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# Incidence of anxiety after traumatic brain injury: a systematic review and meta-analysis

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## Abstract

**Background** Traumatic brain injury (TBI) is defined as acquired cerebral damage caused by an external mechanical impact, which has the potential to lead to transient or enduring debilitation. TBI is associated with many forms of long-lasting psychiatric conditions, including anxiety disorders. As anxiety is highly debilitating by causing impaired social functioning and decreased quality of life for the afflicted, especially in the form of anxiety disorders such as generalized anxiety disorder, certain efforts have been made to explore the factors associated with it, and one such factor is TBI.

**Methods** We searched PubMed, Scopus, and Web of Science on January 26th, 2024 for observational case–control or cohort or cross-sectional studies assessing the incidence of anxiety symptoms or disorders in patients with TBI compared to healthy individuals or the same individuals if pre-TBI information regarding anxiety was available. We calculated the pooled incidence and relative risk (RR) and 95% confidence interval (95CI) using the inverse variance method. Publication bias was assessed using Eggers's regression test. Quality assessment was performed using the Newcastle–Ottawa scale. Sub-group analyses were conducted for the type of anxiety (anxiety disorder vs anxiety symptoms), TBI severity, and type of anxiety disorders.

**Results** The incidence rate of anxiety after traumatic brain injury was 17.45% (95CI: 12.59%, 22.31%) in a total of 705,024 individuals. Moreover, TBI patients were found to be 1.9 times as likely to have anxiety compared to their non-TBI counterparts [Random effects model RR = 1.90 [1.62; 2.23], $p$-value < 0.0001] using a population of 569,875 TBI cases and 1,640,312 non-TBI controls. Sub-group analysis revealed TBI severity was not associated with anxiety and generalized anxiety disorder was the most common type of anxiety disorder reported post-TBI.

**Conclusion** Patients who have experienced a TBI exhibit a significantly greater incidence of anxiety symptoms and anxiety disorders in the aftermath when compared to healthy individuals.

**Keywords** Traumatic brain injury, Anxiety, Anxiety symptoms, Anxiety disorder, Incidence

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## Introduction

Traumatic brain injury (TBI) is an acquired insult to the brain from an external mechanical force that may result in temporary or permanent impairment [1]. TBI has the highest incidence of all common neurological disorders [2], thus constituting a major public health concern. In 2019 alone, TBI had 27.16 million new cases, 48.99 million prevalent cases, and 7.08 million Years lived with disability (YLDs) globally [3]. It is notable that TBI was viewed as an injury event with finite recovery in the past. However, it is now recognized as a chronic condition that can impact various domains of health and function, with some even deteriorating over time [4]. One such important aspect impacted by TBI is neuropsychiatric health. TBI has been recognized as a condition with long-lasting neuropsychiatric consequences including major depressive disorder, post-traumatic stress disorder, and anxiety disorders [5, 6]. Be that as it may, the incidence, extent, and management of these negative sequelae have not been fully defined and require further examination [7].

Anxiety is a prevalent neuropsychiatric illness, with approximately 4.05% of the worldwide populace affected by an anxiety disorder [8]. In addition, anxiety disorders can have debilitating effects on an individual's life including reduced work productivity, diminished social functioning, and decreased quality of life [9]. As a result, extensive efforts have been dedicated to uncovering the root causes of anxiety and mitigating its impact by addressing underlying predisposing factors [10, 11]. One such predisposing factor is TBI, as pooled prevalence estimates indicate a high long-term prevalence of anxiety disorders (36%) among TBI patients [12].

Although the prevalence and risk factors of anxiety among TBI patients have been assessed thorough a systematic review [12], the incidence and risk of developing anxiety after TBI _relative to non-TBI counterparts_ have not yet been systematically quantified across the literature. This quantification is crucial as awareness of this likelihood can aid physicians in providing patients with the necessary medical care. As a result, we set out to determine the incidence of developing anxiety symptomology and disorders in patients with a history of TBI and to compare the risk with a non-TBI patient population.

## Methods

This systematic review and meta-analysis was conducted according to PRISMA guidelines [13]. The protocol for this review was prospectively submitted on PROSPERO (ID: CRD42024519155).

### Search strategy

A comprehensive search of 3 online databases (Pubmed, Scopus, and Web of Science) was conducted on January 26th, 2024, using Mesh terms and keywords synonymous with "Traumatic brain injury" and "Anxiety." No language or publication year limitations were defined.

### Selection criteria

Papers were included if they complied with our predefined PECOS of (P) individuals with a self-reported or author-confirmed history of traumatic brain injury; (E) traumatic brain injury as defined by the authors; (C) healthy controls without TBI during the study period or the same individuals if pre-TBI information regarding Anxiety was available; (O): Anxiety symptomology, self-reported feelings of Anxiety, or diagnosis of Anxiety using a validated assessment scale; (S): observational case–control or cohort or cross-sectional studies.

Exclusion criteria were: (P) participants without confirmed brain trauma; (E) traumatic brain pathology not consistent with traumatic brain injury; (C) no healthy controls and no information regarding pre-TBI Anxiety symptoms or diagnoses; (O) Anxiety symptomology or disorder reported in tandem with other mental illnesses or any illness proven to cause anxiety; (S): in vitro studies, in vivo studies, controlled trials, case reports, and case series. Studies that used the same population were separated, and the one with the larger population was included.

### Study selection

Papers were screened for selection independently by two reviewers in 2 phases—an initial title and abstract screening followed by full-text retrieval and screening. The inconsistencies were addressed by consulting with a third reviewer and discussing them.

### Data extraction

Two reviewers performed data extraction independently using a pre-constructed spreadsheet, with independent validation by a third reviewer. Discrepancies were resolved through discussion. The following items were extracted: author, year of publication, country of first author, sample origin, study type, definition of TBI, type of TBI (mild or moderate or severe TBI), mean/median of age, sample size, male (%), anxiety assessment scale, time of study, and time of follow up from TBI. Missing data were marked as not provided (NP). The type of anxiety was also extracted and categorized into anxiety disorders (i.e. generalized anxiety disorder, panic disorder) or anxiety symptoms above clinical cut-off values. The type of anxiety disorder was also extracted if provided separately.

Due to the inclusion of papers utilizing previous versions of the Diagnostic and Statistical Manual of Mental Disorders, which categorized obsessive compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) as anxiety disorders, we decided to included such diagnoses under the definition of anxiety disorders as well. For the purposes of this review, concussions were categorized as mild traumatic brain injuries.

Data regarding our outcome of interest, the incidence of anxiety, was extracted in two domains: novel cases of Anxiety and total participants in the TBI cohort or anxiety cases and full participants in the TBI and healthy control groups. If data regarding multiple time points were available, the last time point of the Anxiety assessment was extracted.

#### Risk of bias assessment

The risk of bias in the included observational studies was assessed using the Newcastle–Ottawa scale (NOS) [14]. 2 reviewers independently evaluated the quality of the papers using NOS in three domains: selection, comparability, and exposure. The inconsistencies were resolved by conversing with a third reviewer. A total score of < 7 was deemed a high risk of bias.

#### Statistical analysis

Meta-analysis and statistical analysis were performed using R studio's 'meta' package by drawing a forest plot. Between-study heterogeneity was investigated using the $I^2$ test since an $I^2$ of around 25%, 50%, and 75% is considered low, moderate, and high levels of heterogeneity, respectively. Using the inverse variance method, the pooled relative risk (RR) and 95% confidence interval (95CI) were calculated. Both The common (fixed) effect model and random-effects model were calculated, and in case of heterogeneity the random effects model was reported Significance was defined as $p$-value < 0.05. Also, pooled proportion meta-analyses were performed on eligible studies using the inverse variance method. Finally, publication bias was assessed using Egger's regression test. In case multiple time-points were reported, the longest follow-up was used in our analyses.

Sub-group analyses based on the type of TBI (mild vs moderate-severe), the type of anxiety (anxiety disorders vs anxiety symptoms), and the type of anxiety disorder were conducted to investigated heterogeneity.

## Results

Our online database search yielded a total of 2318 papers, of which 1732 were chosen for title-abstract screening after the removal of 586 duplicates. Of these 121 were chosen for full-text retrieval and evaluation and 49 were included in this review. Of the excluded papers, 3 were excluded due to their TBI population suffering from comorbidities (dementia), 1 was excluded due to using a mixed sample of TBI and blast-exposed veterans, one was excluded due to using a mixed sample of TBI and spinal cord injuries, and 68 were excluded due to reporting of means and standard deviations for anxiety assessment scales instead of the number of participants above the scales cut-off or reporting the prevalence of anxiety after TBI and not its incidence (Fig. 1).

22 of the included studies were cohort investigations, 26 were case–control studies, and one study was cross-sectional in design. The studies investigated TBIs that occurred between the 1980s – 2022 and assessed anxiety 1 week [15] to 24 years [16] after TBI. TBI was most commonly defined using the American Congress of Rehabilitation Medicines' definition in 15 studies (loss of consciousness < 30 min or Glasgow coma scale 13–15 or post-traumatic amnesia < 24 h or focal neurological deficits) while 10 studies utilized ICD codes for TBI instead. The type of TBI reported was mostly mTBI, followed by a mixture of varying TBI severities (any TBI).

Most of the included studies used an American population ($n = 26$) while 8 studies used an Australian population instead. The investigated TBI populations mostly had a mean/median age of 30–40 years ($n = 18$) while 11 studies included children or adolescents. 11 of the studies included mostly males in their TBI sample (male > 75%) and one study used a mostly female sample (male < 25%).

Anxiety symptom assessment scales used in the studies varied significantly, with 7 using Hospital Anxiety and Depression Scale (HADS), 3 using diagnostic interview schedule (DIS), 2 using Beck's Anxiety Inventory (BAI), 2 using Neurobehavioral Symptom Inventory (NSI), 2 using the Mini-International Neuropsychiatric Interview (MINI), 2 using the Structured Clinical Interview for DSM (SCID), yet most of the studies ($n = 9$) used ICD codes for anxiety instead. The type of anxiety investigated was mostly anxiety symptoms ($n = 26$), while 23 of the included studies investigated anxiety disorders. The types of anxiety disorders investigated were mostly generalized anxiety disorder (GAD) ($n = 15$), followed by post-traumatic stress disorder (PTSD) and panic disorder (Table 1).

#### Incidence of Anxiety

Among the included studies, 20 papers reported novel cases of anxiety after TBI, the pooled proportion showed an incidence rate of 17.45% (95CI: 12.59%, 22.31%), albeit with significant heterogeneity in a total of 705,024 individuals ($I^2 = 100.0\%$, Fig. 2). Publication bias was not evident according to Egger's test ($p$-value = 0.08). When investigating heterogeneity, 16 studies had reported the incidence of anxiety disorders and 4 studies reported

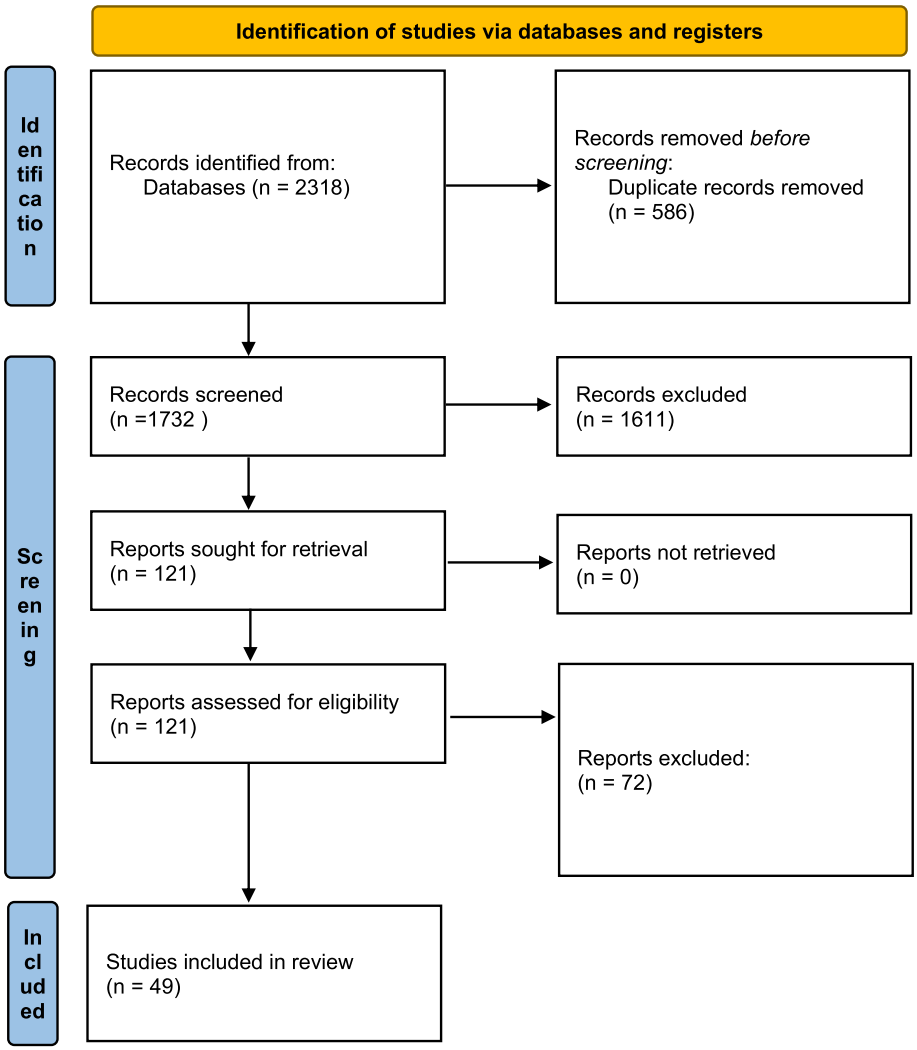


**Fig. 1** PRISMA flowchart

anxiety symptoms, which did not vary significantly. 15 reports of the type of TBI showed no significant difference between mTBI and moderate-severe TBI, and 8 studies had reported the type of anxiety disorders, which showed significant difference between disorders, with GAD and PTSD being the most common disorders and OCD and social anxiety being the least prevalent (Table 2).

### Relative risk of anxiety

33 of the included studies compared anxiety in 569,875 TBI cases with 1,640,312 non-TBI controls, the pooled results of which revealed TBI patients were 1.9 times as likely to be anxious compared to their non-TBI counterparts (RR = 1.90 (95CI: 1.62; 2.23), $p$-value < 0.0001), with high heterogeneity ($I^2 = 99\%$) (Fig. 3). Egger's regression test found no evidence of publication bias in the meta-analysis ($p$-value = 0.184). When investigating heterogeneity, TBI patients were more likely to report anxiety disorders compared to anxiety symptoms when comparing 11 studies assessing anxiety disorders to 21 studies assessing anxiety symptoms. No difference regarding TBI severity and anxiety was evident when comparing 21 mTBI studies to 7 moderate-severe TBI studies. Only 3 studies had reported the type of anxiety disorders and sub-group analysis was therefore avoided (Table 3).

### Quality assessment

Of the 22 cohort studies included, 12 were judged to be of high quality and 10 were of low quality. Furthermore, of the 26 case–control studies, 13 were determined to be high-quality while 13 were of low quality. The single

**Table 1** Characteristics of the included studies

| Author, Year of publication | Sample origin, Study Type | Definition of TBI | Type of TBI | Mean/Median Age | Sample Size (n) | Male (%) | Anxiety assessment scale | Type of anxiety | Time of study | Time of follow up from TBI |
|---|---|---|---|---|---|---|---|---|---|---|
| **Brenner et al. 2023** [17] | USA, Cohort | ICD-9 and ICD-10 codes | Any TBI | NP | 860,892 | 89 | ICD-9 and ICD-10 codes | Anxiety disorders | 2008–2014 | 4–10 years |
| **Laborey et al. 2014** [18] | France, Case–control | ACRM mTBI criteria | mTBI | TBI = median of 36 Control = median of 35 | TBI = 536 Control = 946 | TBI = 63.7 Control = 55.5 | DSM-IV or ICD-10 or RPQ | Anxiety symptoms | 2007–2009 | 3 months |
| **Luis et al. 2002** [19] | USA, Cohort | ACRM mTBI criteria and GCS of < 13 or abnormal CT or depressed skull for moderate/severe TBI | mTBI, moderate TBI, severe TBI | mean of 10.55 years | 64 (42 mTBI + 19 moderate/severe TBI) | 67.18 | DISC-IV | Anxiety Disorders (social phobia, separation Anxiety, specific phobia, panic disorder, generalized anxiety disorder, post-traumatic stress disorder, obsessive compulsive disorder) | NP | 6 months |
| **Ma et al. 2014** [20] | Taiwan, Case–control | ACRM mTBI criteria | mTBI | TBI = mean of 39.53 Control = mean of 29.86 | TBI = 100 Control = 137 | TBI = 35 Control = 34.3 | BAI | Anxiety symptoms | 2011–2012 | 6 weeks |
| **Max and Friedman et al. 2015** [21] | USA and Canada, Cohort | altered GCS and/or abnormal neuroimaging findings | mTBI | mean of 9.79 | 54 | 64.80% | K-SADS-PL | Anxiety disorders (obsessive compulsive disorder , post-traumatic stress disorder, generalized anxiety disorder, simple phobia, social phobia, panic disorder, separation anxiety | 1998–2002 | 24 months |
| **Mortera et al. 2018** [22] | USA, Case–control | NP | Any TBI | TBI = mean of 32.52 Control = mean of 34.85 | TBI = 163 Control = 73 | TBI = 92.0 Control = 87.7 | NSI | Anxiety symptoms | 2009–2013 | Less than a month to more than 3 years |
| **Mrazik et al. 2016** [23] | Canada, Cohort | Self-report | mTBI | between 12–17 years old | 627 | 83.9 | BASC2 | Anxiety symptoms | 2011–2012 | Median of 20 months |
| **O'connor et al. 2005** [24] | Canada, Case–control | ICD-9 codes | mTBI, moderate TBI, severe TBI | TBI = mean of 32.7 Control = NP | TBI = 57 Control = 86 | TBI = 77.2 Control = NP | Head Injury Symptom Checklist | Anxiety symptoms | 1982 | Mean on 10.9 years |
| **Ownsworth et al. 2018** [25] | Australia, Case–control | PTA > 24 h and/or GCS score < 9 (severe TBI) | severe TBI | TBI = mean of 36.56 Control = mean of 39.22 | TBI = 52 Control = 50 | TBI = 75 Control = 70 | DASS-21 | Anxiety symptoms | NP | Mean of 32.25 months |
| **Al Kader. et al 2022** [26] | Pakistan, Case control | NP | mTBI | NP | TBI = 31 control = 31 | TBI = 64.5 control = 80.6 | GAD-7 | Anxiety symptoms | 2021–2022 | NP |

**Table 1** (continued)

| Author, Year of publication | Sample origin, Study Type | Definition of TBI | Type of TBI | Mean/Median Age | Sample Size (n) | Male (%) | Anxiety assessment scale | Type of anxiety | Time of study | Time of follow up from TBI |
|---|---|---|---|---|---|---|---|---|---|---|
| **Fish et al. 2023** [27] | USA, Case control | 5th Consensus Statement on Concussion in Sport | mTBI | TBI = median of 15.7 control = median of 15.1 | TBI = 111 control = 171 | TBI = 47.8% control = 45.0% | PROMIS (Pediatric Short Form) | Anxiety symptoms | 2017–2020 | 28 days |
| **Ponsford et al. 2014** [28] | Australia, Case control | NP | Any TBI | TBI = mean of 39.36 control = mean of 38.70 | TBI = 41 control = 41 | TBI = 70.7% control = 70.7% | HADS | Anxiety symptoms | NP | 1–20 years |
| **Rao et al. 2008** [29] | USA, Cohort | LOC or GCS < 15 or abnormal CT | Any TBI | mean of 43.2 | 54 | 59% | NP | Anxiety disorders (generalized anxiety disorder) | NP (2.5 years) | within 3 months |
| **Starkey et al. 2022** [30] | New Zealand, Case control | GCS 13–15 or PTA < 24 h (mTBI) | mTBI | TBI = median of 40 control = median of 27.5 | TBI = 151 control = 151 | TBI = 51% control = 49% | HADS | Anxiety symptoms | 2010–2011 | 8 years |
| **Sung et al. 2016** [15] | Taiwan, Case control | ACRM mTBI criteria | mTBI | TBI = mean of 45.42 control = mean of 46.98 | TBI = 331 control = 152 | TBI = 38.5% control = 31% | BAI | Anxiety symptoms | 2010–2014 | 1 week |
| **Vanderploeg et al. 2009** [31] | USA, Case–control | Self-report | mTBI | NP | case = 278 control = 548 | case = 100% control = 100% | DIS, Version III-A | Anxiety symptoms | 1980s | NP |
| **Vasa et al. 2004** [32] | USA, Cohort | GCS 3–8 (severe TBI) | severe TBI | mean of 8.2 years | 95 | 57% | preinjury: parent-reported postinjury: DICA | Anxiety disorders (overanxious disorder, separation anxiety, simple phobia, avoidant disorder, post-traumatic stress disorder | 1992–1996 | mean of 23 days |
| **Vassallo et al. 2007** [33] | USA, Case–control | Self-reported LOC or PTA | Any TBI | TBI = mean of 37.90 control = mean of 38.32 | TBI = 271 control = 630 | TBI = 100% control = 100% | DIS, Version III-A | Anxiety disorders ( generalized anxiety disorder, obsessive-compulsive disorder, specific phobia, panic disorder, post-traumatic stress disorder) | 1980s | NP |
| **Whelan-Goodinson et al. 2009** [34] | Australia, Cross-sectional | NP | Any TBI | mean of 37.18 | 100 | 71% | SCID-I | Anxiety disorders ( generalized anxiety disorder,panic,specific phobia,agoraphobia,social phobia,obsessive compulsive disorder) | 2000–2005 | 6 months—5.5 years (mean of 3 years) |

**Table 1** (continued)

| Author, Year of publication | Sample origin, Study Type | Definition of TBI | Type of TBI | Mean/Median Age | Sample Size (n) | Male (%) | Anxiety assessment scale | Type of anxiety | Time of study | Time of follow up from TBI |
|---|---|---|---|---|---|---|---|---|---|---|
| **Pacella et al. 2017** [35] | USA, Case–control | ACRM mTBI criteria | mTBI | TBI = mean of 32 control = mean of 34 | TBI = 39 control = 53 | TBI = 51 control = 55 | Self-report | Anxiety symptoms | 2013–2014 | 14 days |
| **Parcell et al. 2008** [36] | Australia, Case–control | NP | Any TBI | TBI = mean of 38.80 control = mean of 37.80 | TBI = 10 control = 10 | TBI = 60 control = 60 | HADS | Anxiety symptoms | NP | Mean of 516 days |
| **Petrie et al. 2014** [37] | USA, Case–control | ACRM mTBI criteria | mTBI | TBI = mean of 31.6 control = mean of 32.8 | TBI = 34 control = 18 | TBI = 100 control = 94.4 | NSI | Anxiety symptoms | 2004–2005 | Mean of 3.8 years |
| **Ponsford et al. 2011** [38] | Australia, Case control | ACRM mTBI criteria | mTBI | TBI = mean of 34.98 control = mean of 35.40 | TBI = 123 control = 100 | TBI = 74% control = 64% | MINI | Anxiety disorders (generalized anxiety disorder, panic,specific phobia,agoraphobia,social phobia,obsessive compulsive disorder, post-traumatic stress disorder) | 2007–2009 | 3 months |
| **Ashina et al. 2021** [39] | Denmark, Case control | NP | mTBI | TBI = mean of 36.0 control = mean of 35.8 | TBI = 100 control = 100 | TBI = 17% control = 18% | HADS | Anxiety symptoms | 2018–2019 | NP |
| **Ballatori et al. 2023** [40] | USA, Cohort | ICD-9 and ICD-10 codes | mTBI | mean = 50.9 | 206,070 | 56.1 | ICD-9 and ICD-10 codes | Anxiety symptoms | 2010–2019 | up to a year |
| **Ellis et al. 2015** [41] | Canada, Cohort | Clinical symptoms in multiple domains of physical, cognitive, sleep, and neurobehavioral functioning after biomechanical trauma to brain | mTBI | mean = 14.22 years | 174 | 61.49% | NP | Anxiety disordes( generalized anxiety disorder, post-traumatic stress disorder, adjustment disorder with anxiety, separation anxiety disorder, or obsessive–compulsive disorder (OCD)) | 2013–2014 | NA |

**Table 1** (continued)

| Author, Year of publication | Sample origin, Study Type | Definition of TBI | Type of TBI | Mean/Median Age | Sample Size (n) | Male (%) | Anxiety assessment scale | Type of anxiety | Time of study | Time of follow up from TBI |
|---|---|---|---|---|---|---|---|---|---|---|
| **Esterov et al. 2022** [42] | USA, Cohort | LOC, nausea, vomiting, or headache association with the injury followed by hospitalization for rehabilitation, or abnormal CT or X-ray findings | mTBI, moderate TBI, severe TBI | NP | 5,518 | NP | Record linkage | Anxiety disorders | 1976—NP | Mean of 4.7 years |
| **Iverson et al. 2021** [43] | USA, Cohort | NP | mTBI | Mean of 17.3 years | 158 | 45.6 | PCSS | Anxiety symptoms | NP | Mean of 49.04 days |
| **Karver et al. 2012** [44] | USA, Case–control | NP | severe TBI | TBI = Mean of 5 control = Mean of 5.11 | TBI = 86 control = 117 | TBI = 60.4 control = 58 | CBCL | Anxiety symptoms | NP | At least 2 years |
| **Max and Lopez et al. 2015** [45] | USA, Cohort | ACRM mTBI criteria | mTBI | Mean of 9.99 | 125 | 66.4 | K-SADS-PL and NPRS | Anxiety disorders (generalized anxiety disorder, separation anxiety) | 1998–2003 | 12 months |
| **Sundström et al. 2007** [46] | Sweden, Case control | ACRM mTBI criteria | mTBI | TBI = mean of 55.2 control = mean of 55.2 | TBI = 31 control = 62 | TBI = 58.1 control = 58.1 | self-report | Anxiety symptoms | 1988–2000 | 5 years |
| **Yang et al. 2014** [47] | USA, Cohort | trauma-induced alteration of mental status | mTBI | NP | 71 | 74.6 | STAI | Anxiety symptoms | 2007–2011 | 1 week to 12 months |
| **de Koning et al. 2016** [48] | Netherlands, Case–control | ACRM mTBI criteria | mTBI | TBI = mean:40.5 control = 35.8 | TBI = 272 Control = 125 | 62 | HADS | Anxiety symptoms | 2013—2014 | 2 weeks |
| **Bernard et al. 2017** [49] | Australia, Case–control | ACRM mTBI criteria | mTBI | NP | TBI = 46 Control = 55 | TBI = 63.0 Control = 70.9 | self-report | Anxiety symptoms | 2012—2015 | 1 or 2 or 3 months |
| **Albicini et al. 2018** [50] | Australia, Case–control | ACRM mTBI criteria | mTBI, moderate TBI, severe TBI | TBI = Mean of 9 years control = Mean of 10.5 years | TBI = 126 control = 43 | TBI = 60.3 control = 44.2 | CIDI | Anxiety disorders (generalized anxiety disorder, Panic disorder, social phobia, specific phobia, posttraumatic stress disorder) | NP | mean of 13.6 years |

**Table 1** (continued)

| Author, Year of publication | Sample origin, Study Type | Definition of TBI | Type of TBI | Mean/Median Age | Sample Size (n) | Male (%) | Anxiety assessment scale | Type of anxiety | Time of study | Time of follow up from TBI |
|---|---|---|---|---|---|---|---|---|---|---|
| **Albrecht and Abariga et al. 2020** [51] | USA, Cohort | ICD-9 CM codes | Any TBI | TBI = Mean of 54.6 years control = Mean of 49.1 years | TBI = 207,354 control = 414,708 | TBI = 43.3 control = 48.3 | ICD-9 CM codes | Anxiety disorders (generalized anxiety disorder, panic disorder) | 2009—2012 | 2 year |
| **Chin et al. 2020** [52] | q | Barell injury diagnosis matrix | Any TBI | 25.5 years | 4980 | 98.2 | ICD-9 CM codes | Anxiety disorders | 2002—2011 | mean of 5.58 years |
| **Coffeng et al. 2022** [53] | Netherlands, Cohort | ACRM mTBI criteria | mTBI | 44.1 years | 242 | 49.2 | self-report | Anxiety symptoms | 2016—2018 | 2 weeks |
| **Delmonico et al. 2022** [54] | USA, Case–control | ICD-9 CM codes | mTBI | NP | TBI = 9,428 control = 18,856 | 39 | NP | Anxiety Disorders (generalized anxiety disorder, panic disorder, social phobia, posttraumatic stress disorder, specific phobia) | 2000–2007 | 1 year or 2 or 3 or 4 years |
| **Izzy et al. 2022** [55] | USA, Cohort | ICD-9 codes | mTBI, moderate TBI, severe TBI | mTBI = median of 45 moderate /severe TBI = median of 47 | 8702 | 55% | ICD-9 and ICD-10 codes | Anxiety disorders | 2000–2015 | 10 years |
| **Hawley et al. 2003** [56] | UK, Case control | NP | mTBI, moderate TBI, severe TBI | TBI = mean of 9.85 control = NA | TBI = 97 control = 31 | TBI = 66% control = 58.1% % | HADS | Anxiety symptoms | 1992–1998 | 6 month—5 years |
| **Diaz et al. 2012** [57] | Brazil, Cohort | GCS < 9 | severe TBI | mean of 32.33 | 48 | 87.50% | HADS | Anxiety disorders( generalized anxiety disorder) | 2006–2009 | mean of 18 months |
| **Gould et al. 2011** [58] | Australia, Cohort | ACRM mTBI criteria | Any TBI | mean of 34.63 years | 102 | 75.5 | SCID | Anxiety disorders | 2005–2008 | 3, 6 and 12 months |
| **Karr et al. 2019** [59] | Taiwan, Cohort | ACRM mTBI criteria | mTBI | mean of 38.2 years old | 297 | 40.40% | CPCS | Anxiety symptoms | 2010–2017 | mean of 7.7 days |
| **Albrecht and Mullins et al. 2017** [60] | USA, Cohort | ICD-9 codes | Any TBI | mean of 81.0 | 60,276 | 32% | NP | Anxiety disorders | 2006–2010 | 1 year |
| **Albrecht and Peters et al. 2017** [61] | USA, Cohort | ICD-9-CM codes | Any TBI | mean of 81.1 | 96,881 | 34% | ICD-9-CM codes | Anxiety disorder | 2006–2010 | mean of 20.2 months |
| **Albrecht and Wickwire et al. 2020** [62] | USA, Case–control | ICD-9-CM codes | Any TBI | TBI = Mean of 54.6 control = Mean of 49.1 | TBI = 207,354 control = 414,708 | TBI = 43.3 control = 48.3 | ICD-9-CM codes | Anxiety disorder (anxiety and panic disorders, posttraumatic stress disorder) | 2009–2012 | At least 2 years |

**Table 1** (continued)

| Author, Year of publication | Sample origin, Study Type | Definition of TBI | Type of TBI | Mean/Median Age | Sample Size (n) | Male (%) | Anxiety assessment scale | Type of anxiety | Time of study | Time of follow up from TBI |
|---|---|---|---|---|---|---|---|---|---|---|
| **Wilder et al. 2022** [63] | USA, Case–control | ICD-10 and ICD-9 codes | mTBI | TBI = NP control = NP | TBI = 23,012 control = 23,012 | TBI = NP control = NP | ICD-10 and ICD-9 codes | Anxiety disorders (generalized anxiety disorder, panic disorder, post-traumatic stress disorder) | 2015–2016 | 3 years |
| **Max et al. 2021** [16] | USA, Cohort | NP | Any TBI | 34.29 | 45 | 64.4 | MINI | Anxiety disorders (generalized anxiety disorder, post-traumatic stress disorder, obsessive compulsive disorder, panic disorder) | 1992–1994 | 24 years |

*Abbreviations: TBI* Traumatic brain injury, *ICD* International statistical classification of diseases and related health problems, *NP* Not provided, *ACRM* American congress of rehabilitation medicine, m*TBI* mild traumatic brain injury, *DSM*-IV, Diagnostic and statistical manual of mental disorders- fourth edition, *RPQ* Rivermead post-concussion symptoms questionnaire, *GCS* Glasgow coma scale/ *DISC-IV* Diagnostic interview schedule for children- fourth edition, *DIS* Diagnostic interview schedule, *BAI* Beck's anxiety inventory, *K-SADS-PL* Schedule for affective disorders and schizophrenia for school-age children, present and lifetime version. *NRPS* Neuropsychiatric rating schedule, *NSI*: Neurobehavioral symptom inventory, *BASC2* Behavior assessment system for children, 2nd edition, *PTA* Post-traumatic amnesia, *DASS-21* Depression, anxiety, and stress scale- 21 items, *GAD-7* Generalized anxiety disorder questionnaire-7, *PROMIS* Patient-reported outcomes measurement information system, *HADS* Hospital anxiety and depression scale, *DICA* Diagnostic interview for children and adolescents, *SCID* Structured Clinical Interview for *DSM*, *MINI* Mini-international neuropsychiatric interview, *PCSS* Post-concussion symptom scale, *CBCL* Child behavior checklist, *STAI* State-trait anxiety inventory, *CIDI* Composite international diagnostic interview, *CPCS* Checklist of post-concussion symptom

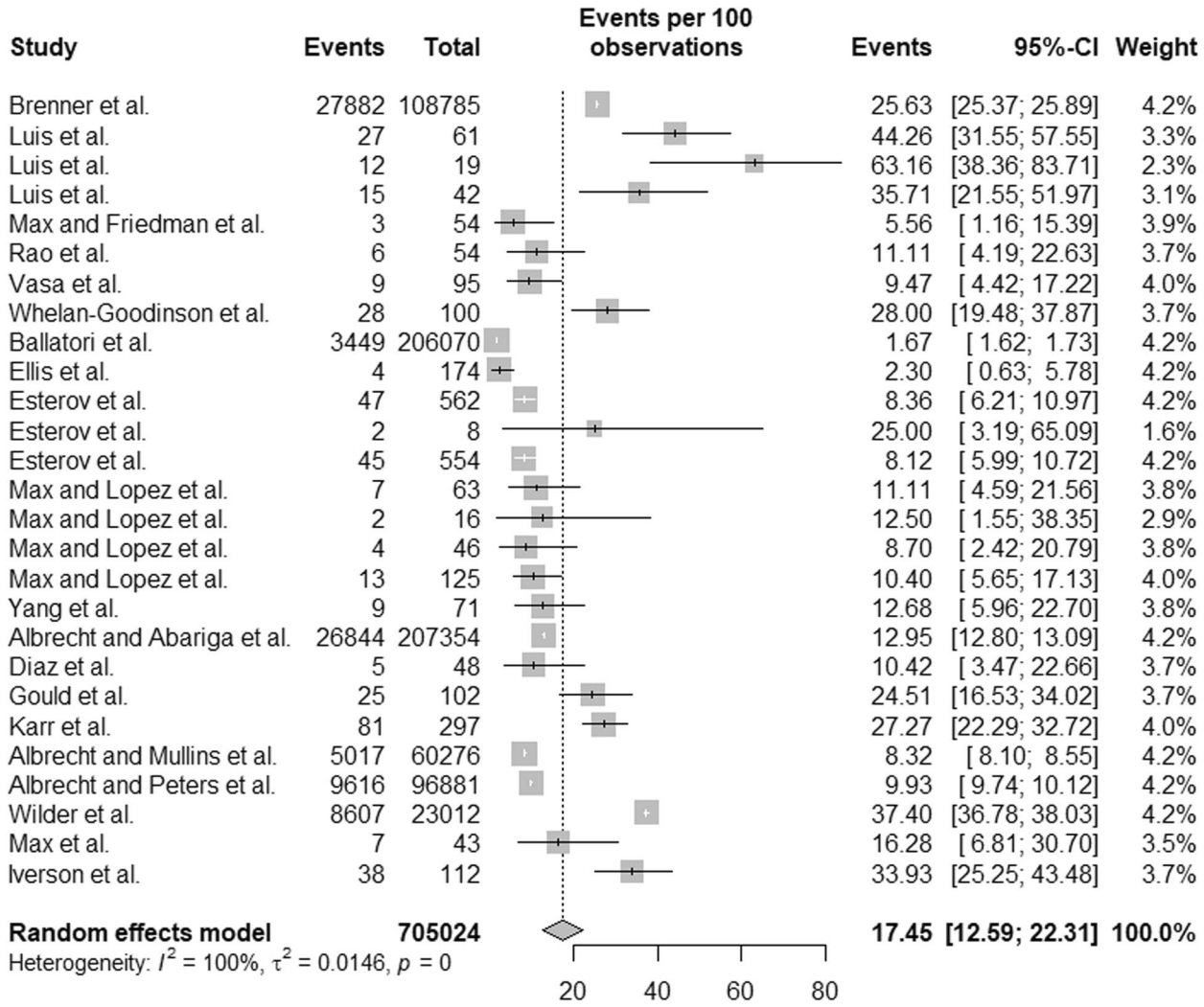


**Fig. 2** Results of meta-analysis for incident anxiety post traumatic brain injury

cross-sectional study included was also judged to be of low quality (Figure S1-3).

## Discussion

To the best of our knowledge, this is the first systematic review to calculate the incidence of anxiety symptoms following TBI. Pooling the results of 20 studies investigating novel cases of anxiety following TBI culminated in an incidence rate of 17.45% among 705,024 TBI patients. 2 reports to date have systematically examined anxiety in relation to TBI. The study by Osborn et al. [64] encompassed 41 studies and demonstrated that 11% of participants were diagnosed with generalized anxiety disorder and 37% reported clinically significant levels of anxiety following TBI. Moreover, anxiety diagnoses and symptomology were most prevalent 2 to 5 years post-injury. On the other hand, Scholten et al. [12] by excluding self-reported anxiety, estimated that the pooled prevalence of anxiety was 19% prior to TBI, and 21% in the first year after TBI. Pooled prevalence estimates increased over time and indicated high long-term prevalence of anxiety disorders (36%). Our meta-analysis is notable in that it provides the first estimate of the incidence of novel anxiety symptoms in the literature, helping to better understand this association. It should be noted that this pooled estimate was marked by a high degree of heterogeneity, which could be partly attributed to diagnostic criteria, interview schedules, and self-report measures, as noted by Osborn et al. The severity of TBI is another potential factor that may have contributed to this heterogeneity, yet our sub-group analyses showed this was not the case. Further direct comparisons are needed in the matter to ascertain our findings, especially on a moderate-severe TBI population. The type of anxiety appears

**Table 2** Sub-group analysis for the incidence of anxiety meta-analysis

| Sub-group | | Number of studies | Number of participants | Proportion (95CI), $I^2$ | *P*-value of sub-group difference |
|---|---|---|---|---|---|
| Type of anxiety | Anxiety disorder | 16 | 498,474 | 17.25% (11.99%, 22.52%), 100% | 0.82 |
| | Anxiety symptoms | 4 | 206,550 | 18.58% (4.24%, 32.92%), 98% | |
| Type of TBI | Mild TBI | 9 | 230,337 | 15.32% (6.25%, 24.39%), 100% | 0.64 |
| | Moderate-severe TBI | 6 | 232 | 19.57% (3.93%, 35.21%), 79% | |
| Type of anxiety disorder | Social anxiety | 4 | 318 | 2.52% (0.55%, 4.49%), 14% | < 0.01 |
| | Separation anxiety | 2 | 296 | 7.34% (0.11%, 14.57%), 79% | |
| | Specific phobia | 2 | 222 | 5.68% (2.29%, 9.08%), 19% | |
| | Generalized anxiety disorder | 8 | 23,607 | 14.09% (7.04%, 21.14%), 100% | |
| | Obsessive compulsive disorder | 3 | 266 | 4.57% (0.80%, 8.35%), 49% | |
| | Post-traumatic stress disorder | 4 | 23,278 | 9.71% (9.33%, 10.09%), 0% | |
| | Panic disorder | 4 | 23,279 | 5.16% (3.64%, 6.68%), 0% | |

*Abbreviations: TBI* Traumatic brain injury

**Table 3** Sub-group analysis for the relative risk of anxiety meta-analysis

| Sub-group | | Number of studies | Number of participants (TBI vs control) | RR (95CI), $I^2$ | *P*-value of sub-group difference |
|---|---|---|---|---|---|
| Type of anxiety | Anxiety disorder | 11 | 566,930 vs 1,636,443 | 2.25 (1.85, 2.73), 100% | < 0.01 |
| | Anxiety symptoms | 21 | 2,845 vs 3,732 | 1.58 (1.29, 2.93) 69% | |
| Type of TBI | Mild TBI | 23 | 39,328 vs 49,363 | 1.82 (1.41, 2.34), 94% | 0.16 |
| | Moderate-severe TBI | 7 | 4,602 vs 4,868 | 2.26 (1.92, 2.67), 10% | |

*Abbreviations: TBI* Traumatic brain injury, *RR* Relative risk

to be a potential factor explaining the heterogeneity, with TBI patients being at a higher risk for anxiety disorders compared to anxiety symptoms. Additionally, we found that the types of anxiety disorders developed after TBI appear to be mostly GAD and PTSD, and rarely social anxiety and OCD. This is in accordance with the previous literature, estimating that 3%—28% develop of TBI patients GAD, 13%—24% develop PTSD, and 2%—15% develop OCD [65].

Another main finding of this report was that pooling the data from 33 reports among 569,875 TBI patients and 1,640,312 non-TBI controls indicated a significant, 1.9-fold risk of anxiety symptomology relative to non-TBI counterparts, albeit with a high degree of heterogeneity. A similar analysis was previously conducted by Osborn et al. [64], calculating an odds ratio of 2.46 of developing clinically significant anxiety symptoms by pooling the data from 10 studies comparing TBI patients and control groups.

A notable consideration in studies evaluating TBI as a potential risk factor for anxiety disorders was the relatively substantial prevalence of pre-existing psychiatric conditions among patients who sustained TBIs, implying what appears to be circular causality between TBIs and psychiatric disorders [66]. In addition, While evidence concerning whether TBIs lead to substance use disorder (SUD) remains inconclusive, there is a presumption that individuals with SUD are generally at a higher risk of experiencing TBIs [67, 68]. As a result, a part of the increased rate of anxiety symptoms may stem from the pre-existing effects of substance use.

Various explanations have been proposed regarding the heightened risk of anxiety disorders following TBI. The first hypothesis is that anxiety symptoms following TBI may be attributed to a reduction in hippocampal size. Wilde et al. utilized imaging techniques to evaluate morphometric changes in children post-TBI, revealing remarkable volume loss in the hippocampus, amygdala, and globus pallidus, with the hippocampus being particularly affected to a larger extent, implying widespread hippocampal damage in TBI [69]. Consistent with this evidence, MRI reports have indicated reduced hippocampal size in patients with certain anxiety disorders [70, 71]. The second explanation is the alterations that occur in the structure and function of the amygdala, which is hallmarked by a significant decline

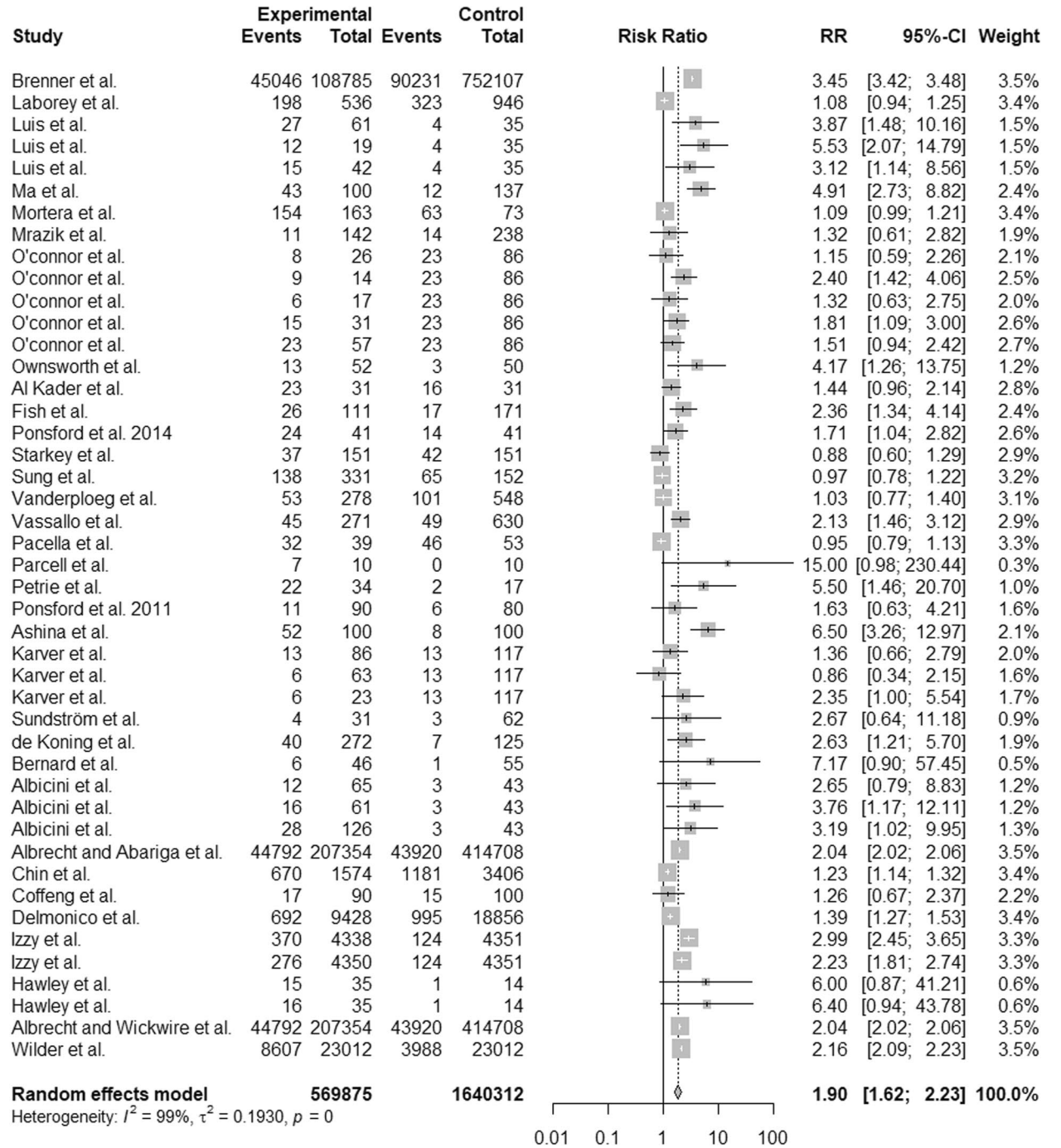


**Fig. 3** Results of meta-analysis for risk of anxiety symptoms after traumatic brain injury compared to control group

in GABAergic interneurons leading to a lower level of inhibition and consequently increased excitability in the amygdala. Additionally, heightened expression and activation of nicotinic acetylcholine receptors were observed post-TBI, exacerbating neuronal excitability within the basolateral amygdala. These mechanisms, among others, collectively contribute to hyperexcitability in the amygdala, ultimately inducing anxiety symptoms [72–76]. Other explanations, such as the dysregulation of the hypothalamo-pituitary-adrenal axis [77–79], remain incompletely recognized at the current state of the art and further research in this regard is necessary.

Our review has several limitations. Firstly, variations in the methodology of the included studies have resulted in a high degree of heterogeneity in our analysis, warranting exercising caution when interpreting our results. In addition, the observational nature of most studies included in this review restricts our ability to draw conclusions about cause-and-effect relationships. Lastly, while we aimed to explore the relative risk of each type of anxiety disorder and their correlation with TBI severity, there was not sufficient data to explore these aspects of the disorders in more depth.

To conclude, our systematic review and meta-analysis revealed a remarkable relative risk of anxiety symptoms in patients sustained TBI, supporting existing research that identifies TBI as a risk factor for anxiety disorders. In addition, we reported the incidence of anxiety symptoms in patients who sustained TBI. These results have implications for planning interventions for individuals with TBI. However, the limitations in explaining this association and the significant heterogeneity in our study underscore the need for cautious interpretation of these findings. Given the limitations and uncertainties in our conclusions, further research is recommended to establish more robust evidence in this context.

## Supplementary Information

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Supplementary Material 1.

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**Data Statement**
The data has not been previously presented orally or by poster at scientific meetings.

**Authors' contributions**
A.S, M.D, MR.M.: Conceptualization, Project Administration, Data curation, Writing- Original Draft, Writing – Review & Editing, Visualization I.M, M.D, S.R, M.M: Validation, Resources, Methodology, Software, Formal analysis, Writing – Original Draft S.O, A.A, M.G: Writing- Original Draft M.B.: Data curation.

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**Availability of data and materials**
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**Competing interests**
The authors declare no competing interests.

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