Title

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Journal

Journal of Neurosurgery, 124(2)

ISSN

0022-3085

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Publication Date

2016-02-01

DOI

10.3171/2015.2.jns14503

Peer reviewed

HHS Public Access

Author manuscript

J Neurosurg. Author manuscript; available in PMC 2017 February 01.

Published in final edited form as:

J Neurosurg. 2016 February ; 124(2): 511–526. doi:10.3171/2015.2.JNS14503.

Traumatic brain injury is associated with subsequent neurologic and psychiatric disease: a meta-analysis

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Abstract

Object—Mild traumatic brain injury (TBI) has been proposed as a risk factor for development of Alzheimer's disease, Parkinson's disease, depression, and other illnesses. This study's objective was to determine the association of prior mild TBI with subsequent diagnosis (i.e., at least one year post-injury) of neurologic or psychiatric disease.

Methods—All studies from 1995–2012 reporting TBI as a risk factor for diagnoses of interest were identified by searching PubMed, study references, and review articles. Reviewers abstracted the data and assessed study design and characteristics.

Results—57 studies met inclusion criteria. A random effects meta-analysis revealed a significant association of prior TBI with subsequent neurologic and psychiatric diagnosis. The pooled odds ratio (OR) for TBI on development of any illness was 1.67 (95% CI 1.44–1.93, $p<.001$). Prior TBI was independently associated with both neurologic [OR 1.55 (95% CI 1.31–1.83, $p<.001$)] and psychiatric [OR 2.00 (95% CI 1.50–2.66, $p<.001$)] outcomes. Analyses of individual diagnoses

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DISCLOSURES

Dr. Perry reports no competing interests. Dr. Pieper reports no competing interests. Mr. Bullock reports no competing interests. Dr. Guskiewicz reports no competing interests. Dr. Berger reports no competing interests. Dr. Kramer reports no competing interests.

found higher odds of Alzheimer's disease, Parkinson's disease, mild cognitive impairment, depression, mixed affective disorders, and bipolar disorder in individuals with previous TBI compared to those without TBI. This association was present when examining only studies of mild TBI and when considering the influence of study design and characteristics. Analysis of a subset of studies found no evidence that multiple TBIs were associated with higher odds of disease than a single TBI.

Conclusions—History of TBI, including mild TBI, is associated with the development of neurologic and psychiatric illness. This indicates that either TBI is a risk factor for heterogeneous pathologic processes or that TBI may contribute to a common pathologic mechanism.

Keywords

dementia; psychiatry; head injury; meta-analysis

INTRODUCTION

Since the 1928 description of the "punch drunk" condition,[48] there has been speculation about a connection between traumatic brain injury (TBI) and late-life neurologic or psychiatric illness. Though this syndrome was later referred to as "dementia pugilistica" because it was thought to uniquely affect boxers,[14] an accumulation of cases in recent years have suggested that repeated brain injury in other sports such as football, soccer, and wrestling might also predispose to neurodegenerative disease[52] and that non-sports-related TBI, such as that sustained on the battlefield, can lead to this same illness.[30] It has recently been proposed that a history of even minor brain injury may predispose certain individuals to develop this pathologic process, now referred to as "chronic traumatic encephalopathy" or CTE[52]. The presentation of CTE is variable and may include neurologic and/or psychiatric manifestations. The current CTE literature suggests two common syndromes: a behavior and mood predominant illness, frequently accompanied by paranoia, which would be diagnosed as psychiatric illness and a predominantly cognitive disorder that is frequently diagnosed as Alzheimer's disease [82]. A third syndrome, which was emphasized by the prior literature on boxers includes motor dysfunction with parkinsonism[14]. Some CTE cases have also been described with motor neuron disease[53, 54]. Epidemiological study of CTE has been significantly limited since it is a pathological, rather than clinical diagnosis, and its presence can only be definitively confirmed after death. There is accumulating evidence, however, that CTE may be a pathologic process that unites seemingly disparate clinical syndromes and reflects a shared vulnerability to cognitive-behavioral-motor dysfunction. Recent studies have found support for a relationship between TBI and risk for later development of these individual neurologic and psychiatric syndromes. Since James Parkinson himself theorized a causative link to trauma in 1817, there has been continuing debate regarding the relationship between TBI and Parkinson's disease,[19] with many[17, 29, 87] but not all[3, 43, 49] studies finding a positive association. Epidemiological studies investigating the risk of Alzheimer's disease after TBI have also shown mixed results. Meta-analyses of these studies in 1991[58] and in 2003[24] have shown an elevated risk. Prior TBI has also been associated with a significantly elevated risk of frontotemporal dementia[70] and although a prior meta-analysis of the risk of TBI on development of amyotrophic lateral sclerosis (ALS) showed a mildly elevated risk,[11]

others have disputed the connection.[93] Although psychiatric symptoms (e.g., depression and anxiety) are common acutely after TBI,[6, 35, 40] whether there are protracted psychiatric sequelae from earlier-life TBI remains poorly understood.[96]

Our aim was to determine the association of mild TBI with the later development of those neurologic and psychiatric illnesses that have previously been linked to TBI and are potential manifestations of CTE. To investigate the wide range of disorders associated with prior TBI, we reviewed the literature examining TBI and subsequent neurologic or psychiatric diagnoses and performed a meta-analysis according to current guidelines[56, 84]. Consistent with the notion that mild TBI may make certain individuals vulnerable to a number of neurologic and psychiatric conditions, we hypothesized that there would be an association between all diagnoses and a history of TBI, including mild TBI.

METHODS

Identification of the studies

Searches were conducted in Medline (1995 to February 2012) using a comprehensive search strategy. We used two components in each search: component A identified papers with keywords “craniocerebral trauma,” “head injury,” “brain injury,” or “concussion.” This was combined with component B or component C. Component B identified papers pertaining to the neurologic disorders of interest (i.e., “neurodegenerative diseases," "mild cognitive impairment," "Alzheimer," "Parkinson," "frontotemporal dementia," "amyotrophic lateral sclerosis," "vascular dementia," or "dementia"), and component C identified papers pertaining to the psychiatric illnesses of interest (i.e., "anxiety disorders," "mood disorders," or "schizophrenia and disorders with psychotic features"). We limited our search to papers in English and humans.

Three additional steps were taken to ensure search comprehensiveness: (1) references from included papers were reviewed, (2) to avoid any bias toward positive results inherent in the search strategy an additional search for “risk factors” for each diagnosis was performed to capture studies with weak or null findings that did not include our search terms in their title, abstract or keywords, (3) the citation lists in review papers were examined. For papers in which the required metrics were not easily identified the authors were contacted. A pair of reviewers (a neurologist and a neuropsychologist) discussed all papers at each stage of the process (Figure 1). Concordance between the reviewers for determining study inclusion was high; in cases of disagreement, studies were discussed until a consensus decision was reached. Ethics committee approval was not needed for this study as it included only analysis of previously published data.

Broad inclusion criteria

We first applied broad inclusion criteria (developed by a team of expert neurologists, neurosurgeons, and neuropsychologists) to select papers for further review.

- Original, peer-reviewed research articles (no case reports)
- Adult subjects over 18 years of age at the time of evaluation (not TBI)

- Presence of TBI without accompanying structural lesion (e.g., subdural hematoma or penetrating brain injury). Though our goal was to specifically examine the effect of mild TBI, in order to capture all pertinent studies, at this search stage we broadly included studies employing the various definitions and labels that are used to refer to minor head trauma (e.g., concussion).
- Presence of neurologic or psychiatric diagnosis
- TBI occurred before the diagnosis of the neurologic or psychiatric disorder (with at least 12 months between the TBI and outcome diagnosis, if specified)

Narrow inclusion criteria

Papers that met broad inclusion criteria were next reviewed in detail. In addition to ensuring adherence to broad criteria, we also confirmed that they met narrow inclusion criteria. If some subjects in a study were reported to have structural lesions, but they could be separated from those without lesions, we only included subjects with mild TBI.

1. *Presence of neurologic or psychiatric disorder*. For neurologic disorders, studies must have utilized consensus diagnostic criteria or clinical evaluation. For psychiatric disorders, diagnoses were based on either criteria (e.g., DSM-IV) or scores from standardized measures (e.g., Beck Depression Inventory).
2. *Inclusion of a control group*. Included studies were cross-sectional, cohort, or case-control studies in which all subjects underwent identical assessment and diagnostic procedures.
3. *TBI preceded neurologic or psychiatric diagnosis*. We excluded studies that reported that the diagnosis of the neurologic or psychiatric disorder had been made less than 12 months post-TBI. For studies in which the date of the TBI was not reported, we included studies of subjects with neurologic or psychiatric illness who were asked about TBI earlier in life.
4. *No redundant subjects across studies*. In cases where multiple papers used the same study cohort we included the most recent papers to capture the largest sample size. If multiple outcome diagnoses were reported in one paper, we included each odds ratio (OR) if the diagnoses were mutually exclusive. If the diagnoses were not mutually exclusive, in the analyses that examined the association of TBI with any neurologic or psychiatric outcome, we chose the broader diagnosis (e.g., dementia was preferred over Alzheimer's disease) or, if that distinction was not possible, we chose the diagnosis with the larger number of subjects.

Assessment of study characteristics

We recorded additional data regarding factors that could influence the relationship between TBI and outcome diagnoses. These included (1) the rigor with which each study employed a 12-month TBI-outcome diagnosis interval, (2) the TBI characteristics required in each study (e.g., whether subjects met accepted criteria for mild TBI or had any individual symptoms such as loss of consciousness), (3) whether the TBI diagnosis was based on patient or informant self-report as opposed to being made by a clinician, derived from medical records,

or based on diagnostic criteria, (4) the study design (cohort, case-control, or cross-sectional), and (5) whether information was provided regarding the number of TBIs sustained by each subject. These data were used in subgroup analyses geared towards assessing whether study characteristics influenced the meta-analysis results.

Statistical Analysis

Primary analyses—The effect of interest for this meta-analysis was the pooled OR. For the majority of the studies (51/57), unadjusted ORs were directly calculated from data extraction. Standard errors were calculated from the logarithm of the OR to allow for symmetry of the estimate on both sides of unity.[23] Where sample sizes were not available the published unadjusted ORs were used. We then applied standard meta-analytic techniques,[34] including weighted estimates of the pooled OR with a 95% confidence interval (CI). For those studies where the raw cell frequencies did not exist and only the standard error of the OR was available, to provide appropriate weighting of the study in the meta-analysis, the standard error of the OR was transformed to the standard error of the logarithm of the OR by linear interpolation. To determine whether there was significant variation among studies, tests of heterogeneity were performed.[34] All analyses were conducted using SAS v9.3 (Cary, NC).

Subgroup analyses—Since the overall analysis was inclusive of various TBI definitions and study characteristics, we next conducted seven additional subgroup analyses to examine whether our results differed when pooling studies with more uniformity of TBI assessment, TBI diagnostic criteria, and study design. When possible, we selected out only those subjects from the total study that met criteria for each subgroup analysis. The result is that for some studies a different number of subjects was included in the overall analysis compared to each subgroup analysis.

Subgroup 1: Effect of time interval between TBI and diagnosis

1. Clearest interval - To ensure that studies with less stringent guidelines about timing of TBI were not significantly impacting our results, we excluded studies with the possibility that some subjects had a less than 12 month interval between TBI and diagnosis.

Subgroups 2–4: Effect of TBI features and severity

2. Brief loss of consciousness – This subgroup included only studies that required that loss of consciousness not exceed 30 minutes. This is the maximum duration established in the mild TBI criteria of the American Congress of Rehabilitation Medicine, Centers for Disease Control, and World Health Organization[10, 42, 59].
3. Required loss of consciousness – We included only studies that required brain injury with loss of consciousness. This subgroup considered the effect of TBI with a uniform minimum severity.
4. Any mild TBI feature – In order to exclude extremely mild or asymptomatic brain injury we performed an analysis including only those studies that required the brain injury be accompanied by any one (or more than one) common feature

of mild TBI, including loss of consciousness, post-traumatic amnesia, Glasgow Coma Scale (GCS) score ≥13, focal neurological deficit, altered mental status, brain injury requiring medical care, or symptoms of the postconcussive syndrome (e.g., headache, dizziness, nausea, photo- or phonophobia, fatigue, sleep difficulty, blurred vision).

Subgroups 5–6: Effect of study design

5. Excluding self-report - In order to assess the impact of recall bias we conducted an additional analysis excluding studies with self-reported TBI.

6. Cohort studies - To eliminate recall bias we also performed an analysis including only cohort studies (rather than cross-sectional or case-control).

Subgroup 7: Effect of number of TBI

7. Repeated injury - Because we were also interested in whether there is a dose effect of TBI on development of later illness, we conducted an additional analysis in which we calculated the odds of neurologic or psychiatric diagnosis in subjects with more than one TBI compared to a single TBI using a subset of studies that provided this information.

Publication bias analysis—To assess for the effect of publication bias on our results we used the Egger method[18] to examine whether the logarithm of the included ORs are predicted by the standard error, which reflects the sample size. We visually examined funnel plots of OR against sample size and the logarithm of the OR against the standard error of the logarithm of the OR and quantified the degree of bias by multiple regression. Using standard error rather than sample size in funnel plots may provide a more accurate visual depiction of whether bias is present[83].

RESULTS

57 papers met narrow inclusion criteria and were used in the meta-analyses[3, 11, 17, 29, 43, 49, 70, 87 1, 2, 5, 7, 8, 9, 15, 16, 20, 22, 25, 27, 31, 32, 33, 37, 45, 47, 51, 55, 57, 60, 61, 62, 63, 64, 65, 67, 68, 69, 71, 72, 73,]. Among the included papers, a sufficient number were found to apply meta-analytic methods for the diagnoses of dementia, Alzheimer's disease, Parkinson's disease, ALS, mild cognitive impairment, depression, psychotic disorders, bipolar disorder, and mixed affective disorder (a combined group of depression and anxiety). Insufficient numbers of studies were found to calculate a pooled OR for frontotemporal dementia, vascular dementia, or anxiety disorders. There was significant heterogeneity among studies ($Q = 381.99$, $df = 58$, $p<.001$), justifying the use of the random effects meta-analysis.

Prior TBI was associated with development of any of the neurologic and psychiatric illnesses of interest [OR 1.67 (95% CI 1.44–1.93), $p<.0001$]. This association was found for both neurologic [OR 1.55 (95% CI 1.31–1.83, $p<.0001$)] and psychiatric [OR 2.00 (95% CI 1.50–2.66, $p<.0001$)] disease in individuals with TBI, and was also found in the following diagnoses: Alzheimer's disease [OR 1.40 (95% CI 1.02–1.90, $p<.05$)], Parkinson's disease

[OR 1.45 (95% CI 1.18–1.78, $p<.001$)], mild cognitive impairment [OR 2.69 (95% CI 1.51–4.77, $p<.001$)], depression [OR 2.14 (95% CI 1.65–2.77, $p<.0001$)], bipolar disorder [OR 1.85 (95% CI 1.17–2.94, $p<.01$)], and mixed affective disorder [OR 1.84 (95% CI 1.50–2.66, $p<.0001$)]. See Table 1 and Figure 2.

Analyses of subgroups revealed a robust relationship between TBI and remote neurologic and psychiatric outcomes. The studies included in each subgroup analysis are specified in Table 1. Table 2 includes the features reported in each study regarding the time interval between TBI and diagnosis, the TBI features and severity, and the study design. Results of the subgroup analyses are reported in Table 3. Overall odds and the independent OR for neurologic, but not psychiatric disease remained significant when only including studies with the clearest greater than 12-month interval between TBI and diagnosis (Subgroup 1). The overall OR was significant among those studies that adhered to mild TBI criteria limiting duration of loss of consciousness to less than 30 minutes (Subgroup 2). The overall OR and OR for any of the studied neurologic and psychiatric diagnoses were also significant when only including studies that required loss of consciousness (Subgroup 3). When including studies that required the presence of at least one mild TBI symptom (Subgroup 4), the overall OR and OR for any of the neurologic and all psychiatric diagnoses of interest remained significant. After eliminating the studies with TBI diagnoses based on self-report (Subgroup 5), the overall OR and OR for neurologic disorders remained significant, though the OR for psychiatric outcomes no longer reached significance. When only cohort studies were included (Subgroup 6), the OR for neurologic outcomes was not significant though the overall OR and OR for psychiatric illness remained significant. The odds were not higher among those that reported more than one TBI compared to those with a single injury (Subgroup 7).

Publication bias analyses did not show evidence of bias in the included studies. Visual inspection of a funnel plot based on sample size showed that three studies with large samples strongly influenced the appearance (Figure 3A). When these studies are removed a more expected funnel shape is appreciated (Figure 3B). Regression indicates that the effects size (the logarithm of the OR) is not significantly predicted by the standard error when all studies are included ($F(1,60)=3.08$, $p=.08$) or when the three large sample studies are excluded ($F(1,57)=1.11$, $p=.30$, Figure 3C).

DISCUSSION

This meta-analysis supports an association between prior TBI and later diagnosis of the relevant neurologic or psychiatric diseases. This association was found independently for both neurologic and psychiatric outcomes. Alzheimer's disease, Parkinson's disease, mild cognitive impairment, depression, mixed affective disorders, and bipolar disorder showed a statistically significant association with prior TBI. The magnitude of effect is comparable across diagnoses, with mild cognitive impairment, depression, and bipolar disorder having the highest OR among those results that reached significance. The OR of Alzheimer's disease in this analysis is comparable to the findings of prior meta-analyses.[24, 58] The OR of ALS was among the highest in the study, and there was some evidence of an association of TBI with dementia and psychotic disorders, but these did not reach statistical significance.

The overall combined OR for the selected neurologic and psychiatric illnesses and for neurologic illness independently in individuals with TBI remained significant when including only articles that explicitly specified a minimum 12-month interval between TBI and outcome diagnosis. The magnitude of association with psychiatric illness, however, did not remain significant. These results suggest that there may be a different time course in which psychiatric and neurologic symptoms manifest after TBI. While psychiatric symptoms are common in the acute phase after mild TBI[6, 21, 35, 40] and some of these may be short-lived manifestations of the injury, others may reflect a more sustained susceptibility to mental illness. The results of this study suggest that TBI is a risk factor for both remote psychiatric and neurologic disease and are consistent with the possibility that both types of illness arise secondary to a common shared pathologic mechanism.

We conducted additional subgroup analyses to determine whether TBI characteristics or methodological factors would influence our findings. The overall OR of TBI remained significant when including only studies that required adherence to typical loss of consciousness criteria for mild TBI, the presence of any specific mild TBI symptom, or loss of consciousness. Though TBI definitions varied widely among studies, these additional analyses support an association of mild TBI with the studied neurologic and psychiatric outcomes. A significant OR for combined neurologic and psychiatric outcomes was also found when eliminating studies that used self-reported diagnosis of TBI and when including only cohort studies. Though statistical significance was lost when assessing the association with psychiatric outcomes when eliminating self-report and the odds of neurologic outcomes among cohort studies, the magnitudes of the ORs were largely consistent with the main analysis, and the change in significance is likely due to the small number of articles in these analyses and resulting loss of power rather than reflecting a weaker association due to recall bias, though this cannot be excluded. Our analyses also suggest that the finding of an association with TBI is unlikely to be due to publication bias, though low power may affect the publication bias test.

The results of this meta-analysis support an association of illness with a single TBI. A relevant associated question is whether this effect is compounded by multiple TBIs. In our analysis of multiple head traumas, the results do not show strong evidence for elevated odds of illness associated with having more than one head trauma compared to a single TBI. Given that only six studies were included in this analysis, lower power may have influenced these results. More research on the relationship between TBI exposure and diagnostic outcomes is needed.

The magnitude of the OR of TBI in this meta-analysis is relatively modest, but comparable to other strongly implicated risk factors. For example, for Alzheimer's disease, the Apolipoprotein E e4 allele is associated with an OR of 1.80–9.05,[41] and obesity with an OR of 1.80.[4] The OR for pesticide exposure and Parkinson's disease is 1.94.[66] Therefore, the presence of a risk factor in an individual does not indicate an inevitable development of disease. The ORs found in this study suggest that others factors modify an individual's susceptibility to develop a neuropsychiatric disorder after TBI. These factors are largely unknown and worthy of further investigation.

The fact that multiple neurodegenerative and psychiatric diagnoses are associated with the same exposure raises questions about possible mechanisms of shared vulnerability. Trauma could predispose the brain to different types of neurodegeneration through common mechanisms such as oxidative stress and microglial activation[77, 99] or induction of plasma proteins associated with degeneration such as MCP-1.[36] Trauma might also activate molecular pathways leading to specific degenerative diseases, such as the finding that Alzheimer's disease-associated proteins including beta amyloid, beta secretase, presenilin-1, and caspase-3 accumulate in axons of brain injured animals.[12] Cleaved forms of the tau protein, which is associated with Alzheimer's disease and frontotemporal lobar degeneration, accumulate after trauma[26] and tau abnormalities after trauma have been found to be independent of beta amyloid effects.[89] The nature of the TBI could also influence the clinical presentation in an individual. For example, boxers may suffer from more torsional injury that could injury brainstem structures such as the substantia nigra, leading to parkinsonism[82]. Genetic variation could also help to explain the susceptibility of individuals to late-life effects of TBI. For example, apolipoprotein E, which is associated with risk of Alzheimer's disease, has shown a variable interaction with mild TBI.[50, 63, 88]

An alternate explanation for the association across diagnostic groups is that the various clinical presentations could be different expressions of a common pathology[28, 78]. Although CTE has been described as a distinct pathological process, the clinical characterization is not clearly established, and case reports suggest cognitive, motor, and psychiatric presentations. This phenotypic variability could lead to a diagnosis of dementia, Parkinson's disease, motor neuron disease, or primary psychiatric illness in different individuals. A study of causes of death among retired National Football League players found a three-fold higher rate of dying from neurodegenerative disease compared to the typical population frequency, with Alzheimer's disease and ALS being the most overrepresented[44], which would be consistent either a shared vulnerability hypothesis across neurodegenerative diseases or a common pathology. This meta-analysis examined clinical, not pathological, studies. Thus, it is unknown whether any of the subjects would have shown characteristic CTE pathology rather than (or in addition to) the more typical neuropathological features associated with their syndromes.

Among the articles that were reviewed, several addressed the association between TBI and clinical outcomes among athletes. These articles assessed the risk of Parkinson's disease among retired Thai traditional boxers,[46] depression and dementia among retired football players,[32, 33] ALS or chronic encephalopathy among soccer players,[13, 39] and chronic TBI in boxers.[38] Only two of the articles[32, 33] that directly evaluated TBI in sports met strict inclusion criteria for this study. The ability of this meta-analysis to inform the questions surrounding the long-term consequences of sports-related mild TBI is therefore limited by this lack in the existing literature. Further longitudinal studies among athletes with appropriate control groups, characterization of head injuries (including severity, number, and exposure to repetitive subconcussive trauma), and assessment of late-life neurologic and psychiatric outcomes will be needed to address this question.

Several limitations of this meta-analysis warrant consideration. One is the possible bias of the included studies. We took several steps to mitigate this possibility. Our search strategy

included a variety of epidemiological studies that focused on many possible risk factors, not just TBI, thereby capturing negative studies that might otherwise have not been published. Our formal analyses also did not support publication bias. Although the strict inclusion criteria should reduce this possibility, variation in the studies themselves (e.g., different criteria for diagnosis of illness, or co-morbid environmental and genetic factors of the study population) limits the generalizability of the results. Variable study quality could also have resulted in heterogeneity, and it is possible that the presence of other confounding factors could have led to the observed association between TBI and later clinical outcomes. For example, patients who sustain a TBI as a result of a fall or motor vehicle accident may have other medical comorbidities (e.g., vascular disease or substance abuse) or differences in socioeconomic status that could predispose to neurologic or psychiatric illness. Another possibility is that the TBI itself could lead to injury of change in lifestyle that could modify risk of a mood disorder. Finally, ill patients who fall and suffer TBI may also undergo more medical testing and therefore be more likely to receive one of these neurologic or psychiatric diagnoses. Only English language studies were reviewed, which could have led to exclusion of some relevant studies. In spite of our criteria regarding an interval between TBI and illness onset, an alternative explanation for the observed association is that some head injuries may have been early manifestations of neurologic or psychiatric disease rather than an independent predisposing factor for illness. The authors of one of the studies concluded this reverse causality was responsible for their findings. They stratified the interval between TBI and diagnosis and found the association between TBI and Parkinson's was no longer present when only looking at TBI that occurred greater than 10 years prior to diagnosis[71].

A major strength of this meta-analysis was the inclusion of a variety of different neurologic and psychiatric outcomes rather than a single diagnosis. By focusing on diagnoses rather than self-reported symptoms or performance on cognitive tests, this study assessed outcomes of sufficient magnitude to affect quality of life. The included studies also come from countries around the world, allowing for more generalizable results. The literature search was comprehensive, making this a rigorous examination of the topic.

CONCLUSIONS

This study supports an association of TBI, including mild TBI, on subsequent development of neurologic and psychiatric illness, including Alzheimer's disease, Parkinson's disease, mild cognitive impairment, depression, mixed affective disorders, and bipolar disorder. Due to limitations and heterogeneity in the existing studies, prospective studies with uniform assessment will be needed to confirm this result and determine the risk conferred by the number and severity of TBI in different settings, such as sports or the military.

Acknowledgments

Dr. Sturm is supported by National Institute on Aging 1K23AG040127. Dr. Peterson is supported by National Cancer Institute Award KM1CA156687. Dr. Boeve receives research support from the National Institute on Aging (P50 AG016574, U01 AG006786, R01 AG032306, and R01 AG041797) and the Mangurian Foundation. Dr. Miller is funded by NIH grants P50AG023501, P01AG019724, P50 AG1657303, and the state of California. Dr. Welsh-Bohmer received funding from the National Institute of Aging (P30 AG28377), from private donors to the Joseph & Kathleen Bryan Alzheimer's Disease Center at Duke University, and from Takeda and Zinfandel Pharmaceutical companies.

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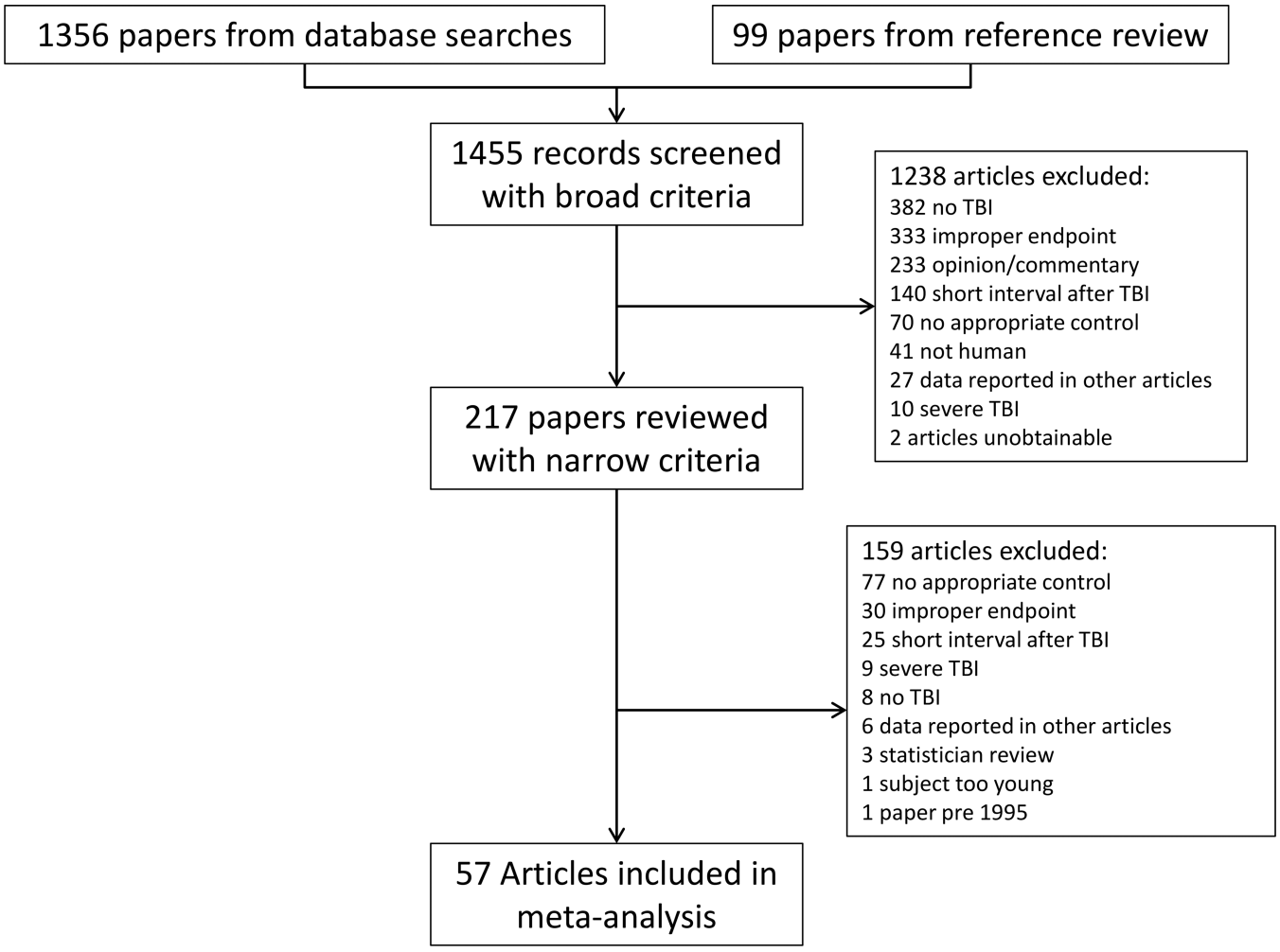

Figure 1.
Flow chart depicting study identification and screening

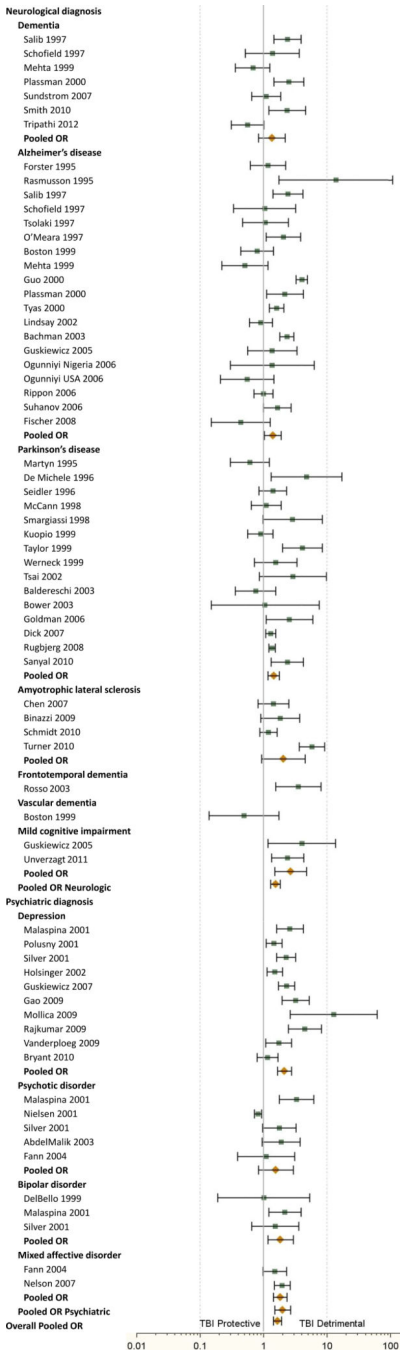

Figure 2.
Individual and pooled odds ratios for all included studies (to be aligned with Table 1).

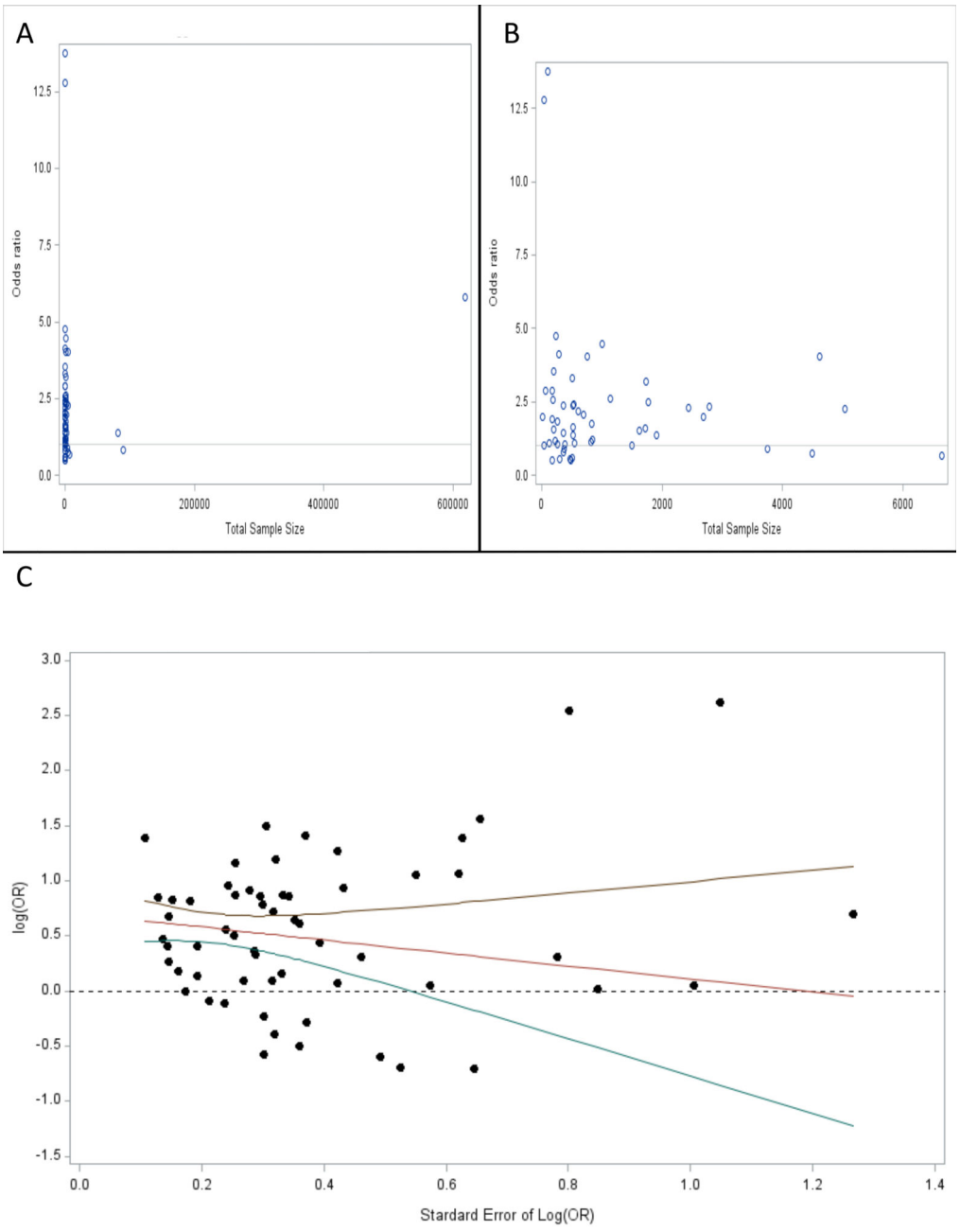

Figure 3.

Publication bias analysis. (A) Funnel plot of OR versus total sample size. (B) Funnel plot of OR versus total sample size after excluding the three studies with largest sample sizes (Rugbjerg 2008, Nielson 2001, and Turner 2010). (C) Plot of the logarithm of the OR after excluding the three largest sample size studies compared to the standard error of the logarithm of the OR showing a regression line and 95% confidence interval with slope that is not statistically significantly different from 0.

Table 1

Individual and pooled odds ratios for all included studies

Study	Cases (# with TBI/ # without TBI)	Controls (# with TBI/ # without TBI)	OR	95% CI
Neurological diagnosis				
Dementia				
Salib 1997[b,c,d,e]	96/266	23/153	2.40	1.46–3.95
Schofield 1997[b,e,g]	6/41	21/198	1.38	0.52–3.61
Mehta 1999[d,e,g]	11/118	788/5728	0.68	0.36–1.26
Plassman 2000[b,e,f,g]	28/26	520/1202	2.49	1.45–4.29
Sundstrom 2007[b,e,h]	25/156	46/316	1.10	0.65–1.86
Smith 2010[e]	31/14	154/164	2.36	1.21–4.60
Tripathi 2012[e]	22/128	35/115	0.56	0.31–1.02
Pooled OR			**1.36**	**0.84–2.19**
Alzheimer's disease				
Forster 1995[b]	25/84	22/87	1.18	0.62–2.25
Rasmusson 1995[b,d,e]	20/48	1/33	13.75	1.76–107.53
Salib 1997[a]	53/145	23/153	2.43	1.42–4.17
Schofield 1997[a]	4/34	23/205	1.05	0.34–3.22
Tsolaki 1997	14/47	15/54	1.07	0.47–2.45
O'Meara 1997[b,e]	32/317	16/326	2.06	1.11–3.82
Boston 1999	30/192	23/117	0.79	0.44–1.43
Mehta 1999[a]	6/85	788/5728	0.51	0.22–1.18
Guo 2000[e]	394/1782	127/2313	4.03	3.27–4.96
Plassman 2000[a]	17/18	520/1202	2.18	1.12–4.27
Tyas 2000	203/821	93/605	1.61	1.23–2.10
Lindsay 2002[g]	28/151	603/2963	0.91	0.60–1.38
Bachman 2003[e]	397/1538	84/760	2.34	1.82–3.00
Guskiewicz 2005[e]	15/7	1148/732	1.37	0.56–3.37
Ogunniyi Nigeria 2006[g]	2/60	11/450	1.36	0.30–6.30
Ogunniyi USA 2006[g]	5/84	37/344	0.55	0.21–1.45
Rippon 2006[e]	72/78	648/700	1.00	0.71–1.40
Suhanov 2006[d,e]	46/214	30/230	1.65	1.00–2.71
Fischer 2008[g]	4/86	37/352	0.44	0.15–1.27
Pooled OR			**1.40**	**1.02–1.90**
Parkinson's disease				
Martyn 1995[e]	11/156	35/301	0.61	0.30–1.23

Study	Cases (# with TBI/ # without TBI)	Controls (# with TBI/ # without TBI)	OR	95% CI
De Michele 1996[d,e]	13/103	3/113	4.75	1.32–17.16
Seidler 1996[e]	.	.	1.40	0.85–2.30
McCann 1998[d,e]	.	.	1.10	0.64–1.90
Smargiassi 1998[d,e]	13/73	5/81	2.88	0.98–8.49
Kuopio 1999[d,e,h]	39/84	84/162	0.90	0.56–1.42
Taylor 1999[b,e]	35/105	11/136	4.12	2.00–8.50
Werneck 1999	17/75	14/96	1.55	0.72–3.35
Tsai 2002[b,e]	11/19	5/25	2.89	0.86–9.75
Baldereschi 2003[d,e,g]	8/105	403/3980	0.75	0.36–1.56
Bower 2003[b,c,e,f]	2/183	2/193	1.05	0.15–7.57
Goldman 2006[b,c,e,h]	20/73	9/84	2.56	1.10–5.96
Dick 2007[d,e]	.	.	1.30	1.09–1.55
Rugbjerg 2008[b,e,f]	409/13194	1513/66792	1.37	1.22–1.53
Sanyal 2010	27/148	25/325	2.37	1.33–4.23
Pooled OR			**1.45**	**1.18–1.78**
Amyotrophic lateral sclerosis				
Chen 2007[b,e,h]	24/85	42/213	1.43	0.82–2.51
Binazzi 2009[b]	16/61	23/162	1.85	0.91–3.73
Schmidt 2010[b,e,h]	84/157	185/412	1.19	0.87–1.64
Turner 2010[b,e,f,g]	41/34	106552/511831	5.79	3.68–9.13
Pooled OR			**2.07**	**0.94–4.56**
Frontotemporal dementia				
Rosso 2003[b,e]	19/61	10/114	3.55	1.55–8.11
Vascular dementia				
Boston 1999	3/31	23/117	0.49	0.14–1.75
Mild cognitive impairment				
Guskiewicz 2005[e]	19/3	450/286	4.03	1.18–13.73
Unverzagt 2011[g]	.	.	2.40	1.34–4.30
Pooled OR			**2.69**	**1.51–4.77**
Pooled OR Neurologic			**1.55**	**1.31–1.83**
Psychiatric diagnosis				
Depression				
Malaspina 2001	107/661	22/355	2.61	1.62–4.21
Polusny 2001[b,c,e,g]	.	.	1.47	1.10–1.97
Silver 2001[e]	40/243	321/4430	2.27	1.60–3.23
Holsinger 2002[b,c,e,f,g]	96/160	387/974	1.51	1.14–2.00

Study	Cases (# with TBI/ # without TBI)	Controls (# with TBI/ # without TBI)	OR	95% CI
Guskiewicz 2007[e]	206/63	1272/893	2.30	1.71–3.08
Gao 2009	38/497	28/1174	3.21	1.95–5.28
Mollica 2009[d,e]	10/3	6/23	12.78	2.65–61.56
Rajkumar 2009[d,e]	19/108	33/840	4.48	2.46–8.15
Vanderploeg 2009[b,e,g]	36/43	242/505	1.75	1.09–2.79
Bryant 2010[b,c,e,f,g]	56/265	77/419	1.15	0.79–1.68
Pooled OR			**2.14**	**1.65–2.77**
Psychotic disorder				
Malaspina 2001	22/107	22/355	3.32	1.77–6.23
Nielsen 2001[b,e,f]	278/7854	3394/78710	0.82	0.72–0.93
Silver 2001[a]	12/89	349/4584	1.77	0.96–3.27
AbdelMalik 2003[b]	23/44	22/80	1.90	0.95–3.79
Fann 2004[a]	.	.	1.10	0.39–3.10
Pooled OR			**1.57**	**0.83–2.97**
Bipolar disorder				
DelBello 1999[b,c,d,e,g]	4/17	3/13	1.02	0.19–5.37
Malaspina 2001	28/207	22/355	2.18	1.22–3.91
Silver 2001[a]	6/51	355/4622	1.53	0.65–3.59
Pooled OR			**1.85**	**1.17–2.94**
Mixed affective disorder				
Fann 2004[b,f,g]	.	.	1.50	0.98–2.30
Nelson 2007[b]	76/248	318/2045	1.97	1.49–2.62
Pooled OR			**1.84**	**1.44–2.36**
Pooled OR Psychiatric			**2.00**	**1.50–2.66**
Overall Pooled OR			**1.67**	**1.44–1.93**

[a] Studies that were not included in the overall analysis or pooled neurologic/psychiatric analyses because diagnostic groups within the study were not mutually exclusive. Studies that were included in subgroup analyses:

[b] clearest interval between TBI and symptom onset,

[c] meeting mild TBI criteria for loss of consciousness,

[d] requiring loss of consciousness,

[e] requiring at least one mild TBI feature,

[f] TBI diagnoses not based on self-report,

[g] cohort studies, and

[h] analysis of risk of repeated TBI

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Table 2

Design and TBI features reported for each included study

Study	Study design	Age at head injury, mean	Interval between injury and diagnosis, mean	Required TBI characteristics	Additional TBI information
Neurological diagnosis					
Dementia					
Salib (1997)	Case-control		7.3 years	None given	Grouped by with or without LOC
Schofield (1997)	Cohort			LOC or PTA	
Mehta (1999)	Cohort		Grouped	LOC	Grouped by LOC< or > 15 minutes
Plassman (2000)	Cohort			MC and LOC or PTA or nondisplaced skull fracture	Excluded if penetrated dura or resulted in significant sequelae 3 months after TBI, severity ranked with mild group having LOC or PTA<30 minutes and no skull fracture
Sundstrom (2007)	Case-control		≥5 years	MC	
Smith (2010)	Cross-sectional			None given	
Tripathi (2012)	Case-control			LOC or PTA or a symptom of PCS	
Alzheimer's disease					
Forster (1995)	Case-control	Grouped (in adulthood or childhood)		None given	
Rasmusson (1995)	Case-control	27.2 in sporadic Alzheimer's group, 45.2 in familial Alzheimer's group	>5 years (mean 33.4 years in sporadic Alzheimer's group, 18.67 in familial Alzheimer's group)	None given	Excluded if head injury resulted in "immediate, permanent cognitive or functional impairment," head injury with LOC reported separately. Distinction made between mild and severe but not defined.
Salib (1997)	Case-control		7.9 years	None given	Grouped by with or without LOC
Schofield (1997)	Cohort		14.5 years	LOC or PTA	
Tsolaki (1997)	Case-control			None given	
O'Meara (1997)	Case-control	46 (range 10–85)	34 years (range 1-72)	MC or LOC	

Study	Study design	Age at head injury, mean	Interval between injury and diagnosis, mean	Required TBI characteristics	Additional TBI information
Boston (1999)	Case-control			None given	
Mehta (1999)	Cohort		Grouped	LOC	Grouped by LOC< or > 15 minutes
Guo (2000)	Case-control			MC or LOC	
Plassman (2000)	Cohort			MC and LOC or PTA or nondisplaced skull fracture	Excluded if penetrated dura or resulted in significant sequelae 3 months after TBI, severity ranked with mild group having LOC or PTA<30 minutes and no skull fracture
Tyas (2000)	Cross-sectional			None given	
Lindsay (2002)	Cohort			None given	Both with and without LOC
Bachman (2003)	Case-control			MC	
Guskiewicz (2005)	Cross-sectional			AMS and one symptom of PCS	
Ogunniyi Nigeria (2006)	Cohort			None given	
Ogunniyi USA (2006)	Cohort			None given	
Rippon (2006)	Cross-sectional			LOC or PTA	
Suhanov (2006)	Case-control			LOC	
Fischer (2008)	Cohort			None given	
Parkinson's disease					
Martyn (1995)	Case-control			LOC or MC	
De Michele (1996)	Case-control			LOC	
Seidler (1996)	Case-control			PTA or PCS	
McCann (1998)	Case-control			LOC	
Smargiassi (1998)	Case-control			LOC	
Kuopio (1999)	Case-control			None given	Records number with and without LOC and duration of LOC < or > 5 minutes
Taylor (1999)	Case-control	16.3	36.5 years	LOC or AMS or ND or PCS	
Werneck (1999)	Case-control			None given	
Tsai (2002)	Case-control	18.5	17.2 years	LOC or PTA or PCS or ND	
Baldereschi (2003)	Cohort			LOC	

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Study	Study design	Age at head injury, mean	Interval between injury and diagnosis, mean	Required TBI characteristics	Additional TBI information
Bower (2003)	Case-control		>3 years (range 3–55, median 29 years for TBI of all severities in study)	PTA	Excluded from this group if LOC>1 minute, PTA>30 minutes, or imaging abnormal. Mild TBI with LOC, moderate, and severe TBI analyzed separately
Goldman (2006)	Case-control	25.7	36.9 years (range 2–70), separate analysis reported of only those >10 years	LOC or PTA	
Dick (2007)	Case-control			LOC	
Rugbjerg (2008)	Case-control		Grouped, >1 year data used	MC	Excluded if imaging abnormal
Sanyal (2010)	Case-control			None given	
Amyotrophic lateral sclerosis					
Chen (2007)	Case-control	Grouped	Grouped	MC	
Binazzi (2009)	Case-control	Grouped	Grouped	None given	
Schmidt (2010)	Case-control	Grouped	Grouped (2–80+ years)	LOC or MC	
Turner (2010)	Cohort			MC	
Frontotemporal dementia					
Rosso (2003)	Case-control			PCS or LOC or PTA	
Vascular dementia					
Boston (1999)	Case-control			None given	
Mild cognitive impairment					
Guskiewicz (2005)	Cross-sectional			AMS and one symptom of PCS	
Unverzagt (2011)	Cohort			None given	
Psychiatric diagnosis					
Depression					
Malaspina (2001)	Case-control			None given	Severity grouped by LOC duration with “severe” TBI having LOC >15 minutes

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Study	Study design	Age at head injury, mean	Interval between injury and diagnosis, mean	Required TBI characteristics	Additional TBI information
Polusny (2001)	Cohort		>1 year (1–2.33 years)	AMS or LOC	LOC >20 minutes excluded
Silver (2001)	Cross-sectional			LOC or AMS	
Holsinger (2002)	Cohort	20.9 (includes some not in analysis)		MC + LOC or PTA or nondisplaced skull fracture	Excluded if penetrated dura or resulted in significant sequelae 3 months after TBI
Guskiewicz (2007)	Cross-sectional			AMS and one symptom of PCS	
Gao (2009)	Cross-sectional			None given	
Mollica (2009)	Cross-sectional			LOC, PTA, and ND	
Rajkumar (2009)	Cross-sectional			LOC	
Vanderploeg (2009)	Cohort		16 years	LOC or PTA or AMS	Excluded if admitted to hospital
Bryant (2010)	Cohort	37.8	1 year	GCS≥13	Excluded if focal deficit, imaging abnormal, or LOC>30 minutes
Psychotic disorder					
Malaspina (2001)	Case-control			None given	Severity grouped by duration LOC with “severe” TBI having LOC >15 minutes
Nielson (2001)	Case-control		Grouped (>1 year)	MC	ICD9 code for concussion included, excluded if skull fracture or intracranial hemorrhage
Silver (2001)	Cross-sectional			LOC or AMS	
AbdelMalik (2003)	Case-control	<17	Median 12 years		Closed head injuries without intracranial hemorrhage or other immediate sequelae
Fann (2004)	Cohort		3 years		By ICD9 codes - Excluded if imaging abnormal or LOC>1 hour
Bipolar disorder					
DelBello (1999)	Cross-sectional	10.7	6.3 years	LOC	
Malaspina (2001)	Case-control			None given	Severity grouped by duration LOC with “severe” TBI having LOC >15 minutes
Silver (2001)	Cross-sectional			LOC or AMS	

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Study	Study design	Age at head injury, mean	Interval between injury and diagnosis, mean	Required TBI characteristics	Additional TBI information
Mixed affective disorder					
Fann (2004)	Cohort		3 years		By ICD9 codes - Excluded if imaging abnormal or LOC>1 hour
Nelson (2007)	Cross-sectional		>1 year	None given	

"Grouped" refers to data presented in the paper by stratification or division of subjects into groups without an available mean.

AMS – alteration in mental status, GCS – Glasgow Coma Scale, LOC – loss of consciousness, MC – injury for which medical care was received, ND – Neurological deficit, PCS – post-concussion syndrome (e.g., headache, dizziness, nausea, photo- or phonophobia, fatigue, sleep difficulty, blurred vision), PTA – post-traumatic amnesia, TBI –traumatic brain injury

Table 3

Results of subgroup analyses

Analysis	Odds ratio	95 % confidence interval	Statistical significance
Risk of TBI when including only studies with clearest interval on:			
All neurologic and psychiatric outcomes	1.75	1.43–2.14	*p*<.001
All neurologic outcomes	2.05	1.55–2.71	*p*<.001
All psychiatric outcomes	1.38	0.95–2.00	*p*=.09
Risk of TBI when including only studies meeting mild TBI requirements for maximum duration of loss of consciousness	1.54	1.18–2.01	*p*=.001
Risk of TBI when including only studies requiring associated loss of consciousness on:			
All neurologic and psychiatric outcomes	1.69	1.18–2.44	*p*<.01
All neurologic outcomes	1.33	1.00–1.75	*p*<.05
All psychiatric outcomes	4.09	1.36–12.32	*p*=.01
Risk of TBI when including only studies requiring a mild TBI feature on:			
All neurololgic and psychiatric outcomes	1.70	1.42–2.05	*p*<.0001
All neurologic outcomes	1.67	1.36–2.07	*p*<.0001
All psychiatric outcomes	1.81	1.23–2.66	*p*<.01
Risk of TBI when eliminating studies with TBI diagnosis based on self-report on:			
All neurologic and psychiatric outcomes	1.62	1.14–2.31	*p*<.01
All neurologic outcomes	2.38	1.01–5.62	*p*<.05
All psychiatric outcomes	1.18	0.81–1.71	*p*=.39
Risk of TBI when including only cohort studies on:			
All neurologic and psychiatric outcomes	1.38	1.02–-1.87	*p*<.05
All neurologic outcomes	1.27	0.72–2.25	*p*=.41
All psychiatric outcomes	1.45	1.23–1.71	*p*<.0001
Risk of multiple TBIs vs one TBI on any outcome diagnosis	1.10	0.72–1.70	*p*=.65