	UL					
Model							0.0419	-0.0582
Marshall CT grade	0.132	-0.402	0.666	0.266	0.067	0.623		
Gender	-0.033	-0.703	0.636	0.335	-0.014	0.921		
Employment status	-0.033	-0.468	0.650	0.280	0.044	0.747		
LOC	0.020	-0.802	0.842	0.410	0.004	0.961		
PTA	0.248	-0.605	1.101	0.425	0.078	0.563		
GCS	0.132	-0.800	0.540	0.329	-0.064	0.695		
Mechanism	-0.315	-1.442	0.911	0.563	-0.075	0.578		
Constant	1.616	0.322	2.910	0.644		0.015		

Table 8. Results of the multiple linear regression model predicting square root transformed HADS-D total scores. *Note. B* = unstandardized regression coefficient; CI = confidence interval; *LL* = lower limit; *UL* = upper limit; *SE B* = standard error of the coefficient; β = standardized coefficient; R^2 = coefficient of determination; $\Delta R2$ = adjusted R^2

In the multivariate regression sensitivity analyses conducted on the original data only, the regression model did not significantly predict HADS-A total scores ($F(7,42) = 0.909$; $p = 0.509$; $R^2 = 0.132$, adjusted $R^2 = -0.013$), sqrt(HADS-D total scores) ($F(7,42) = 0.499$; $p = 0.830$; $R^2 = 0.077$, adjusted $R^2 = -0.77$), or sqrt(PCL-5 total scores) ($F(7,42) = 0.895$; $p = 0.520$; $R^2 = 0.130$, adjusted $R^1 = -0.015$). None of the independent variables added statistically significantly to any of the models ($p > 0.000926$). See Appendices G, H and I for summary tables of the statistics from these sensitivity analyses.

In the multivariate regression sensitivity analyses performed across the imputed datasets where only gender, employment status and mechanism of injury were controlled for, the regression model did not significantly predict HADS-A total scores ($F(4, 67.7) = 0.680$; $p = 0.608$; mean $R^2 = 0.043$; mean adjusted $R^2 = -0.0120$), sqrt(HADS-D total scores) ($F(4, 67.6) = 0.220$; $p = 0.926$; mean $R^2 = 0.0180$; mean adjusted $R^2 = -0.0385$), or sqrt(PCL-5 total scores) ($F(4, 67.9) = 0.260$; $p = 0.900$; mean $R^2 = 0.0173$; mean adjusted $R^2 = -0.0389$). None of the independent variables added statistically to any of the models ($p > 0.000926$). See Appendices J, K and L for summary tables of the statistics from these sensitivity analyses.

4. Discussion

In this prospective study of 75 moderate-severe TBI patients from eight trauma centres across Europe, no significant associations were found between Marshall CT grade of brain injury severity at baseline and scores on the HADS or PCL-5 at 12-month follow-up. There were no significant associations even when potential confounders including gender, employment status at the time of injury, GCS, LOC, PTA and mechanism of injury (assault vs. accidental) were controlled for in multivariate analyses.

In univariate analyses there were no statistically significant associations between Marshall CT grade and HADS-A, HADS-D or PCL-5 total scores. However, there were statistically significant differences in demographic, injury-related and clinical variables between Marshall CT grades I-III and IV-VI in the following variables: study centre attended, level of education, ICU and hospital admission durations, GCS score, LOC duration, PTA duration, types of brain injury pathology, and procedures undergone (including ICP monitoring and neurosurgery). This indicates that Marshall CT grade was associated with TBI severity, as expected since it is a system for classifying TBI severity. There was also a significant association with 12-month GOS-E scores, consistent with previous literature

(Thelin *et al.*, 2017). Differences across study centres could reflect differences in application of the Marshall CT criteria, or differences in injury severity across centres.

Only two studies (both conducted at the same UK centre and analysing the same participants) have previously examined the association between Marshall CT grade and self-reported PTSD symptoms after TBI (Bown *et al.*, 2019; Qureshi *et al.*, 2019). These cross-sectional studies found that higher Marshall CT grades were associated with lower PTSD Checklist for DSM-IV – Civilian Version (PCL-C) total scores (Bovin *et al.*, 2016). Bown et al. (2019) hypothesised that more severe injuries result in more peri-traumatic amnesia, which may have a protective effect against PTSD (Bryant *et al.*, 2009; Bown *et al.*, 2019). Important differences between these two studies and the current study include: the use of different PTSD self-report measures (PCL-C vs PCL-5); different follow-up periods (5.1 months vs 12-months); cross-sectional vs prospective study designs; and different centres and locations (single UK centre vs eight European centres in the current study). In Qureshi et al's (2019) multivariate analysis, they also controlled for different potential confounders compared to the current study (sex, age, quality of life, GCS and concussion and depression symptoms). These methodological differences could explain why they found statistically significant associations between Marshall CT grade and self-reported PTSD symptoms whilst the current study did not.

Another notable finding from the current study is the lack of association found between any of the variables controlled for in multivariate analyses (gender, employment status, PTA, LOC, GCS, and mechanism of injury) and self-reported depression, anxiety and PTSD symptoms at 12-months. Previous literature on the prognostic utility of these variables is mixed (Rosenthal, Christensen and Ross, 1998; Osborn, Mathias and Fairweather-Schmidt, 2016b; Scholten *et al.*, 2016; Cnossen *et al.*, 2017; Singh *et al.*, 2017). There are some meta-analyses which have managed to identify consistent predictors of post-TBI psychiatric disorders. For example, Cnossen et al (2016) found in their meta-analysis that female gender, shorter PTA duration and early post-traumatic symptoms were associated with increased risk of post-TBI PTSD. However, many of these meta-analyses (including

Cnossen et al's (2016)) only included studies assessing PTSD using structured clinical interviews. These associations may not persist when PTSD is assessed using self-report measures, as in the current study.

Indeed, there are many methodological differences across studies which could help to explain the heterogeneity of findings in the literature. For example, different studies have different inclusion and exclusion criteria, recruit patients with different TBI severities, measure variables differently and follow-up patients for different durations of time. How variables are defined in statistical analyses may also vary (e.g., in this study predictors were dichotomised in multivariate analyses). There may also be differences in findings across different locations. Indeed, there is considerable variation within and between countries in healthcare access and care pathways after TBI, which could influence observed associations between variables (Steyerberg *et al.*, 2019; Volovici *et al.*, 2019). Future research could investigate factors moderating the relationships between predictors and post-TBI psychiatric outcomes to better understand this variability. It could also explore interactions between predictors (e.g., sex, race, age, level of education, etc.) to explore how intersections between them influence psychiatric outcomes after TBI.

Future research could also build on this study by exploring whether the prognostic utility of Marshall CT grade could be improved by taking into account other clinical features observed on CT scans. Limitations of the Marshall CT classification include its difficulty in classifying patients with multiple injuries and the fact that it does not take into account lesion type or location (Mohammadifard *et al.*, 2018). Another criticism is that TBI patients can be categorised as grade V, even if they have a lesion volume less than $25cm^3$, if they have undergone neurosurgical evacuation. It has been suggested that groups V and VI should therefore be combined to improve its predictive power (Mohammadifard *et al.*, 2018). Future research could investigate this. It could also examine whether combining Marshall CT grade with other information about structural brain abnormalities (e.g., from CT scans or more precise neuroimaging techniques such as MRI) could improve its predictive value. Given that research is increasingly conceptualising psychiatric disorders as conditions reflecting altered

distributed neural networks (Pol and Bullmore, 2013; Lanius *et al.*, 2015; Nicholson *et al.*, 2020), changes in brain functioning or connectivity (e.g., detected using functional MRI or diffusion tensor imaging) could also make promising candidate predictors of post-TBI psychiatric outcomes.

4.1. *Strengths and limitations*

This is the first prospective, multi-centre international study to examine associations between Marshall CT grade and self-reported anxiety, depression and PTSD symptoms after moderate-severe TBI. It also conducts an exploratory analysis of univariate associations between Marshall CT grade and a broad range of demographic, injury and clinical characteristics and outcomes.

The current study used the TBI common data elements framework to ensure high-quality, standardised data collection (Maas *et al.*, 2010). A strength of this is that it facilitates comparisons with other studies. Data collection could have been further improved by: providing more expansive options for gender identity, and determining patients' own attributions of TBI intentionality, rather than using accidental versus assault mechanisms of injury as a proxy (Bown *et al.*, 2019).

The strengths of the present study's consecutive sampling strategy include its speed and convenience. However, the fact that it is non-random means it may have introduced selection bias (Pannucci and Wilkins, 2010). This study included TBI patients who were unable to consent, as long as assent and permission from their next of kin or nominated/personal consultee were provided. This enabled the ethical inclusion of people with more severe TBI, who are more often excluded from research.

The advantages of using self-report measures such as the HADS and PCL-5 to measure psychiatric symptoms are that they are quick and simple to administer. However, they are sometimes criticised for not being as reliable as gold-standard structured diagnostic interviews. This is due to difficulties with differential diagnosis because of items assessing

non-specific symptoms and overlapping symptoms between TBI and psychiatric disorders (e.g., irritability, sleep problems, impaired concentration) and TBI-related impairments such as difficulties with attention, memory and impaired self-awareness (Moore, Terryberry-Spohr and Hope, 2006; Prigatano and Sherer, 2020). Patients could also be in denial of their difficulties, or overstate difficulties (e.g., to access more support or compensation) (Bivona *et al.*, 2019). Despite these limitations, the HADS and PCL-5 are validated measures of psychiatric symptoms in TBI populations (Whelan-Goodinson, Ponsford and Schönberger, 2009; Dahm, Wong and Ponsford, 2013; Geier *et al.*, 2019; van Praag *et al.*, 2020; von Steinbuechel *et al.*, 2021) and are widely used in clinical practice and research. Furthermore, as researchers conducting 12-month follow-ups were not blinded to predictors, the use of self-report measures with standardised scoring procedures reduced the risk of ascertainment bias, improving the study's internal validity.

Only 75/311 (24.1%) of the total BIO-AX-TBI sample had a completed 12-month HADS or PCL-5 measures and so were included in the current analysis. 16 were excluded due to death, and 61 due to not being enrolled by July 2019. The remainder of the excluded participants likely dropped out of the study, creating a risk of attrition bias. Compared to those enrolled by July 2019 with no completed HADS or PCL-5 measure at 12-months, participants included in the current analysis had a statistically significantly higher level of education, longer PTA duration and retrograde amnesia prevalence. Participants who dropped out before 12-month follow-up may therefore have had less severe TBIs (and so perhaps required less support) or faced more financial barriers to continued participation (if lower levels of education are taken as a proxy for lower socioeconomic status) (American Psychological Association, 2017). Given that longer PTA duration is associated with decreased risk of PTSD (Cnossen *et al.*, 2017) and more severe TBI is inversely associated with anxiety (Osborn, 2016), it is possible that that drop-outs experienced worse psychiatric outcomes on average than those included in the analysis.

Based on the current study's findings it is possible to confidently discount the existence of a large effect size between Marshall CT grade and HADS or PCL-5 scores one-year after moderate-severe TBI in the BIO-AX-TBI cohort. However, the current study's limited sample size (n = 75) may have made it underpowered to detect smaller effects. There is therefore a possibility that the current study's non-significant findings could be false negative results (type II errors). Future research studies could investigate whether a smaller effect size exists between Marshall CT grade and post-TBI HADS and PCL-5 scores by analysing larger samples, thereby increasing statistical power and reducing the risk of type II errors.

A strength of the statistical analysis is the use of multiple imputation to account for missing data. This method reduces bias due to missing data, improves validity and results in robust statistics (Kang, 2013). In addition, the fact that there were also no significant associations found when the multiple regression analyses were conducted on only the original data indicates that the results were robust to the imputation of missing values, increasing confidence in them.

The current study's multivariate analyses enabled six potential confounders to be controlled for whilst examining the association between Marshall CT grade and 12-month HADS-A, HADS-D and PCL-5 total scores. These confounders were dichotomised so that a variety could be controlled for whilst adhering to the 10:1 rule (Tabachnick and Fidell, 2001). However, a cost of this is that it reduces the amount of information provided about the relationships between each level of the categorical predictors and the psychiatric outcomes. Had the sample size been larger, it would have been possible to statistically control for more potential confounders, reducing residual confounding. However, even then, some known confounders were not measured in the BIO-AX-TBI study, such as substance use on admission, extracranial trauma, pain, medication, treatments received, and pre-injury and early post-injury levels of psychiatric symptoms (Bombardier *et al.*, 2006; Scholten *et al.*, 2016; Juengst, Kumar and Wagner, 2017; Yue *et al.*, 2020). The internal validity of the

current study could have been increased by measuring and controlling for more confounders and/or having healthy and orthopaedic trauma control groups (Wilde *et al.*, 2019).

The exclusion of certain groups (e.g., people with previous TBIs requiring hospitalisation, significant disability from any cause, cardiac arrests or significant pre-injury neurological or psychiatric conditions) helped to control for these potential confounders. However, these exclusions also limit the generalisability of the findings to these patient populations. This study also only included centres in Europe, patients with moderate-severe TBI, only assessed psychiatric outcome at 12-months post-TBI, and recruited a predominantly white male sample. The findings may therefore not generalise to more diverse TBI patient populations (e.g., females, ethnic minorities, people with mild TBI, and people living in other geopolitical and cultural contexts). More research with more diverse participant populations is needed to investigate this. Further research could also investigate longitudinal changes in associations between Marshall CT grade and psychiatric symptoms after TBI.

5. Conclusions

This prospective, multi-centre, international study did not find any significant associations between Marshall CT grade (a measure of brain injury severity) and HADS-A, HADS-D or PCL-5 scores 12-months after moderate-severe TBI. It also found no significant associations between these psychiatric outcomes and gender, employment status at the time of injury, mechanism of injury (accidental vs. assault), LOC, PTA, or GCS. Future research could build on this study by replicating it in larger, more diverse TBI patient populations. The relationship between diffuse axonal injury could be examined further by combining Marshall CT grades with other CT scan abnormalities. Further research could also explore the prognostic value of finer structural, functional and connectivity changes after TBI obtained using more sensitive neuroimaging techniques (e.g., MRI, functional MRI, or diffusion tensor imaging). This will help to develop a more comprehensive understanding of the biopsychosocial factors associated with psychiatric outcome after TBI. In turn, this could aid the early

prevention, identification and treatment of mental health disorders after TBI, improving the quality of life of TBI survivors.

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Part 3: Critical appraisal

1. Introduction

This critical appraisal reflects on my experience of conducting the research included in this thesis. I will discuss my prior theoretical orientation and experiences, and how the process of conducting this research has changed my perspectives. A more in-depth discussion of the challenges faced, and the generalisability and implications of the findings is also presented.

2. Prior experiences and theoretical orientation

I was drawn to conducting research in the field of traumatic brain injury (TBI) due to my interest in the interface between physical and mental health. During my studies I became particularly interested in TBI and determinants of outcome after TBI. Through further reading, it became apparent that predictors of psychiatric outcome after TBI have still not been well-characterised. I therefore decided to make this the focus of my thesis.

I was keen to take-up the opportunity to analyse data from the BIO-AX-TBI study – a relatively-large, high-quality prospective cohort study. I was motivated to develop my quantitative analysis skills, and knew that it would not be possible to collect this volume of high-quality data myself within the scope of this thesis. I was also keen to gain experience of conducting systematic reviews and meta-analyses, understanding these to be rigorous and relatively objective methods representing the highest level of evidence available.

3. Learning from conducting the systematic review and meta-analysis

3.1. Subjectivity in systematic reviews and meta-analyses

Upon starting to design the protocol for my systematic review and meta-analysis, it quickly became apparent that subjectivity is involved at every stage – from formulating the research question, to deciding inclusion and exclusion criteria, choosing sources to search, evaluating risk of bias (even when structured tools are used), and interpreting and discussing results. Indeed, research shows that interpreting data from systematic reviews and meta-analyses is

a highly subjective process, even when reviewers have extensive experience (Shrier et al., 2008). Factors influencing these subjective decisions can include: knowledge, personal values and preferences, and resistance to change (Shrier et al., 2008). This highlighted to me the importance of transparency about decision-making, and about the review's strengths and limitations so that the findings can be interpreted in context.

Efforts were made to reduce subjectivity in the review by specifying a clear protocol a priori, and using recommended tools for data extraction and risk of bias assessments (the CHARMS checklist (Moons et al., 2014) and QUIPs tool (Hayden, van der Windt, Cartwright, Côté, & Bombardier, 2013), respectively). However, flexibility is still sometimes needed. For example, in this review, the inclusion criteria were adjusted part-way through the study selection process to further limit the scope. This decision was made due to too many papers meeting the eligibility criteria being returned by the search; it would not have been practically feasible to include all of them. This decision to narrow the scope was clearly documented in the write-up, and the rationale explained.

In the write-up, it was also acknowledged that whilst it was not possible within the timeframe, enlisting a second independent reviewer to also complete the study selection, data extraction and risk of bias assessment processes could have increased the accuracy of these procedures. Inter-reviewer reliability could then be calculated, and any discrepancies resolved through consensus and involvement of a third party where necessary (Cochrane, 2002). This would have helped to further reduce subjectivity in these steps.

3.2. The comprehensiveness is limited by the evidence available

The comprehensiveness of systematic reviews and meta-analyses is limited by the evidence available. Efforts were made to maximise the completeness of this meta-analytic review. These included: searching multiple databases, grey literature, and reference lists and citations of relevant papers. Authors were also contacted to request missing data where needed. However, despite this, the data included will still have been influenced by biases

such as publication bias, selective outcome reporting, and inappropriate statistical manipulations (e.g., “p-hacking”) (Cochrane, 2002; Greco, Zangrillo, Biondi-Zoccai, & Landoni, 2013; Head, Holman, Lanfear, Kahn, & Jennions, 2015). These biases skew published findings towards significant results, resulting in systematic reviews and meta-analyses that are also skewed towards significant findings.

These biases are reinforced by pressures at different levels of the system. For example – academia has a “publish or perish” culture (Rawat & Meena, 2014). The reputations of researchers and institutions are dependent upon their publication records. To secure funding, they must publish frequently and in high-impact journals. Top tier journals tend to favour novel, positive findings (Grimes, Bauch, & Ioannidis, 2018). This creates pressure across the system to publish significant results, resulting in significant results being disproportionately represented in the literature. This can create bias in the results of systematic reviews and meta-analyses towards significant findings. It was not possible to use funnel plots to explore the risk of this bias in the current review, due to insufficient numbers of studies in the meta-analyses (Cochrane, 2002). However, an additional action that could have been taken to reduce the risk of publication bias could have been to contact prominent researchers to enquire about any unpublished data they have access to.

3.3. The quality of included studies limits the validity of the findings

Conclusions of systematic reviews and meta-analyses are also limited by the quality of the studies included. Assessing the risk of bias in the current review’s included studies highlighted common methodological shortcomings, including: high attrition rates; lack of reporting of reasons for drop-out or differences in key characteristics between drop-outs and retained participants; lack of blinding; and problems with statistical analyses (e.g., underpowered analyses, failures to correct for multiple comparisons, and inadequate reporting of multivariate model performance). Such limitations are not specific to the field of TBI. For example, research suggests that the majority of studies in psychology are under-

powered (Maxwell, 2004). Conducting systematic reviews helps to highlight these limitations, enabling recommendations to be made to improve the quality of future research.

4. Challenges encountered in the empirical paper

4.1. Lack of influence over study design

Early on in the process of conducting the empirical research project, some of the challenges inherent in conducting secondary analyses become apparent. One such challenge is the inability to influence the study design. Since the data has already been collected, all that can be done is to make the most of what is available. This can introduce some limitations to the study. For example, in the BIO-AX-TBI study, certain potential confounders of associations between predictors and psychiatric outcomes were not measured (e.g., prior psychiatric history, substance use on admission, early post-injury symptoms). Therefore, these variables could not be controlled for in multivariate analyses and so they may have still confounded the results. Likewise, self-reported psychiatric outcomes were only assessed at one time point (12 months post-TBI). It was therefore not possible to draw conclusions about associations between predictors and psychiatric outcomes at other time points. To investigate these associations longitudinally, psychiatric outcomes would need to be measured at multiple time-points (e.g., 3 months, 6 months, 9 months, 18 months, 2 years+ after TBI). An advantage of using self-report measures is that they make this more feasible, given that they are quick and inexpensive to administer (Hjollund, 2009).

4.2. Handling missing data

The majority of papers included in the meta-analytic review dealt with missing data by excluding it from analyses (using either pairwise or listwise deletion). However, this has been criticised since it is inefficient, reduces statistical power and can introduce attrition bias if there are systematic differences between retained participants and drop-outs (Nunan,

Aronson, & Bankhead, 2018). A loss to follow-up of 5% or more can raise concerns about attrition bias (Schulz & Grimes, 2002). Studies can take several steps to mitigate this. For example, they can make every effort to reduce attrition and can over-recruit beyond the minimum number of participants needed (Hindmarch et al., 2015). Given that it was not possible for me to influence the BIO-AX-TBI study design, I accounted for missing data in the empirical study by using multiple imputation methods instead.

There are many different possible ways of imputing missing data. Single imputation techniques (e.g., mean imputation or regression imputation) account for missing data by imputing a single value for each missing value (Lodder, 2013). The disadvantage of single imputation techniques is that they do not capture the uncertainty associated with the missing value, since they do not incorporate any error variance (J. W. Graham, 2009; Lodder, 2013). Multiple imputation, on the other hand, randomly draws multiple imputations from a distribution of imputations and incorporates additional error variance for each imputation (Lodder, 2013). This results in the production of multiple imputed datasets, which can then each be analysed and the results pooled (Lodder, 2013; Rubin, 1976). Multiple imputation is a powerful, widely-used and extensively studied technique (Lodder, 2013). It was therefore utilised in the empirical paper. Sensitivity analyses were also conducted to explore the robustness of the results to imputation. This involved conducting the multiple regression analyses on the original dataset only (with pairwise exclusion of missing data) as well as on the multiply imputed datasets. The significance of the results from these analyses did not differ, indicating that the results were robust to imputation.

4.3. Challenges in statistical analysis

Though a relatively large dataset for a prospective cohort study in the field of psychology, the size of the BIO-AX-TBI study was still relatively small compared to other “big data” sources (e.g., data from national registers). Sample size limits statistical power, and so restricts the statistical analyses that can be performed. For example, it limits the number of

predictor variables that can be included in multivariate analyses before statistical overfitting occurs, where the statistical model starts to describe the random error in the data rather than the relationships between variables (Moons et al., 2015; Pavlou et al., 2015). Overfitting reduces the generalisability of the model, and can lead to misleading p-values, regression coefficients and goodness-of-fit statistics (e.g., R^2 or adjusted-R^2) (Frost, 2017).

The review highlighted that in some studies, too many predictors were incorporated into multivariate analyses relative to the number of overall cases or events. This places those models at risk of overfitting. To avoid this in the empirical paper, the 10:1 rule was adhered to. The 10:1 rule is a rule of thumb for how many predictor parameters can be estimated from the data to reduce the risk of overfitting (Tabachnick & Fidell, 2001). However, a disadvantage of this is that it limits the number of confounding variables that can be controlled for. Whilst those selected for inclusion were based on theory and existing evidence, not all potential confounders could be included due to the limited sample size.

Predictors/confounders were also dichotomised to adhere to the 10:1 rule. This reduces the information provided about the associations between that predictor and the psychiatric outcomes, compared to including multiple levels of categorical predictors. For example, race was dichotomised into Caucasian versus non-Caucasian race. However, had the sample size been larger, it would have been more informative to include more diverse categories describing race. Future research should aim to do this. It could also investigate interactions between predictors (e.g., sex, race, age, level of education) to explore how intersections between these various aspects of identity influence psychiatric outcomes after TBI.

Statistical power in the empirical study was reduced by fact that corrections needed to be made for multiple statistical comparisons. It is recommended that corrections are made for multiple testing when it is important to avoid a type I (false positive) error, as was the case for the multivariate analyses in the empirical study (Armstrong, 2014). Therefore, a Bonferroni correction was applied, which provides more conservative probability thresholds for statistical tests, and so reduces the risk of type I errors (Linehan, Tutek, Heard, &

Armstrong, 1994). The systematic review highlighted that most studies in this area fail to make corrections for multiple comparisons, which can lead to misleading false positive results.

The systematic review also revealed that most papers presenting multivariate models did not report any goodness-of-fit measures (e.g., R^2 or adjusted R^2) or measures of model performance (e.g., calibration measures, discrimination measures or classification measures). Internal or external validation was also not performed for any of the models. This may be due to often relatively small sample sizes, or the aims of analyses being more exploratory than predictive. However, it does make it more difficult to draw conclusions about the likely clinical utility of the models. Future research should report these measures where possible. In the empirical paper, R^2 and adjusted-R^2 was reported for each of the multivariate models. However, model performance was not evaluated due to the limited sample size and the fact that none of the models or regression coefficients were significant.

5. Implications for future research, clinical practice and policy-making

5.1. Implications for clinical practice and policy

This research has focused on identifying predictors of self-reported psychiatric symptoms after TBI. Identifying predictors could enable them to be screened for in clinical practice. This would help to identify TBI patients at risk of adverse mental health outcomes, enabling interventions to prevent and treat psychiatric disorders to be targeted where needed.

Identifying predictors of post-TBI mental health disorders could also inform wider-scale actions to reduce risk. For example, the meta-analyses showed that number of years of education was significantly associated with reduced risk of PTSD after TBI. If the robustness of this predictor is proven through further research, then wider-scale policies, initiatives and movements to increase access to education (e.g., by improving the quality of schools, investing in more support for vulnerable families, funding programmes to improve school attendance) could help to reduce the incidence of PTSD after TBI.

5.2. Implications for research

Though the meta-analyses identified potential promising predictors of self-reported PTSD after TBI, the limited number of studies available and high heterogeneity in some of the meta-analyses means that more research is needed to confirm their predictive utility. Future research could also investigate longitudinal changes in these associations, interactions between predictors, factors moderating associations, and the mechanisms underpinning them. Furthermore, it could investigate novel or promising under-researched predictors (e.g., longitudinal changes in brain functioning or connectivity measured with magnetic resonance imaging or diffusion tensor imaging).

This quantitative research could be complemented by qualitative research exploring the views of key stakeholders, such as TBI patients, family members, carers, clinicians, and policy-makers. Qualitative approaches could be used to investigate their perspectives on risk and protective factors for psychiatric disorders after TBI, the potential mechanisms underpinning these associations, and moderating factors. It could also explore their views on how to intervene effectively to prevent and treat mental health difficulties after TBI. This could help to inform clinical practice, policy-making and directions for future research. Such research would be valuable, especially given the relative lack of qualitative compared to quantitative research in these areas.

The BIO-AX-TBI study involved patients and research participants in the development of the study via regular participant involvement events (N. S. N. Graham et al., 2020). Extending this co-production, for example, by involving key stakeholders in data collection, analysis, and the interpretation and dissemination of results could help to further increase the quality of the research and its impact (UK Research and Innovation, 2022).

Most of the studies in the systematic review were conducted in the US or in European countries (as was the BIO-AX-TBI study). It is a widely acknowledged issue that published psychology research is largely conducted in Western, educated, industrialised, rich and democratic (WEIRD) nations (Henrich, Heine, & Norenzayan, 2010). It is therefore

unknown whether the findings of this research would translate to other countries, especially since there can be considerable between-country variation in population health and healthcare system operation (including how they are funded, their capacity, utilisation, access, and quality) (Papanicolas, Mossialos, Gundersen, Woskie, & Jha, 2019). Further research in more geographically diverse locations is needed to investigate this.

The inclusion and exclusion criteria of studies included in the review also limit the generalisability of the findings. For example, many of the studies excluded participants with: pre-TBI psychiatric histories, comorbid neurological disorders, previous TBI, people in custody, and pregnant people. The exclusion of such groups helps to control for these potentially confounding factors, thereby increasing internal validity. However, a disadvantage is that these groups are then excluded from research and so the findings may not be generalisable to them. This is concerning since these groups represent a substantial portion of people experiencing TBI. For example, Dams-O'Connor et al. (2013) found that 23% of individuals seeking emergency department care for a TBI reported previous TBI with loss of consciousness. Furthermore, most included studies recruited predominantly Caucasian, male participants. This means that the findings may not be generalisable to more diverse populations (e.g., females, people from black and minority ethnic groups, people with disabilities). These groups are already marginalised by society and experience inequalities in access to effective healthcare (Williams, Buck, & Babalola, 2020). Their continued exclusion and under-representation in research could further perpetuate these inequalities due to the fact that research informs future research, clinical practice, policy-making and commissioning of services. It is clear that more research is needed recruiting more demographically diverse samples.

Engaging with this research from a social constructionist perspective helps to reflect on the research in a self-reflexive way, facilitating critical consideration of the generalisability of the findings (and indeed, the generalisability of any research conducted in WEIRD nations) to other countries and communities. Social constructionism proposes that meanings are developed in coordination with others, rather than reflecting a physical reality (Littlejohn

& Foss, 2012). From the social constructionist perspective, even concepts such as 'mental health' can be viewed as socially-constructed and so existing within a particular cultural and socio-political context.

In Western healthcare systems, the approach to recovery is often very Eurocentric (Tuffour, Simpson, & Reynolds, 2019). Distress is conceptualised in terms of mental disorders, rooted in individual psychopathology and underpinned by a biomedical model, and treated with pharmacological or psychological interventions (Summerfield, 2001). However, conceptualisations of distress can vary between cultures and over time. They influence how people understand and experience distress, the meanings they attribute to it, how it is expressed, the types of support believed to be helpful and where that support is sought from (Summerfield, 2001). Caution therefore needs to be exercised in generalising findings and implications to other cultures and communities.

The global mental health movement has often been criticised for trying to impose Western models of mental illness cross-culturally in a top-down manner (Whitley, 2015). It is argued that it disregards the culturally-determined nature of mental illness, resulting in diagnoses that are inappropriate, solutions that are locally-incongruent, and traditional systems of mental health healing being marginalised (Cooper, 2016; Fernando, 2011; Summerfield, 2013). Instead, it has been suggested that a preferable approach would be to conduct research that takes a bottom-up ethnographic approach grounded in other communities in order to take into account local ecologies of suffering (Jadhav, Jain, Kannuri, Bayetti, & Barua, 2015).

6. Conclusions

Conducting this research has not been without its challenges. However, it has been an overall positive experience. It has provided me with an opportunity to develop skills in conducting systematic reviews, meta-analyses and quantitative analyses of complex datasets. I now have a more nuanced understanding of the strengths and limitations of these

approaches. Indeed, conducting this research has greatly enhanced my ability to critically appraise scientific literature – a fundamental skill in both clinical practice and research. Taking on a leading role throughout the research process has been valuable for both my personal and professional development, and it has been rewarding working on research that has potential implications for future research, clinical practice and policy-making. The findings represent another important step further towards improving prognostication in TBI, and so improving outcomes for TBI survivors.

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Appendix A: PTSD Checklist for DSM-IV – Civilian version (PCL-C)

PTSD CheckList – Civilian Version (PCL-C)

Client's Name: _____

Instruction to patient: Below is a list of problems and complaints that veterans sometimes have in response to stressful life experiences. Please read each one carefully, put an "X" in the box to indicate how much you have been bothered by that problem *in the last month*.

No.	Response	Not at all (1)	A little bit (2)	Moderately (3)	Quite a bit (4)	Extremely (5)
1.	Repeated, disturbing *memories, thoughts, or images* of a stressful experience from the past?					
2.	Repeated, disturbing *dreams* of a stressful experience from the past?					
3.	Suddenly *acting* or *feeling* as if a stressful experience *were happening* again (as if you were reliving it)?					
4.	Feeling *very upset* when *something reminded* you of a stressful experience from the past?					
5.	Having *physical reactions* (e.g., heart pounding, trouble breathing, or sweating) when *something reminded* you of a stressful experience from the past?					
6.	Avoid *thinking about* or *talking about* a stressful experience from the past or avoid *having feelings* related to it?					
7.	Avoid *activities* or *situations* because they *remind you* of a stressful experience from the past?					
8.	Trouble *remembering important parts* of a stressful experience from the past?					
9.	Loss of *interest in things that you used to enjoy?*					
10.	Feeling *distant* or *cut* off from other people?					
11.	Feeling *emotionally numb* or being unable to have loving feelings for those close to you?					
12.	Feeling as if your *future* will somehow be *cut short*?					
13.	Trouble *falling* or *staying asleep*?					
14.	Feeling *irritable* or having *angry outbursts*?					
15.	Having *difficulty concentrating*?					
16.	Being *"super alert"* or watchful on guard?					
17.	Feeling *jumpy* or easily startled?					

PCL-M for DSM-IV (11/1/94) Weathers, Litz, Huska, & Keane National Center for PTSD - Behavioral Science Division

Appendix B: PTSD Checklist for DSM-5 (DSM-5)

PCL-5

Instructions: Below is a list of problems that people sometimes have in response to a very stressful experience. Please read each problem carefully and then circle one of the numbers to the right to indicate how much you have been bothered by that problem in the past month.

In the past month, how much were you bothered by:	Not at all	A little bit	Moderately	Quite a bit	Extremely
1. Repeated, disturbing, and unwanted memories of the stressful experience?	0	1	2	3	4
2. Repeated, disturbing dreams of the stressful experience?	0	1	2	3	4
3. Suddenly feeling or acting as if the stressful experience were actually happening again (as if you were actually back there reliving it)?	0	1	2	3	4
4. Feeling very upset when something reminded you of the stressful experience?	0	1	2	3	4
5. Having strong physical reactions when something reminded you of the stressful experience (for example, heart pounding, trouble breathing, sweating)?	0	1	2	3	4
6. Avoiding memories, thoughts, or feelings related to the stressful experience?	0	1	2	3	4
7. Avoiding external reminders of the stressful experience (for example, people, places, conversations, activities, objects, or situations)?	0	1	2	3	4
8. Trouble remembering important parts of the stressful experience?	0	1	2	3	4
9. Having strong negative beliefs about yourself, other people, or the world (for example, having thoughts such as: I am bad, there is something seriously wrong with me, no one can be trusted, the world is completely dangerous)?	0	1	2	3	4
10. Blaming yourself or someone else for the stressful experience or what happened after it?	0	1	2	3	4
11. Having strong negative feelings such as fear, horror, anger, guilt, or shame?	0	1	2	3	4
12. Loss of interest in activities that you used to enjoy?	0	1	2	3	4
13. Feeling distant or cut off from other people?	0	1	2	3	4
14. Trouble experiencing positive feelings (for example, being unable to feel happiness or have loving feelings for people close to you)?	0	1	2	3	4
15. Irritable behavior, angry outbursts, or acting aggressively?	0	1	2	3	4
16. Taking too many risks or doing things that could cause you harm?	0	1	2	3	4
17. Being "superalert" or watchful or on guard?	0	1	2	3	4
18. Feeling jumpy or easily startled?	0	1	2	3	4
19. Having difficulty concentrating?	0	1	2	3	4
20. Trouble falling or staying asleep?	0	1	2	3	4

Appendix C: Systematic review search strategy

Embase

1. exp head injury/

2. exp concussion/

3. exp 'brain injury assessment'/

4. exp Coma/

5. concus*.ti,ab,kw.

6. contus*.ti,ab,kw.

7. neurotraum*.ti,ab,kw.

8. tbi.ti,ab,kw.

9. mtbi.ti,ab,kw.

10. coma*.ti,ab,kw.

11. ((brain or head or crani* or intracrani* or skull* or cerebr* or capitis or hemisphere*) adj3 (injur* or trauma* or posttrauma* or post-trauma* or damag* or lesion* or fracture*)).ti,ab,kw.

12. or/1-11

13. exp injury/

14. exp 'posttraumatic stress disorder'/

15. exp accident/

16. exp emergency/

17. exp Emergency care/

18. exp emergency ward/

19. exp Violence/

20. trauma*.ti,ab,kw.

21. posttrauma*.ti,ab,kw.

22. post-trauma*.ti,ab,kw.

23. injur*.ti,ab,kw.

24. tbi.ti,ab,kw.

25. mtbi.ti,ab,kw.

26. accident*.ti,ab,kw.

27. emergen*.ti,ab,kw.

28. violen*.ti,ab,kw.

29. or/13-28

30. exp Anxiety/

31. exp Anxiety Disorder/

32. anxi*.ti,ab,kw.

33. phobi*.ti,ab,kw.

34. agoraphobi*.ti,ab,kw.

35. panic.ti,ab,kw.

36. ocd.ti,ab,kw.

37. gad.ti,ab,kw.

38. (obsessi* adj3 compulsi*).ti,ab,kw.

39. ptsd.ti,ab,kw.

40. ((posttraumatic or post-traumatic or postconcussion* or post-concussion* or post-concussional or postconcussional) adj3 (stress* or syndrom*)).ti,ab,kw.

41. ((psychologic* or psychology or neuropsychologic* or psychiatr* or emotion*) adj3 (outcome* or develop* or well-being or wellbeing or disabil* or progres* or adjust* or function* or consequenc* or sequel* or symptom*)).ti,ab,kw.

42. exp 'anxiety assessment'/

43. HADS.ti,ab,kw.

44. HADS-A.ti,ab,kw.

45. STAI.ti,ab,kw.

46. BAI.ti,ab,kw.

47. GAD-7.ti,ab,kw.

48. GAD-2.ti,ab,kw.

49. GAD2.ti,ab,kw.

50. GAD7.ti,ab,kw.

51. PAS.ti,ab,kw.

52. PDSS-SR.ti,ab,kw.

53. PDSS.ti,ab,kw.

54. "PSS-SR".ti,ab,kw.

55. SPIN.ti,ab,kw.

56. TSQ.ti,ab,kw.

57. "Trauma Screening Questionnaire".ti,ab,kw.

58. Y-BOCS.ti,ab,kw.

59. SAS.ti,ab,kw.

60. LSAS.ti,ab,kw.

61. OASIS.ti,ab,kw.

62. PHQ-4.ti,ab,kw.

63. PHQ4.ti,ab,kw.

64. "Patient Health Questionnaire-4".ti,ab,kw.

65. "Patient Health Questionnaire 4".ti,ab,kw.

66. PSWQ.ti,ab,kw.

67. "Penn State Worry Questionnaire".ti,ab,kw.

68. (feel* adj3 (apprehens* or dread* or disaster* or worr* or fear* or terror*)).ti,ab,kw.

69. (anxi* adj3 (scale* or measure* or outcome* or questionnaire*)).ti,ab,kw.

70. or/30-69

71. exp Prevalence/

72. exp Incidence/

73. Prognosis/

74. exp 'prediction/ and forecasting'/

75. Epidemiology/

76. exp Risk Factor/

77. etiology/

78. Incidenc*.ti,ab,kw.

79. prevalen*.ti,ab,kw.

80. predict*.ti,ab,kw.

81. prognos*.ti,ab,kw.

82. (risk adj3 factor*).ti,ab,kw.

83. epidemiolog*.ti,ab,kw.

84. ((indicator* or variable* or characteristic* or examination* or assessment* or measure* or association* or determinant*) adj3 (psycholog* or psychiatr*)).ti,ab,kw.

85. or/71-84

86. 12 and 29 and 70 and 85

87. limit 86 to english language

88. exp animals/ not humans/

89. 87 not 88

Medline

1. exp Craniocerebral Trauma/

2. exp Brain Injuries, Traumatic/

3. Glasgow Coma Scale/

4. Coma/

5. concus*.ti,ab,kw.

6. contus*.ti,ab,kw.

7. neurotraum*.ti,ab,kw.

8. tbi.ti,ab,kw.

9. mtbi.ti,ab,kw.

10. coma*.ti,ab,kw.

11. ((brain or head or crani* or intracrani* or skull* or cerebr* or capitis or hemisphere*) adj3 (injur* or trauma* or posttrauma* or post-trauma* or damag* or lesion* or fracture*)).ti,ab,kw.

12. or/1-11

13. exp "Wounds and Injuries"/

14. exp Stress Disorders, Traumatic/

15. exp Accidents/

16. exp Emergencies/

17. exp Emergency Treatment/

18. exp Emergency Service, Hospital/

19. exp Violence/

20. trauma*.ti,ab,kw.

21. posttrauma*.ti,ab,kw.

22. post-trauma*.ti,ab,kw.

23. injur*.ti,ab,kw.

24. tbi.ti,ab,kw.

25. mtbi.ti,ab,kw.

26. accident*.ti,ab,kw.

27. emergen*.ti,ab,kw.

28. violen*.ti,ab,kw.

29. or/13-28

30. exp Anxiety/

31. exp Anxiety Disorders/

32. Stress Disorders, Post-Traumatic/

33. anxi*.ti,ab,kw.

34. phobi*.ti,ab,kw.

35. agoraphobi*.ti,ab,kw.

36. panic.ti,ab,kw.

37. ocd.ti,ab,kw.

38. gad.ti,ab,kw.

39. (obsessi* adj3 compulsi*).ti,ab,kw.

40. ptsd.ti,ab,kw.

41. ((posttraumatic or post-traumatic or postconcussion* or post-concussion* or post-concussional or postconcussional) adj3 (stress* or syndrom*)).ti,ab,kw.

42. ((psychologic* or psychology or neuropsychologic* or psychiatr* or emotion*) adj3 (outcome* or develop* or well-being or wellbeing or disabil* or progres* or adjust* or function* or consequenc* or sequel* or symptom*)).ti,ab,kw.

43. Psychiatric status rating scales/

44. exp Manifest Anxiety Scale/

45. HADS.ti,ab,kw.

46. HADS-A.ti,ab,kw.

47. STAI.ti,ab,kw.

48. BAI.ti,ab,kw.

49. GAD-7.ti,ab,kw.

50. GAD-2.ti,ab,kw.

51. GAD2.ti,ab,kw.

52. GAD7.ti,ab,kw.

53. PAS.ti,ab,kw.

54. PDSS-SR.ti,ab,kw.

55. PDSS.ti,ab,kw.

56. "PSS-SR".ti,ab,kw.

57. SPIN.ti,ab,kw.

58. TSQ.ti,ab,kw.

59. "Trauma Screening Questionnaire".ti,ab,kw.

60. Y-BOCS.ti,ab,kw.

61. SAS.ti,ab,kw.

62. LSAS.ti,ab,kw.

63. OASIS.ti,ab,kw.

64. PHQ-4.ti,ab,kw.

65. PHQ4.ti,ab,kw.

66. "Patient Health Questionnaire-4".ti,ab,kw.

67. "Patient Health Questionnaire 4".ti,ab,kw.

68. PSWQ.ti,ab,kw.

69. "Penn State Worry Questionnaire".ti,ab,kw.

70. (feel* adj3 (apprehens* or dread* or disaster* or worr* or fear* or terror*)).ti,ab,kw.

71. (anxi* adj3 (scale* or measure* or outcome* or questionnaire*)).ti,ab,kw.

72. or/30-71

73. exp Prevalence/

74. exp Incidence/

75. Prognosis/

76. Epidemiology/

77. exp Risk Factors/

78. exp Anxiety/et or exp Anxiety Disorders/et

79. Incidenc*.ti,ab,kw.

80. prevalen*.ti,ab,kw.

81. predict*.ti,ab,kw.

82. prognos*.ti,ab,kw.

83. (risk adj3 factor*).ti,ab,kw.

84. etiolog*.ti,ab,kw.

85. epidemiolog*.ti,ab,kw.

86. ((indicator* or variable* or characteristic* or examination* or assessment* or measure* or association* or determinant*) adj3 (psycholog* or psychiatr*)).ti,ab,kw.

87. or/73-86

88. 12 and 29 and 72 and 87

89. limit 88 to english language

90. exp animals/ not humans/ [papers about just animals]

91. 89 not 90

PsycInfo

1. exp 'head injuries'/

2. exp 'brain damage'/

3. exp 'brain injuries'/

4. exp Coma/

5. concus*.ti,ab.

6. contus*.ti,ab.

7. neurotraum*.ti,ab.

8. tbi.ti,ab.

9. mtbi.ti,ab.

10. coma*.ti,ab.

11. ((brain or head or crani* or intracrani* or skull* or cerebr* or capitis or hemisphere*) adj3 (injur* or trauma* or posttrauma* or post-trauma* or damag* or lesion* or fracture*)).ti,ab.

12. or/1-11

13. exp 'traumatic brain injury'/

14. exp 'posttraumatic stress disorder'/

15. exp trauma/

16. exp violence/

17. exp accidents/

18. exp 'emergency medicine'/

19. trauma*.ti,ab.

20. posttrauma*.ti,ab.

21. post-trauma*.ti,ab.

22. injur*.ti,ab.

23. tbi.ti,ab.

24. mtbi.ti,ab.

25. accident*.ti,ab.

26. emergen*.ti,ab.

27. violen*.ti,ab.

28. or/13-27

29. exp Anxiety/

30. exp Anxiety Disorders/

31. Stress Disorders, Post-Traumatic/

32. anxi*.ti,ab.

33. phobi*.ti,ab.

34. agoraphobi*.ti,ab.

35. panic.ti,ab.

36. ocd.ti,ab.

37. gad.ti,ab.

38. (obsessi* adj3 compulsi*).ti,ab.

39. ptsd.ti,ab.

40. ((posttraumatic or post-traumatic or postconcussion* or post-concussion* or post-concussional or postconcussional) adj3 (stress* or syndrom*)).ti,ab.

41. ((psychologic* or psychology or neuropsychologic* or psychiatr* or emotion*) adj3 (outcome* or develop* or well-being or wellbeing or disabil* or progres* or adjust* or function* or consequenc* or sequel* or symptom*)).ti,ab.

42. exp psychiatric symptoms/

43. HADS.ti,ab.

44. HADS-A.ti,ab.

45. STAI.ti,ab.

46. BAI.ti,ab.

47. GAD-7.ti,ab.

48. GAD-2.ti,ab.

49. GAD2.ti,ab.

50. GAD7.ti,ab.

51. PAS.ti,ab.

52. PDSS-SR.ti,ab.

53. PDSS.ti,ab.

54. "PSS-SR".ti,ab.

55. SPIN.ti,ab.

56. TSQ.ti,ab.

57. "Trauma Screening Questionnaire".ti,ab.

58. Y-BOCS.ti,ab.

59. SAS.ti,ab.

60. LSAS.ti,ab.

61. OASIS.ti,ab.

62. PHQ-4.ti,ab.

63. PHQ4.ti,ab.

64. "Patient Health Questionnaire-4".ti,ab.

65. "Patient Health Questionnaire 4".ti,ab.

66. PSWQ.ti,ab.

67. "Penn State Worry Questionnaire".ti,ab.

68. (feel* adj3 (apprehens* or dread* or disaster* or worr* or fear* or terror*)).ti,ab.

69. (anxi* adj3 (scale* or measure* or outcome* or questionnaire*)).ti,ab.

70. or/29-69

71. Prognosis/

72. exp Epidemiology/

73. exp etiology/

74. exp Risk Factors/

75. Incidenc*.ti,ab.

76. prevalen*.ti,ab.

77. predict*.ti,ab.

78. prognos*.ti,ab.

79. (risk adj3 factor*).ti,ab.

80. etiolog*.ti,ab.

81. epidemiolog*.ti,ab.

82. ((indicator* or variable* or characteristic* or examination* or assessment* or measure* or association* or determinant*) adj3 (psycholog* or psychiatr*)).ti,ab.

83. or/71-82

84. 12 and 28 and 70 and 83

85. limit 84 to english language

86. exp animals/ not humans/ [papers about just animals]

87. 85 not 86

Web of Science

Query link: https://www.webofscience.com/wos/woscc/summary/39c1d83e-14b5-42e9-801f-b6a6cb046e3c-041f8dbc/relevance/1

(((TS=(concus* OR contus* OR neurotraum* or tbi or mtbi or coma* or ((brain or head or crani* or intracrani* or skull* or cerebr* or capitis or hemisphere*) NEAR/3 (injur* or trauma* or posttrauma* or post-trauma* or damag* or lesion* or fracture*)))) AND TS=(trauma* or posttrauma* or post-trauma* or injur* or tbi or mtbi or accident* or emergen* or violen*)) AND TS=(anxi* or phobi* or agoraphobi* or panic or ocd or gad or (obsessi* NEAR/3 compulsi*) or ptsd or ((posttraumatic or post-traumatic or postconcussion* or post-concussion* or post-concussional or postconcussional) NEAR/3 (stress* or syndrom*)) or ((psychologic* or psychology or neuropsychologic* or psychiatr* or emotion*) NEAR/3 (outcome* or develop* or well-being or wellbeing or disabil* or progres* or adjust* or function* or consequenc* or sequel* or symptom*)) or HADS or HADS-A OR STAI OR BAI or GAD-7 OR GAD7 OR GAD-2 OR GAD2 OR PAS OR PDSS-SR OR PDSS OR PSS-SR OR SPIN OR TSQ OR Y-BOCS OR SAS OR LSAS OR OASIS OR PHQ-4 OR PHQ4 OR "Patient Health Questionnaire 4" OR "Patient Health Questionnaire-4" OR PSWQ OR "Penn State Worry Questionnaire" OR (feel* NEAR/3 (apprehens* or dread* or disaster* or worr* or fear* or terror*)) OR (anxi* NEAR/3 (scale* or measure* or outcome* or questionnaire*)))) AND TS=(incidenc* OR prevalen* OR predict* OR prognos* OR (risk NEAR/3 factor*) OR etiolog* OR epidemiolog* OR ((indicator* or variable* or characteristic* or examination* or assessment* or measure* or association* or determinant*) NEAR/3 (psycholog* or psychiatr*)))

Cochrane library

#48 GAD-7:ti,ab,kw 938

#49 GAD7:ti,ab,kw 101

#50 GAD-2:ti,ab,kw 34

#51 GAD2:ti,ab,kw 3

#52 PAS:ti,ab,kw 1404

#53 PDSS-SR:ti,ab,kw 24

#54 PDSS:ti,ab,kw 236

#55 PSS-SR:ti,ab,kw 17

#56 SPIN:ti,ab,kw 1191

#57 TSQ:ti,ab,kw 53

#58 "Trauma Screening Questionnaire":ti,ab,kw 6

#59 Y-BOCS:ti,ab,kw 421

#60 SAS:ti,ab,kw 3463

#61 LSAS:ti,ab,kw 170

#62 OASIS:ti,ab,kw 318

#63 PHQ-4:ti,ab,kw 80

#64 PHQ4:ti,ab,kw 3

#65 "Patient Health Questionnaire-4":ti,ab,kw 32

#66 "Patient Health Questionnaire 4":ti,ab,kw 32

#67 PSWQ:ti,ab,kw 133

#68 "Penn State Worry Questionnaire":ti,ab,kw 203

#69 MeSH descriptor: [Prevalence] explode all trees 4714

#70 MeSH descriptor: [Incidence] explode all trees 10313

#71 MeSH descriptor: [Prognosis] explode all trees 160150

#72 MeSH descriptor: [Epidemiology] explode all trees 41

#73 MeSH descriptor: [Risk Factors] explode all trees 25154

#74 incidenc*:ti,ab,kw 125560

#75 prevalen*:ti,ab,kw 47203

#76 predict*:ti,ab,kw 101916

#77 prognos*:ti,ab,kw 46228

#78 (risk NEAR/3 factor*):ti,ab,kw 71069

#79 etiolog*:ti,ab,kw 89104

#80 epidemiolog*:ti,ab,kw 61438

#81 ((indicator* or variable* or characteristic* or examination* or assessment* or measure* or association* or determinant*) NEAR/3 psycholog* or psychiatr*):ti,ab,kw 36409

#82 #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 OR #78 or #79 OR #80 or #81 517664

#83 MeSH descriptor: [Brain Injuries] explode all trees 2479

#84 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #83 17322

#85 MeSH descriptor: [Mental Health] explode all trees 1682

#86 #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 Or #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 or #85 90651

#87 #27 and #82 and #84 and #86 592

Google scholar

“brain|head|cranial|cerebral injury|injuries|trauma|damage|lesion|fracture”|concussion|coma|contusion|tbi|mtbi

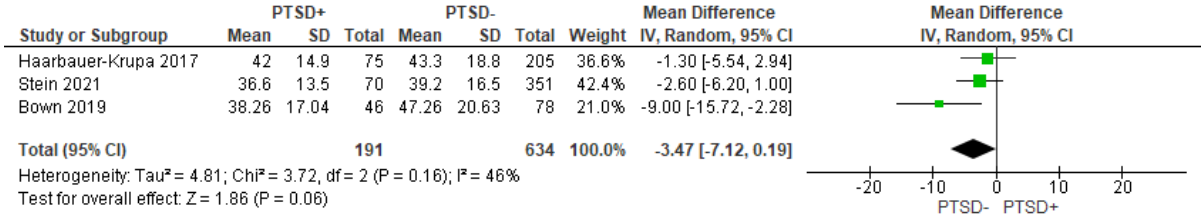
trauma|traumatic|posttraumatic|post-traumatic|injury|accident|tbi|mtbi|emergency

anxiety|”mental health”|psychological|ocd|”obsessive compulsive”|agoraphobia|phobia|panic|worry|ptsd|post-traumatic|posttraumatic|gad

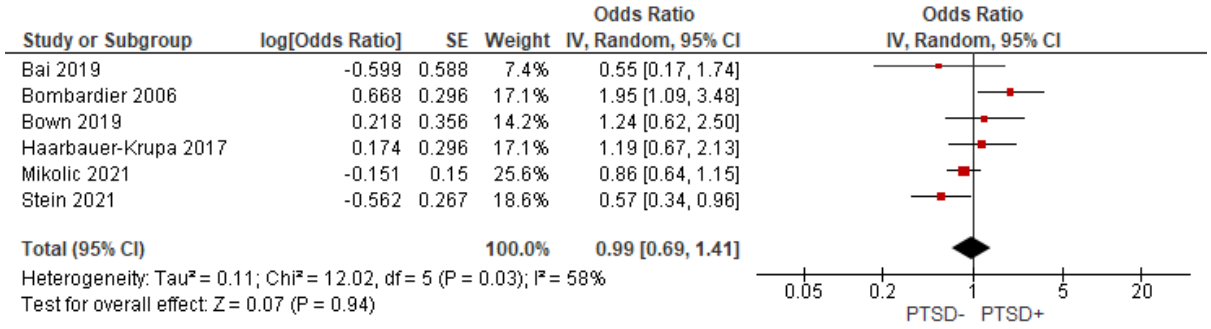
prevalence|incidence|epidemiology|”risk factor”|prognosis|predictor

Appendix D: Forest plots of meta-analyses of univariable predictors of self-reported post-traumatic stress disorder after traumatic brain injury

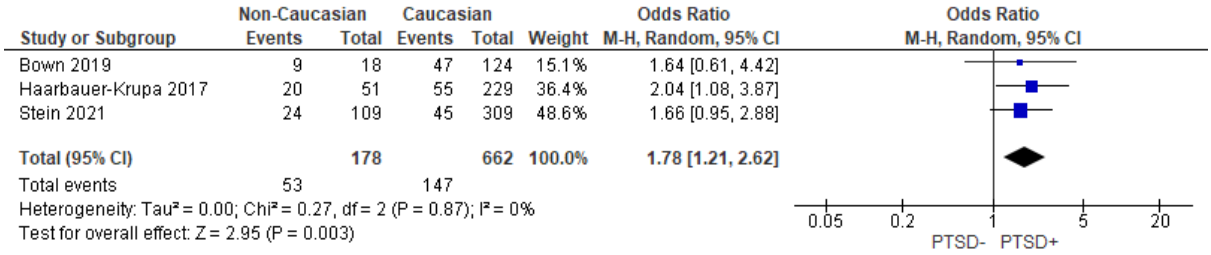
1. Age (years; continuous)



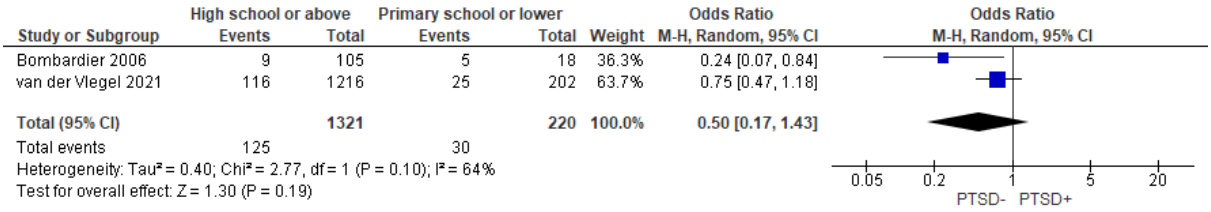
2. Male gender (ref: female)



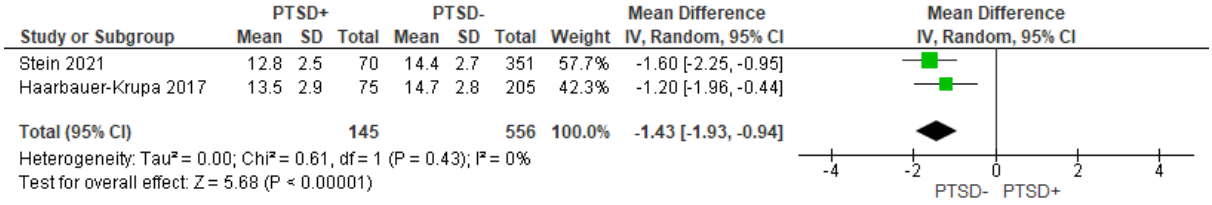
3. Non-Caucasian race (ref: Caucasian race)



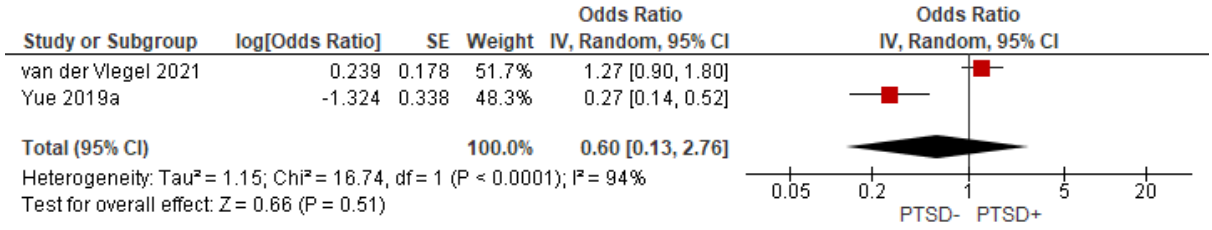
4. High school or above level of education (ref: primary school or lower)



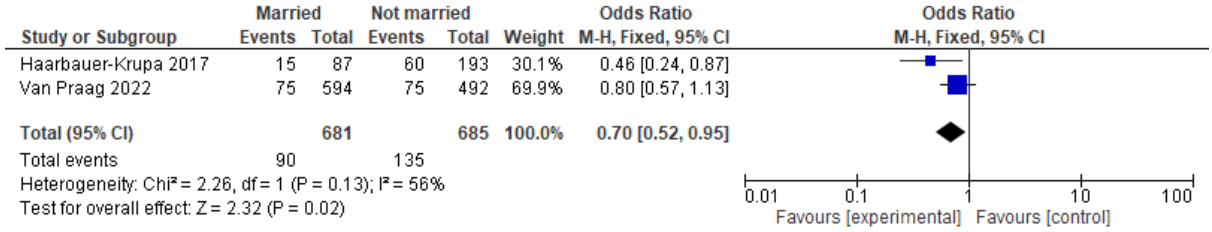
5. Years of education (continuous)



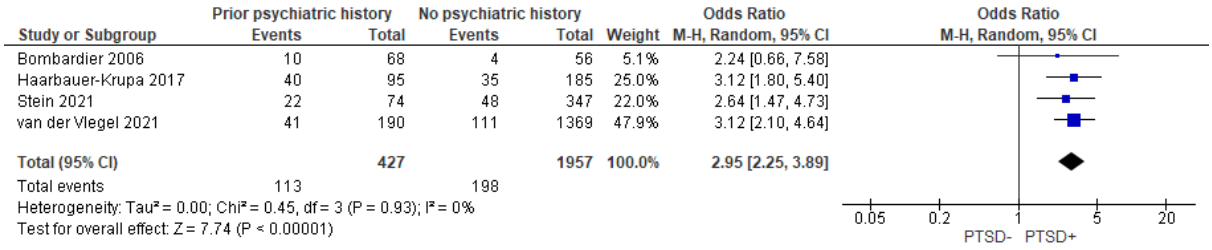
6. Employed at the time of injury (ref: unemployed at the time of injury)



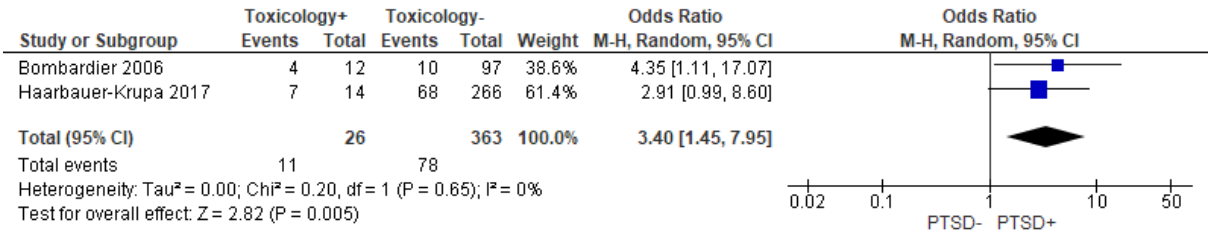
7. Married marital status (ref: not married)



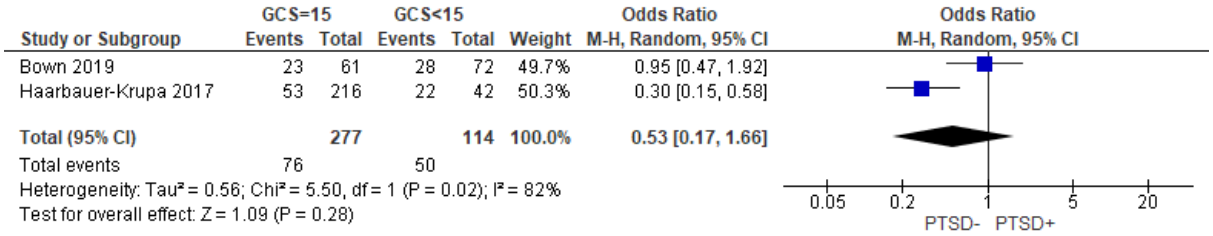
8. Pre-TBI psychiatric history (ref: none)



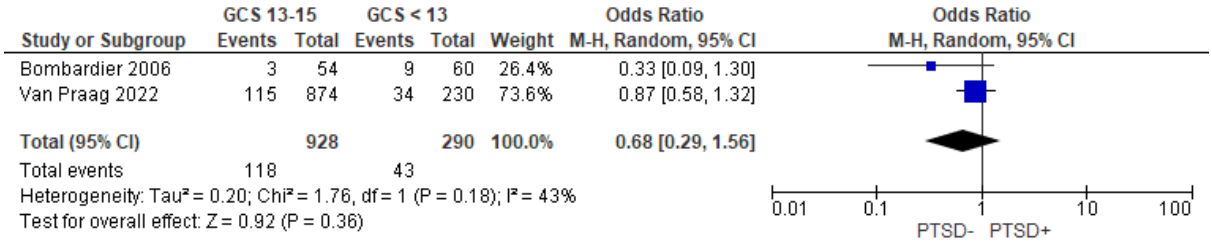
9. Positive toxicology screen on admission (ref: negative toxicology screen)



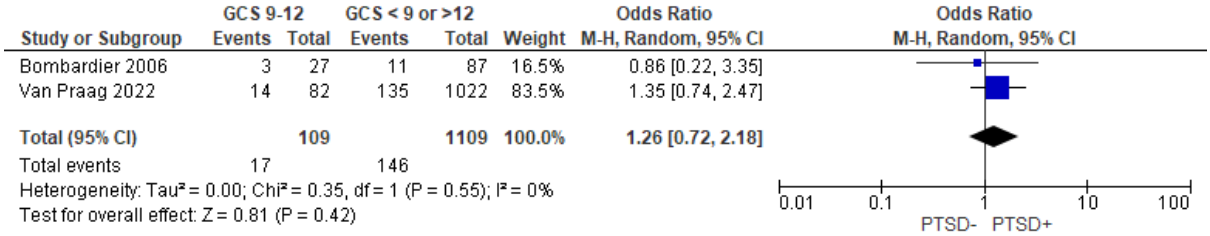
10. GCS score = 15 (ref: GCS score < 15)



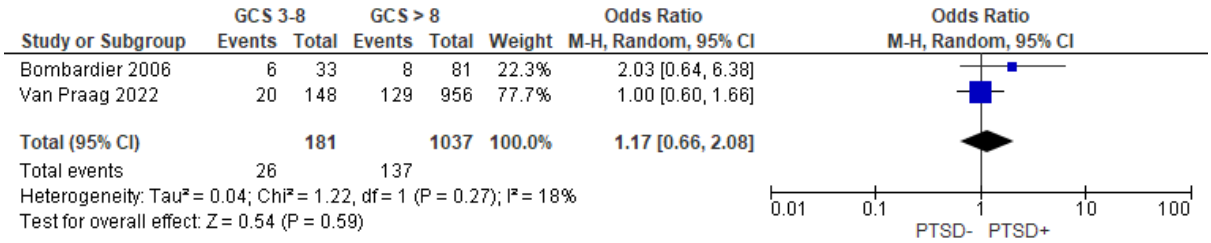
11. GCS score 13-15 (ref: GCS score < 13)



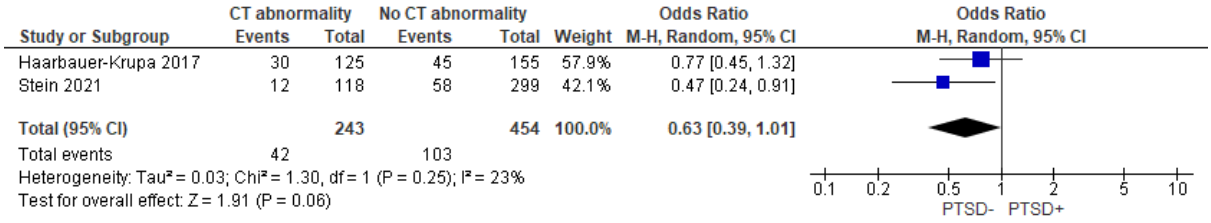
12. GCS score 9-12 (ref: GCS score < 9 or > 12)



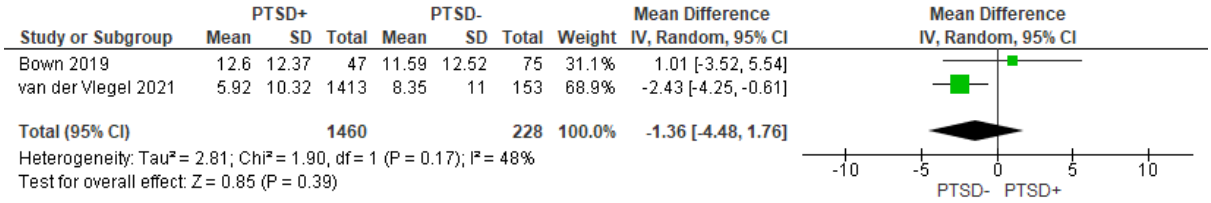
13. GCS score < 9 (ref: GCS score > 8)



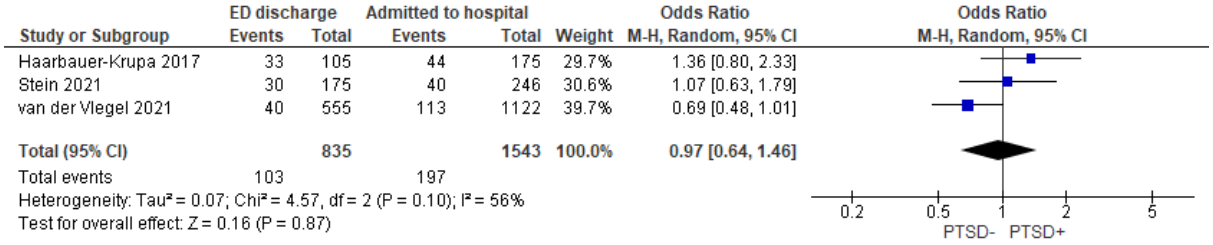
14. CT scan abnormality (ref: no CT scan abnormality)



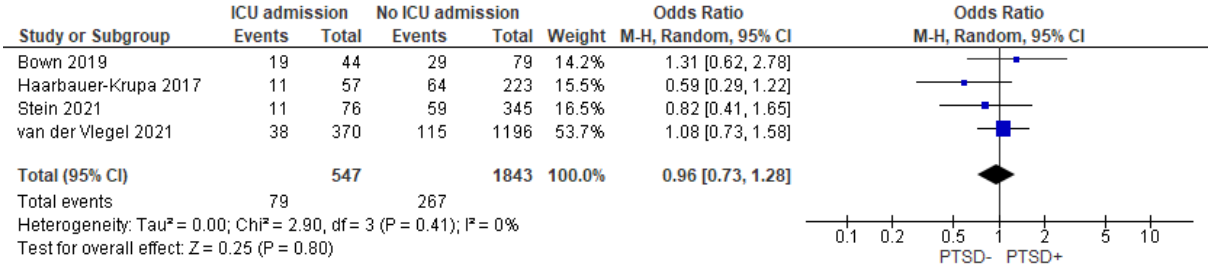
15. Hospital admission duration (days; continuous)



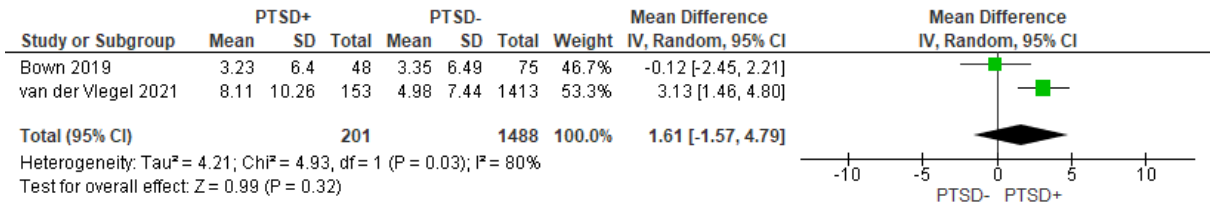
16. Discharge from emergency department (ref: hospital discharge with or without intensive care unit admission)



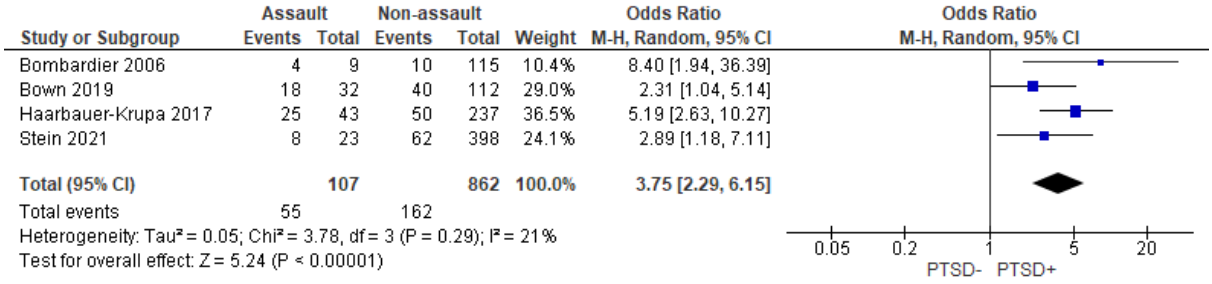
17. Admission to ICU (ref: no ICU admission)



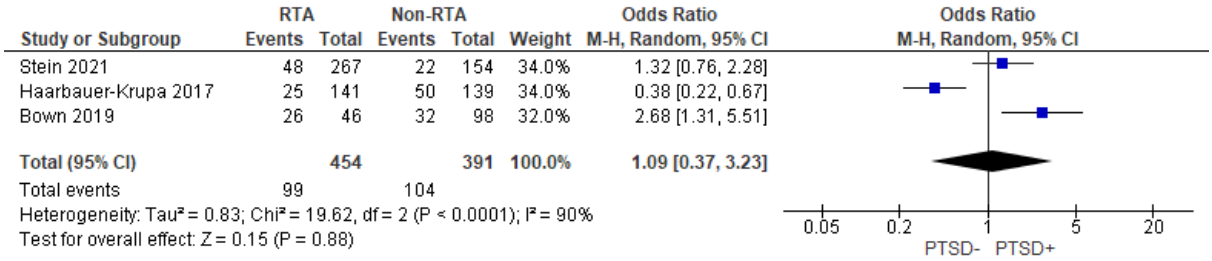
18. ICU admission duration (days; continuous)



19. Assault mechanism of injury (ref: non-assault mechanism of injury)



20. Road traffic accident mechanism of injury (ref: other causes)



Appendix E: Sensitivity analyses results: results of meta-analyses of univariable predictors of self-reported post-traumatic stress disorder following traumatic brain injury including only studies with cross-sectional designs

Predictor	Number of participants (number of studies)	Pooled effect size meta-analysis odds ratio (95% CI) (unless specified otherwise)	Heterogeneity (I^2)
Age (years; MD [95% CI])	701 (2)*	-2.06 (-4.80, 0.69)	0%
Male gender (vs female)	5020 (4)*	1.01 (0.64, 1.58)	72%***
Non-Caucasian race (vs Caucasian)	698 (2)	1.81 (1.19, 2.75)**	0%
Level of education (High school diploma or above vs lower)	1541 (2)	0.50 (0.17, 1.43)	64%***
Level of education (years; MD [95% CI])	701 (2)	-1.43 (-1.93, -0.94)**	0%
Employed at baseline (vs unemployed)	1641 (2)	0.60 (0.13, 2.76)	94%***
Married marital status	1366 (2)	0.65 (0.38, 1.10)	56%***
Prior psychiatric history	2384 (4)	2.95 (2.25, 3.89)**	0%
Positive toxicology screen	389 (2)	3.40 (1.45, 7.95)**	0%
ED GCS = 15 (vs < 15)	N/A	N/A	N/A
ED GCS 13-15 (vs <13)	1218 (2)	0.68 (0.29, 1.56)	43%
ED GCS 9-12 (vs < 9 or > 12)	1218 (2)	1.26 (0.72, 2.18)	0%
ED GCS < 9 (vs > 8)	1218 (2)	1.17 (0.66, 2.08)	18%
CT intracranial lesion	697 (2)	0.63 (0.39, 1.01)	23%
Hospital admission duration (days; MD [95% CI]	N/A	N/A	N/A
ED discharge (versus hospital or ICU admission)	2378 (3)	0.97 (0.64,1.46)	56%***
ICU admission (vs ED discharge or hospital admission without ICU)	2267 (3)*	0.91 (0.65, 1.26)	7%
ICU length of stay (days; MD [95% CI])	N/A	N/A	N/A
Assault mechanism of injury (vs non-assault)	1940 (4)*	3.80 (2.52, 5.73)**	3%
RTA mechanism of injury (vs non-RTA)	1816 (3)*	0.86 (0.42, 1.74)	85%***

Note: CI = Confidence Interval; ED = Emergency Department; ICU = Intensive Care Unit; pMD = Pooled Mean Difference; pOR = Pooled Odds Ratio; RTA = Road Traffic Accident. * = indicates predictors for which the original meta-analyses contained cross sectional studies, meaning that the results are now different in this sensitivity analysis. ** = $p < 0.05$. *** = High heterogeneity ($I^2 > 50\%$). N/A = meta-analysis not performed due to only one study remaining after the exclusion of cross-sectional studies.

Appendix F: Sensitivity analyses results: results of meta-analyses of univariable predictors of self-reported post-traumatic stress disorder following traumatic brain injury excluding the study by Bombardier et al. (2006).

Predictor	Number of participants (number of studies)	Pooled effect size meta-analysis odds ratio (95% CI) (unless specified otherwise)	Heterogeneity (I^2)
Age (years; MD [95% CI])	831 (3)	-3.47 (-7.12, 0.19)	46%
Male gender (vs female)	5081 (5)*	0.86 (0.65, 1.13)	42%
Non-Caucasian race (vs Caucasian)	840 (3)	1.78 (1.21, 2.62)**	0%
Level of education (High school diploma or above vs lower)	N/A	N/A	N/A
Level of education (years; MD [95% CI])	701 (2)	-1.43 (-1.93, -0.94)**	0%
Employed at baseline (vs unemployed)	1641 (2)	0.60 (0.13, 2.76)	94%***
Married marital status	1366 (2)	0.65 (0.38, 1.10)	56%***
Prior psychiatric history	2260 (3)*	3.00 (2.26 – 3.97)**	0%
Positive toxicology screen	N/A	N/A	N/A
ED GCS = 15 (vs < 15)	391 (2)	0.53 (0.17, 1.66)	82%
ED GCS 13-15 (vs <13)	N/A	N/A	N/A
ED GCS 9-12 (vs < 9 or > 12)	N/A	N/A	N/A
ED GCS < 9 (vs > 8)	N/A	N/A	N/A
CT intracranial lesion	697 (2)	0.63 (0.39, 1.01)	23%
Hospital admission duration (days; MD [95% CI]	1688 (2)	-1.36 (-4.48, 1.76)	48%
ED discharge (versus hospital or ICU admission)	2378 (3)	0.97 (0.64, 1.46)	56%***
ICU admission (vs ED discharge or hospital admission without ICU)	2390 (4)	0.96 (0.73, 1.28)	0%
ICU length of stay (days; MD [95% CI])	1689 (2)	1.61 (-1.57, 4.79)	80%***
Assault mechanism of injury (vs non-assault)	1960 (4)*	3.25 (2.24, 4.70)**	0%
RTA mechanism of injury (vs non-RTA)	1960 (4)	1.10 (0.56, 2.17)	85%***

Table 5. CI = Confidence Interval; ED = Emergency Department; ICU = Intensive Care Unit; pMD = Pooled Mean Difference; pOR = Pooled Odds Ratio; RTA = Road Traffic Accident. * = indicates predictors for which the original meta-analyses contained cross sectional studies, meaning that the results are now different in this sensitivity analysis. ** = $p < 0.05$. *** = High heterogeneity ($I^2 > 50\%$). N/A = meta-analysis not performed due to only one study remaining after the exclusion of Bombardier et al's (2006) study.

Appendix G: Results of the multiple linear regression analysis predicting HADS-A total scores using the original data only (with pairwise exclusion of missing data) (sensitivity analysis)

The regression model on the original data only did not statistically significantly predict HADS-A total scores ($F(7, 39) = 0.620$, $p = 0.736$, $R^2 = 0.100$, adjusted $R^2 = -0.061$. None of the seven independent variables added statistically significantly to the prediction ($p > 0.000926$).

HADS-A total scores	*B*	95% CI for *B*		*SE B*	β		R^2	$\Delta R2$
		LL	UL					
Model							0.100	-0.061
Marshall CT grade	0.098	2.437	2.437	1.157	0.013	0.933		
Gender	-1.498	-4.745	1.750	1.606	-0.163	0.357		
Employment status	0.212	-2.574	2.999	1.378	0.026	0.878		
LOC	0.543	-3.443	4.529	1.971	0.046	0.784		
PTA	-0.172	-4.071	3.727	1.928	-0.015	0.929		
Mechanism	-3.122	2.203	2.203	2.633	-0.197	0.243		
GCS	-1.092	1.406	1.406	1.235	-0.149	0.382		
Constant	6.559	0.508	12.611	2.992		0.034		

Note. B = unstandardized regression coefficient; CI = confidence interval; *LL* = lower limit; *UL* = upper limit; *SE B* = standard error of the coefficient; β = standardized coefficient; R^2 = coefficient of determination; $\Delta R2$ = adjusted R^2

Appendix H: Results of the multiple linear regression analysis predicting square root transformed HADS-D total scores using the original data only (with pairwise exclusion of missing data) (sensitivity analysis)

The regression model on the original data only did not statistically significantly predict square root transformed HADS-D total scores ($F(7, 39) = 0.491$, $p = 0.836$, $R^2 = 0.081$, adjusted $R^2 = -0.084$. None of the seven independent variables added statistically significantly to the prediction ($p > 0.000926$).

Sqrt(HADS-D total scores)	*B*	95% CI for *B*		*SE B*	β	*p*	R^2	$\Delta R2$
		LL	UL					
Model							0.081	-0.084
Marshall CT grade	0.265	-0.354	0.885	0.306	0.137	0.392		
Gender	0.017	-0.844	0.877	0.425	0.007	0.969		
Employment status	0.069	-0.670	0.807	0.365	0.032	0.852		
LOC	0.203	-0.853	1.258	0.522	0.066	0.700		
PTA	0.163	-0.870	1.196	0.511	0.053	0.751		
Mechanism	-0.702	-2.112	0.709	0.697	-0.169	0.321		
GCS	-0.142	-0.803	0.520	0.327	-0.074	0.667		
Constant	1.414	-0.189	3.016	0.792		0.082		

Table 2. Results of the multiple regression analysis predicting square root transformed PCL-5 total scores (only including the original dataset). *B* = unstandardized regression coefficient; CI = confidence interval; *LL* = lower limit; *UL* = upper limit; *SE B* = standard error of the coefficient; β = standardized coefficient; R^2 = coefficient of determination; $\Delta R2$ = adjusted R^2

Appendix I: Results of the multiple linear regression analysis predicting square root transformed PCL-5 total scores using the original data only (with pairwise exclusion of missing data) (sensitivity analysis)

The regression model on the original data only did not statistically significantly predict square root transformed HADS-D total scores ($F(7, 39) = 0.684$, $p = 0.685$, $R^2 = 0.109$, adjusted $R^2 = -0.051$. None of the seven independent variables added statistically significantly to the prediction ($p > 0.000926$).

Sqrt(PCL-5 total scores)	*B*	95% CI for *B*		*SE B*	β	*p*	R^2	ΔR^2
		LL	UL					
Model							0.109	-0.051
Marshall CT grade	0.124	-1.009	1.258	0.560	0.035	0.825		
Gender	-0.138	-1.711	1.436	0.778	-0.031	0.861		
Employment status	-0.230	-1.580	1.120	0.668	-0.059	0.732		
LOC	1.518	-0.413	3.449	0.955	0.266	0.120		
PTA	0.747	-1.142	2.636	0.934	0.131	0.429		
Mechanism	0.819	-1.761	3.399	1.276	0.106	0.525		
GCS	-0.209	-1.419	1.001	0.598	-0.059	0.728		
Constant	1.550	-1.382	4.482	1.449		0.291		

Table 3. Results of the multiple regression analysis predicting square root transformed PCL-5 total scores (only including the original dataset). *B* = unstandardized regression coefficient; CI = confidence interval; *LL* = lower limit; *UL* = upper limit; *SE B* = standard error of the coefficient; β = standardized coefficient; R^2 = coefficient of determination; ΔR^2 = adjusted R^2.

Appendix J: Results of the multiple linear regression analysis predicting HADS-A total scores only controlling for gender, employment status, mechanism of injury (with pairwise exclusion of missing data) (sensitivity analysis)

The regression model on the imputed data only controlling for gender, employment status and mechanism of injury did not statistically significantly predict HADS-A total scores (F(4, 67.7) = 0.680, p = 0.608, mean R^2 = 0.0429, mean adjusted-R^2 = -0.0118. None of the four independent variables added statistically significantly to the prediction (p > 0.000926).

HADS-A total scores	*B*	95% CI for *B*		*SE B*	β	*p*	R^2	Δ*R2*
		LL	UL					
Model							0.0429	-0.0118
Marshall CT grade	-0.162	-2.04	1.72	0.940	-0.021	0.864		
Gender	-1.48	-3.90	0.931	1.21	-0.159	0.225		
Employment status	0.424	-1.63	2.48	1.03	0.0526	0.682		
Mechanism	-1.90	-5.99	2.18	2.04	-0.118	0.355		
Constant	6.26	4.13	8.39	1.07		0.000		

Note. B = unstandardized regression coefficient; CI = confidence interval; *LL* = lower limit; *UL* = upper limit; *SE B* = standard error of the coefficient; β = mean standardized coefficient; R^2 = mean coefficient of determination; Δ*R2* = mean adjusted R^2

Appendix K: Results of the multiple linear regression analysis predicting sqrt(HADS-D total scores) only controlling for gender, employment status, mechanism of injury (with pairwise exclusion of missing data) (sensitivity analysis)

The regression model on the imputed data only controlling for gender, employment status and mechanism of injury did not statistically significantly predict square root transformed HADS-D total scores ($F(4, 67.6) = 0.220$, $p = 0.926$, mean $R^2 = 0.0177$, mean adjusted-$R^2 = -0.0385$. None of the four independent variables added statistically significantly to the prediction ($p > 0.000926$).

Sqrt(HADS-D total scores)	*B*	95% CI for *B*		*SE B*	β	*p*	R^2	$\Delta R2$
		LL	UL					
Model							0.0177	-0.0385
Marshall CT grade	0.127	-0.400	0.653	0.263	0.0648	0.632		
Gender	0.037	-0.600	0.675	0.319	0.0154	0.907		
Employment status	0.0641	-0.480	0.608	0.273	0.0307	0.815		
Mechanism	-0.392	-1.44	0.656	0.524	-0.0927	0.458		
Constant	1.74	1.174	2.30	0.282		0.000		

Note. B = unstandardized regression coefficient; CI = confidence interval; *LL* = lower limit; *UL* = upper limit; *SE B* = standard error of the coefficient; β = mean standardized coefficient; R^2 = mean coefficient of determination; $\Delta R2$ = mean adjusted R^2

Appendix L: Results of the multiple linear regression analysis predicting sqrt(PCL-5 total scores) only controlling for gender, employment status, mechanism of injury (with pairwise exclusion of missing data) (sensitivity analysis)

The regression model on the imputed data only controlling for gender, employment status and mechanism of injury did not statistically significantly predict square root transformed PCL-5 total scores ($F(4, 67.9) = 0.220$, $p = 0.9258$, mean $R^2 = 0.0173$, mean adjusted-$R^2 = -0.0389$. None of the four independent variables added statistically significantly to the prediction ($p > 0.000926$).

Sqrt(PCL-5 total scores)	*B*	95% CI for *B*		*SE B*	β	*p*	R^2	$\Delta R2$
		LL	UL					
Model							0.0173	-0.0389
Marshall CT grade	0.0797	-0.845	1.004	0.462	0.0223	0.864		
Gender	0.182	-0.973	1.34	0.579	0.0408	0.754		
Employment status	-0.353	-1.35	0.639	0.497	-0.0923	0.480		
Mechanism	0.748	-0.845	1.00	0.462	0.097	0.424		
Constant	3.41	2.38	4.43	0.513		0.000		

Note. B = unstandardized regression coefficient; CI = confidence interval; *LL* = lower limit; *UL* = upper limit; *SE B* = standard error of the coefficient; β = mean standardized coefficient; R^2 = mean coefficient of determination; $\Delta R2$ = mean adjusted R^2