Association of traumatic brain injury with subsequent neurological and psychiatric disease: a meta-analysis

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OBJECTIVE Mild traumatic brain injury (TBI) has been proposed as a risk factor for the 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 the subsequent diagnosis (that is, at least 1 year postinjury) of neurological or psychiatric disease.

METHODS All studies from January 1995 to February 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 designs and characteristics.

RESULTS Fifty-seven studies met the inclusion criteria. A random effects meta-analysis revealed a significant association of prior TBI with subsequent neurological and psychiatric diagnoses. The pooled odds ratio (OR) for the development of any illness subsequent to prior TBI was 1.67 (95% CI 1.44–1.93, $p < 0.0001$). Prior TBI was independently associated with both neurological (OR 1.55, 95% CI 1.31–1.83, $p < 0.0001$) and psychiatric (OR 2.00, 95% CI 1.50–2.66, $p < 0.0001$) outcomes. Analyses of individual diagnoses revealed higher odds of Alzheimer's disease, Parkinson's disease, mild cognitive impairment, depression, mixed affective disorders, and bipolar disorder in individuals with previous TBI as 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 demonstrated 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 neurological and psychiatric illness. This finding indicates that either TBI is a risk factor for heterogeneous pathological processes or that TBI may contribute to a common pathological mechanism.

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KEY WORDS dementia; psychiatry; head injury; meta-analysis; traumatic brain injury

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 neurological 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 has suggested that repeated brain injury in other sports, such as football, soccer, and wrestling, might also predispose to neurodegenerative

disease⁵² and that nonsports-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 can predispose certain individuals to develop this pathological process, now referred to as “chronic traumatic encephalopathy” (CTE).⁵² The presentation of CTE is variable and can include neurological and/or psychiatric manifestations. The current CTE literature suggests 2 common syndromes: a behavior- and mood-predominant

ABBREVIATIONS ALS = amyotrophic lateral sclerosis; CI = confidence interval; CTE = chronic traumatic encephalopathy; LOC = loss of consciousness; OR = odds ratio; TBI = traumatic brain injury.

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illness frequently accompanied by paranoia, which would be diagnosed as a psychiatric illness, and a predominantly cognitive disorder that is frequently diagnosed as Alzheimer's disease.⁸² A third syndrome, which was emphasized in the prior literature on boxers, includes motor dysfunction with parkinsonism.¹⁴ Some CTE cases have also been described with motor neuron disease.^{53,54} The epidemiological study of CTE has been significantly limited since it is a pathological rather than a clinical diagnosis and its presence can only be definitively confirmed after death. However, there is accumulating evidence that CTE may be a pathological 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 the risk for later development of these individual neurological 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 1991⁵⁸ and in 2003²⁴ 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 relationship between prior TBI and the subsequent development of amyotrophic lateral sclerosis (ALS) showed a mildly elevated risk,¹¹ others have disputed the connection.⁹³ Although psychiatric symptoms (for example, 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 clarify the association between mild TBI and the later development of those neurological and psychiatric illnesses that have 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 neurological or psychiatric diagnoses and performed a meta-analysis according to current guidelines.^{56,84} Given the notion that mild TBI may make certain individuals vulnerable to a number of neurological 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 Studies

Searches were conducted in MEDLINE (January 1995 to February 2012) using a comprehensive search strategy. We used 2 components in each search: component A identified papers with the key words "craniocerebral trauma," "head injury," "brain injury," or "concussion." This was combined with component B or C. Component B identified papers pertaining to the neurological disorders of interest (that is, "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 (that is, "anxiety disorders," "mood disorders," or "schizophrenia and disorders with psychotic features"). We limited our search to papers in English and in 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 key words; and 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 (Fig. 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); subjects older than 18 years of age at the time of evaluation (not TBI); TBI without accompanying structural lesion (for example, subdural hematoma or penetrating brain injury); although our goal was to specifically examine the effect of mild TBI, 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, for example, concussion); neurological or psychiatric diagnosis; and TBI occurred before the diagnosis of the neurological or psychiatric disorder (with at least 12 months between the TBI and outcome diagnosis, if specified).

Narrow Inclusion Criteria

Papers that met the broad inclusion criteria were next reviewed in detail. In addition to ensuring adherence to the broad criteria, we confirmed that papers met the 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 included only those subjects with mild TBI. The narrow inclusion criteria consisted of the following: 1) the presence of a neurological or psychiatric disorder. For neurological disorders, studies must have used consensus diagnostic criteria or clinical evaluation. For psychiatric disorders, diagnoses were based on either criteria (for example, those in the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*) or scores from standardized measures (for example, Beck Depression Inventory). 2) The study had a control group. Included studies were cross-sectional, cohort, or case-control studies in which all subjects underwent identical assessment and diagnostic procedures. 3) The TBI preceded the neurological or psychiatric diagnosis. We ex-

FIG. 1. Flowchart depicting study identification and screening.

cluded studies in which the diagnosis of the neurological 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 only those whose subjects with neurological or psychiatric illness had been asked about TBI earlier in life. 4) There could be 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 1 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 neurological or psychiatric outcome, we chose the broader diagnosis (for example, 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, including 1) the rigor with which each study employed a 12-month TBI–outcome diagnosis interval; 2) the TBI characteristics required in each study (for example, whether subjects met accepted criteria for mild TBI or had any individual symptoms such as loss of consciousness [LOC]); 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 about the number of TBIs sustained by

each subject. These data were used in subgroup analyses geared toward 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 of 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-analytical techniques,³⁴ including weighted estimates of the pooled OR with a 95% confidence interval (CI). For those studies in which 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 version 9.3 (SAS Institute Inc.). A *p* value < 0.05 was significant.

Subgroup Analyses

Since the overall analysis was inclusive of various TBI definitions and study characteristics, we conducted 7 additional subgroup analyses to determine whether our results differed when pooling studies with more uniformity of TBI assessment, TBI diagnostic criteria, and study de-

sign. When possible, we selected only those subjects from the overall cohort who met the criteria for each subgroup analysis. Consequently, for some studies, a different number of subjects was included in the overall analysis compared with each subgroup analysis.

Subgroup 1: Effect of Time Interval Between TBI and Diagnosis. To ensure that studies with less stringent guidelines about the timing of TBI were not significantly impacting our results, in Subgroup 1 we excluded analyses in which the subjects had possibly less than a 12-month interval between TBI and a diagnosis.

Subgroups 2–4: Effect of TBI Features and Severity. Subgroup 2 included only studies that required an LOC not exceeding 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}

Subgroup 3 included only studies that required brain injury with LOC. This subgroup considered the effect of TBI with a uniform minimum severity.

In Subgroup 4, to exclude extremely mild or asymptomatic brain injury, we performed an analysis of studies that required the brain injury to be accompanied by any 1 (or more than 1) common feature of mild TBI, including LOC, posttraumatic amnesia, Glasgow Coma Scale (GCS) score ≥ 13 , focal neurological deficit, altered mental status, brain injury requiring medical care, or symptoms of the postconcussive syndrome (for example, headache, dizziness, nausea, photo- or phonophobia, fatigue, sleep difficulty, blurred vision).

Subgroups 5–6: Effect of Study Design. In Subgroup 5, to assess the impact of recall bias, we conducted an analysis excluding studies with self-reported TBI. In Subgroup 6, to eliminate recall bias, we also performed an analysis of only cohort studies (rather than cross-sectional or case-control studies).

Subgroup 7: Effect of Number of TBIs. Because we were also interested in whether there is a dose effect of TBI on the development of later illness, in Subgroup 7 we calculated the odds of a neurological or psychiatric diagnosis in subjects with more than 1 versus 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 method¹⁸ to examine whether the logarithm of the included ORs were predicted by the standard error, which reflects the sample size. We visually examined funnel plots of ORs against sample size and the logarithm of the ORs against the standard error of the logarithm of the ORs and quantified the degree of bias by multiple regressions. Using standard error rather than sample size in funnel plots may provide a more accurate visual depiction of whether bias is present.⁸³

Results

Fifty-seven papers met the narrow inclusion criteria and were used in the meta-analysis.^{1–3,5,7–9,11,15–17,20,22,25,27,29,31–33,37,43,45,47,49,51,55,57,60–65,67–76,79–81,85–87,90–95,97,98} Among the in-

cluded papers, a sufficient number were found to apply meta-analytical 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 ($Q = 381.99$, $df = 58$, $p < 0.001$), justifying the use of the random-effects meta-analysis.

Prior TBI was associated with the development of any of the neurological and psychiatric illnesses of interest (OR 1.67, 95% CI 1.44–1.93, $p < 0.0001$). This association was found for both neurological (OR 1.55, 95% CI 1.31–1.83, $p < 0.0001$) and psychiatric (OR 2.00, 95% CI 1.50–2.66, $p < 0.0001$) diseases in individuals with TBI and was also found for the following diagnoses: Alzheimer's disease (OR 1.40, 95% CI 1.02–1.90, $p < 0.05$), Parkinson's disease (OR 1.45, 95% CI 1.18–1.78, $p < 0.001$), mild cognitive impairment (OR 2.69, 95% CI 1.51–4.77, $p < 0.001$), depression (OR 2.14, 95% CI 1.65–2.77, $p < 0.0001$), bipolar disorder (OR 1.85, 95% CI 1.17–2.94, $p < 0.01$), and mixed affective disorder (OR 1.84, 95% CI 1.50–2.66, $p < 0.0001$; Table 1 and Fig. 2).

Analyses of subgroups revealed a robust relationship between TBI and remote neurological 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 ORs for neurological, but not psychiatric, disease remained significant when including only studies with the clearest interval longer than 12 months between TBI and diagnosis (Subgroup 1). The overall OR was significant among studies that adhered to mild TBI criteria limiting the duration of LOC to less than 30 minutes (Subgroup 2). The overall OR and the ORs for any of the studied neurological and psychiatric diagnoses were also significant when including only studies that required LOC (Subgroup 3). When including studies that required the presence of at least 1 mild TBI symptom (Subgroup 4), the overall OR and the OR for any of the neurological and all psychiatric diagnoses of interest remained significant. After eliminating studies with TBI diagnoses based on self-reports (Subgroup 5), the overall OR and the OR for neurological disorders remained significant, although the OR for psychiatric outcomes no longer reached significance. When only cohort studies were included (Subgroup 6), the OR for neurological outcomes was not significant, although the overall OR and the OR for psychiatric illness remained significant. The odds were not higher among studies that reported more than 1 TBI versus 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 3 studies with large samples strongly influenced the appearance of the plot (Fig. 3A). When these 3 studies were removed, a more expected funnel shape could be appreciated (Fig. 3B). Re-

TABLE 1. Individual and pooled ORs for all included studies

Authors & Year	Cases (no. w/ TBI/no. w/o TBI)	Controls (no. w/ TBI/no. w/o 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
Sundström 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 ^a	11/156	35/301	0.61	0.30–1.23
De Michele 1996 ^{d,e}	13/103	3/113	4.75	1.32–17.16
Seidler 1996 ^a	NA	NA	1.40	0.85–2.30
McCann 1998 ^{d,e}	NA	NA	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}	NA	NA	1.30	1.09–1.55
Rugbjerg 2008 ^{b,e,f}	409/13,194	1513/66,792	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

(continued)

TABLE 1. Individual and pooled ORs for all included studies (*continued*)

Authors & Year	Cases (no. w/ TBI/no. w/o TBI)	Controls (no. w/ TBI/no. w/o TBI)	OR	95% CI
Neurological diagnosis (<i>continued</i>)				
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	106,552/511,831	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	NA	NA	2.40	1.34–4.30
Pooled OR			2.69	1.51–4.77
Pooled OR, neurological			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}	NA	NA	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
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 2002 ^{b,e,f}	278/7854	3394/78,710	0.82	0.72–0.93
Silver 2001a	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	NA	NA	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 2001a	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}	NA	NA	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

NA = data not available.

^a Studies not included in the overall analysis or pooled neurological/psychiatric analyses because diagnostic groups within the study were not mutually exclusive. Studies included in subgroup analyses: ^bthose with the clearest interval between TBI and symptom onset, ^cthose meeting mild TBI criteria for LOC, ^dthose requiring LOC, ^ethose requiring at least 1 mild TBI feature, ^fthose with TBI diagnoses not based on self-reports, ^gcohort studies, and ^hthose analyzing the risk of repeated TBI.

FIG. 2. Individual and pooled ORs for all included studies. Figure is available in color online only.

gression indicated that the effects size (the logarithm of the ORs) was not significantly predicted by the standard error when all studies were included ($F(1,60) = 3.08$, $p = 0.08$) or when the 3 large sample studies were excluded ($F(1,57) = 1.11$, $p = 0.30$; Fig. 3C).

Discussion

This meta-analysis supports an association between prior TBI and later diagnosis of the relevant neurological or psychiatric diseases. This association was found independently for both neurological 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, depres-

sion, and bipolar disorder having the highest OR among results that reached significance. The OR for Alzheimer's disease in this analysis is comparable to the findings of prior meta-analyses.^{24,58} The OR for 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 associations did not reach statistical significance.

The overall combined OR for the selected neurological and psychiatric illnesses and for neurological 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 neurological symptoms manifest after

TABLE 2. Summary of study and TBI features for each included study

Authors & Year	Study Design	Mean Age at Head Injury (yrs)	Mean Interval Btwn Injury & Diagnosis	Required TBI Characteristics	Additional TBI Information
Neurological diagnosis					
Dementia					
Saib 1997	Case-control		7.3 yrs	None given	Grouped as w/ or w/o LOC
Schofield 1997	Cohort			LOC or PTA	
Mehta 1999	Cohort		Grouped	LOC	Grouped by LOC $\leq$ or >15 min
Plassman 2000	Cohort			MC & LOC or PTA or non-displaced skull fracture	Excluded if penetrated dura or resulted in significant sequelae 3 mos after TBI; severity ranked w/ mild group having LOC or PTA <30 min & no skull fracture
Sundström 2007	Case-control		≥ 5 yrs	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 (adulthood or childhood)		None given	
Rasmusson 1995	Case-control	27.2 in sporadic Alzheimer's group, 45.2 in familial Alzheimer's group	>5 yrs (mean 33.4 yrs in sporadic Alzheimer's group, 18.67 yrs in familial Alzheimer's group)	None given	Excluded if head injury resulted in "immediate, permanent cognitive or functional impairment"; head injury w/ LOC reported separately; distinction made btwn mild & severe but not defined
Saib 1997	Case-control		7.9 yrs	None given	Grouped as w/ or w/o LOC
Schofield 1997	Cohort		14.5 yrs	LOC or PTA	
Tsolaki 1997	Case-control			None given	
O'Meara 1997	Case-control	46 (range 10–85)	34 yrs (range 1–72 yrs)	MC or LOC	
Boston 1999	Case-control			None given	
Mehta 1999	Cohort		Grouped	LOC	Grouped by LOC $\leq$ or > 15 min
Guo 2000	Case-control			MC or LOC	
Plassman 2000	Cohort			MC & LOC or PTA or non-displaced skull fracture	Excluded if penetrated dura or resulted in significant sequelae 3 mos after TBI; severity ranked w/ mild group having LOC or PTA <30 min & no skull fracture
Tyas 2000	Cross-sectional			None given	
Lindsay 2002	Cohort			None given	Both w/ & w/o LOC
Bachman 2003	Case-control			MC	
Guskiewicz 2005	Cross-sectional			AMS & 1 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	

(continued)

TABLE 2. Summary of study and TBI features for each included study (continued)

Authors & Year	Study Design	Mean Age at Head Injury (yrs)	Mean Interval Btwn Injury & Diagnosis	Required TBI Characteristics	Additional TBI Information
Neurological diagnosis (continued)					
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 w/ & w/o LOC & duration of LOC < or ≥ 5 min
Taylor 1999	Case-control	16.3	36.5 yrs	LOC or AMS or ND or PCS	
Werneck 1999	Case-control			None given	
Tsai 2002	Case-control	18.5	17.2 yrs	LOC or PTA or PCS or ND	
Baldereschi 2003	Cohort			LOC	
Bower 2003	Case-control		>3 yrs (range 3–55 yrs, median 29 yrs for TBI of all severities in study)	PTA	Excluded from this group if LOC >1 min, PTA >30 min, or imaging abnormal; mild TBI w/ LOC, moderate, and severe TBI analyzed separately
Goldman 2006	Case-control	25.7	36.9 yrs (range 2–70 yrs), separate analysis of only those w/ >10 yrs	LOC or PTA	
Dick 2007	Case-control			LOC	
Rugbjerg 2008	Case-control		Grouped, >1 yr data used	MC	Excluded if imaging abnormal
Sanyal 2010	Case-control			None given	
ALS					
Chen 2007	Case-control	Grouped	Grouped	MC	
Binazzi 2009	Case-control	Grouped	Grouped	None given	
Schmidt 2010	Case-control	Grouped	Grouped (2–80+ yrs)	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 & 1 symptom of PCS	
Unverzagt 2011	Cohort			None given	

(continued)

TABLE 2. Summary of study and TBI features for each included study (continued)

Authors & Year	Study Design	Mean Age at Head Injury (yrs)	Mean Interval Btwn Injury & Diagnosis	Required TBI Characteristics	Additional TBI Information
Psychiatric diagnosis					
Depression					
Malaspina 2001	Case-control			None given	Severity grouped by LOC duration w/ "severe" TBI having LOC >15 min
Polusny 2001	Cohort		>1 yr (1–2.33 yrs)	AMS or LOC	LOC >20 min excluded
Silver 2001	Cross-sectional			LOC or AMS	
Holsinger 2002	Cohort	20.9 (includes some not in analysis)		MC & LOC or PTA or non-displaced skull fracture	Excluded if penetrated dura or resulted in significant sequelae 3 mos after TBI
Guskiewicz 2007	Cross-sectional			AMS & 1 symptom of PCS	
Gao 2009	Cross-sectional			None given	
Mollica 2009	Cross-sectional			LOC, PTA, & ND	
Rajkumar 2009	Cross-sectional			LOC	
Vanderploeg 2009	Cohort		16 yrs	LOC or PTA or AMS	Excluded if admitted to hospital
Bryant 2010	Cohort	37.8	1 yr	GCS score ≥ 13	Excluded if focal deficit, imaging abnormal, or LOC >30 min
Psychotic disorder					
Malaspina 2001	Case-control			None given	Severity grouped by duration LOC w/ "severe" TBI having LOC >15 min
Nielsen 2002	Case-control		Grouped (>1 yr)	MC	ICD-9 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 yrs		Closed head injuries w/o intracranial hemorrhage or other immediate sequelae
Fann 2004	Cohort		3 yrs		By ICD-9 codes; excluded if imaging abnormal or LOC >1 hr
Bipolar disorder					
DeBello 1999	Cross-sectional	10.7	6.3 yrs	LOC	
Malaspina 2001	Case-control			None given	Severity grouped by duration of LOC w/ "severe" TBI having LOC >15 min
Silver 2001	Cross-sectional			LOC or AMS	
Mixed affective disorder					
Fann 2004	Cohort		3 yrs		By ICD-9 codes; excluded if imaging abnormal or LOC >1 hr
Nelson 2007	Cross-sectional		>1 yr	None given	

AMS = alteration in mental status; GCS = Glasgow Coma Scale; Grouped = data presented in the paper by stratification or division of subjects into groups without an available mean; MC = injury for which medical care was received; ND = neurological deficit; PCS = postconcussion syndrome (for example, headache, dizziness, nausea, photo- or phonophobia, fatigue, sleep difficulty, blurred vision); PTA = posttraumatic amnesia.

TABLE 3. Results of subgroup analyses

Analysis	OR	95% CI	p Value
Risk of TBI, including only studies w/ clearest interval			
All neurological & psychiatric outcomes	1.75	1.43–2.14	<0.001
All neurological outcomes	2.05	1.55–2.71	<0.001
All psychiatric outcomes	1.38	0.95–2.00	0.09
Risk of TBI, including only studies meeting mild TBI requirements for max duration of LOC	1.54	1.18–2.01	0.001
Risk of TBI, including only studies requiring associated LOC			
All neurological & psychiatric outcomes	1.69	1.18–2.44	<0.01
All neurological outcomes	1.33	1.00–1.75	<0.05
All psychiatric outcomes	4.09	1.36–12.32	0.01
Risk of TBI, including only studies requiring a mild TBI feature			
All neurological & psychiatric outcomes	1.70	1.42–2.05	<0.0001
All neurological outcomes	1.67	1.36–2.07	<0.0001
All psychiatric outcomes	1.81	1.23–2.66	<0.01
Risk of TBI, eliminating studies w/ TBI diagnosis based on self-report			
All neurological & psychiatric outcomes	1.62	1.14–2.31	<0.01
All neurological outcomes	2.38	1.01–5.62	<0.05
All psychiatric outcomes	1.18	0.81–1.71	0.39
Risk of TBI, including only cohort studies			
All neurological & psychiatric outcomes	1.38	1.02–1.87	<0.05
All neurological outcomes	1.27	0.72–2.25	0.41
All psychiatric outcomes	1.45	1.23–1.71	<0.0001
Risk of multiple TBIs vs 1 TBI on any outcome diagnosis	1.10	0.72–1.70	0.65

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 neurological disease and are consistent with the possibility that both types of illness arise secondary to a common shared pathological mechanism.

We conducted additional subgroup analyses to determine whether TBI characteristics or methodological factors would influence our findings. The overall OR for TBI remained significant when including only studies that required adherence to typical LOC criteria for mild TBI, the presence of any specific mild TBI symptom, or LOC. Though TBI definitions varied widely among studies, these additional analyses supported an association of mild TBI with the neurological and psychiatric outcomes of interest. A significant OR for combined neurological and psychiatric outcomes was also found when eliminating studies that used self-reported diagnoses of TBI and when including only cohort studies. Though statistical significance was lost when assessing the association with psychiatric outcomes when eliminating self-reports and the odds of neurological outcomes among cohort studies, the magnitudes of the ORs were largely consistent with the main analysis, and the change in significance was probably attributable to the small number of articles in these analyses and the resulting loss of power rather than a reflection of a weaker association due to recall bias, although

this cannot be excluded. Our analyses also suggested that the finding of an association with TBI is unlikely to be attributable to publication bias, although low power may affect the publication bias test.

The results of our meta-analysis support an association between illness and 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 1 head trauma versus a single TBI. Given that only 6 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 for 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* $\epsilon 4$ 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 other factors modify an individual's susceptibility to develop a neuropsychiatric disorder after TBI. These factors are largely unknown and thus 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

FIG. 3. Publication bias analysis. **A:** Funnel plot of ORs versus total sample size. **B:** Funnel plot of ORs versus total sample size after excluding the 3 studies with the largest sample sizes (Rugbjerg 2008, Nielsen 2002, and Turner 2010). **C:** Plot of the logarithm of the ORs after excluding the 3 largest sample size studies compared with the standard error of the logarithm of the ORs showing a regression line and 95% CI with slope that is not statistically significantly different from 0. Figure is available in color online only.

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 an individual's clinical presentation. For example, boxers

may suffer from more torsional injury that could damage 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 the risk of Alzheimer's disease, has shown 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, its 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 revealed a 3-fold higher rate of death from neurodegenerative disease compared with the typical population frequency, with Alzheimer's disease and ALS being the most overrepresented,⁴⁴ which would be consistent with either a shared vulnerability hypothesis across neurodegenerative diseases or a common pathology. In this meta-analysis we 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.

Several of the reviewed articles 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 2 of the articles^{32,33} that directly evaluated TBI in sports met the strict inclusion criteria for our study. The ability of our meta-analysis to inform questions surrounding the long-term consequences of sports-related mild TBI is therefore limited by restricted data 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 the assessment of late-life neurological 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, although 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, and thus 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 (for example, different criteria for the diagnosis of illness, or comorbid environmental and genetic factors of the study population) limits the generalizability of our 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 the result of a fall or motor vehicle accident may have other medical comorbidities (for example, vascular disease or substance abuse) or differences in socioeconomic status that could predispose to neurological or psychiatric illness. Another possibility is that the TBI itself could lead to an injury or a change in lifestyle that could modify the risk for a mood disorder. Finally, ill patients who fall and suffer TBI may also undergo more medical testing and therefore may be more likely to receive one of these neurological or psychiatric diagnoses. Only English-language studies were reviewed, which could have led to the exclusion of some relevant studies. Despite our criteria regarding an interval between TBI and the onset of illness, an alterna-

tive explanation for the observed association is that some head injuries may have been early manifestations of neurological or psychiatric disease rather than an independent predisposing factor for illness. The authors of 1 of the included studies concluded this reverse causality was responsible for their findings.⁷¹ They stratified the interval between TBI and diagnosis and found that the association between TBI and Parkinson's was no longer present when only looking at TBI that occurred more than 10 years prior to diagnosis.

A major strength of our meta-analysis was the inclusion of a variety of different neurological and psychiatric outcomes rather than a single diagnosis. By focusing on diagnoses rather than self-reported symptoms or patient performance on cognitive tests, we assessed outcomes of sufficient magnitude to affect quality of life. The included studies also came 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, with the subsequent development of neurological and psychiatric illness, including Alzheimer's disease, Parkinson's disease, mild cognitive impairment, depression, mixed affective disorders, and bipolar disorder. Because of limitations in and the heterogeneity of existing studies, prospective studies with uniform assessment are 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.

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Disclosure

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Conception and design: Perry, Sturm, Boeve, Miller, Guskiewicz, Berger, Kramer, Welsh-Bohmer. Acquisition of data: Perry, Sturm, Bullock. Analysis and interpretation of data: Perry, Sturm, Peterson, Pieper. Drafting the article: Perry, Sturm, Peterson, Pieper. Critically revising the article: Bullock, Boeve, Miller, Guskiewicz, Berger, Kramer, Welsh-Bohmer. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Perry. Statistical analysis: Peterson, Pieper.

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