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The Development of Posttraumatic Stress Disorder after Mild Traumatic Brain Injury in Civilian Populations: A Meta-Analysis

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Abstract

Background: Posttraumatic stress disorder (PTSD) is an anxiety disorder following exposure to a traumatic event. Recent studies demonstrate that mild traumatic brain injury (mTBI) is strongly associated with PTSD among soldiers returning from Iraq. However, the effect of mTBI on development of PTSD in civilian populations is quite controversial. The study is aimed at identifying whether mTBI contributes to an increased risk of PTSD in civilian populations as it happens in the service members.

Methods: A comprehensive search of literature was undertaken in order to identify published studies on PTSD associated with mTBI. mTBI was defined according to the American Congress of Rehabilitation Medicine (ACRM). PTSD was operationalized as the presence of symptoms consistent with those defined by the *Diagnostic and Statistical Manual of Mental Disorders*. The effect of mTBI on the development of PTSD was assessed with odds ratio (OR) with 95% confidence intervals (CIs).

Results: The pooled data consisted of 1222 mTBI patients and 1468 general trauma participants. 14% of mTBI patients reported PTSD, and 9% of general trauma patients developed PTSD. Or of the pooled studies indicates a 61% increase in the prevalence of PTSD, suggesting that mTBI might increase the risk of development of PTSD in civilian settings (or 1.61, 95% CI 1.25-2.06. p=0.0002, I^2=0%). The occurrence of PTSD was not significantly different among 3-months, 6-months and 12-months follow up subgroups (p=0.28). A sensitivity analysis shows the results are affected by sequential exclusion of study reported by Bryant et al. (2010). When Bryant et al. data were removed, OR of the other six studies demonstrates that the prevalence of PTSD in mTBI and general trauma groups doesn't significantly differ (OR 1.30, 95% CI 0.88-1.93. p=0.19, I^2=0%). The study from Bryant et al contributed 57% of patients to overall data, which was derived from four levels I trauma centers across three states in Australia.

Conclusion: Our data indicate that mTBI patients are more prone to develop PTSD than general trauma patients without mTBI in civilian settings.

Keywords: Mild traumatic brain injury; Minor brain injury; Posttraumatic stress disorder; Anxiety.

Introduction

Traumatic brain injury (TBI) is a major public health problem. In the United States, more than 1.5 million individuals sustain TBI every year [1]. It is estimated that almost 320,000 deployed American personnel may have suffered varying degrees of TBI [2]. Mild TBI (mTBI) is the most frequent type of TBI among both veteran and civilian populations. In the civilian sector, the majority of cases with mTBI are associated with early symptoms that typically resolve within a few days to a few months post injury [3-6]. However, a minority of individuals continue to complain of ongoing post concussive somatic, cognitive, and/or behavioral symptoms that may lead to long-term functional limitation [7-10].

Posttraumatic stress disorder (PTSD) is an anxiety disorder characterized by reexperiencing, avoidance, and hyper arousal symptoms following exposure to a traumatic event. Historically, it was argued that trauma survivors with mTBI have no painful traumatic memories and, therefore cannot develop core PTSD symptoms characterized by intrusive re-experiencing of the event. However, evidence has accrued showing that PTSD symptoms can develop after mTBI [11-16]. Recent studies demonstrate that mTBI are strongly associated with PTSD among soldiers returning from Iraq [17]. On examination of multiple potential predictors of PTSD including non-TBI-related injuries, only combat intensity and mTBI with loss of consciousness (LOC) were significantly associated with PTSD once other variables were controlled. These findings suggest that mTBI might increase the likelihood of developing PTSD in service members. There has been extensive debate in the literature regarding whether mTBI has a strong effect on the development of PTSD in civilian populations [18-28]. So far, the published data investigating the incidence of PTSD after mTBI in civilian populations are difficult to interpret due to variations in the methodology and conflicting results. As indicated in a recent study by the World Health Organization Collaborating Centre Task Force on mTBI, different criteria used to define mTBI and lack of control groups or comparison of inappropriate control groups have been often found in the existing literature [29].

The current study employed meta-analysis to integrate the available literature on the incidence of PTSD associated with mTBI and bring

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a more clear evidence for the question whether PTSD can confer the risk of PTSD development after mTBI in civilian populations with a rigorous methodological quality assessment.

Materials and Methods

Selection of studies

A comprehensive search of Pubmed and PSYCHInfo databases was undertaken in order to identify published studies on PTSD associated with mTBI. Key search terms included "mild traumatic brain injury", "minor traumatic brain injury", "mild brain injury", "minor brain injury", "mild head injury", "minor head injury", "mild closed head injury", "minor closed head injury", "mild head trauma" and "minor head trauma". These search terms were paired with "posttraumatic stress", "posttraumatic stress disorder" and "anxiety disorder". The search was limited to English language published in peer-reviewed journals from January 1980 to December 2013 that involved human subjects and presented primary data. Reference lists from the relevant studies were searched for additional references.

Inclusion criteria

Original studies were considered for inclusion in the meta-analysis if they met with the following criteria: (1) adult civilians were studied; (2) mTBI was defined according to the American Congress of Rehabilitation Medicine (ACRM) [30]; (3) PTSD was operationalized as the presence of symptoms consistent with those defined by the *Diagnostic and Statistical Manual of Mental Disorders (DSM-III, SDM-III-R, DSM IV, or DSM-IV-TR)* [31-33], which were assessed through clinical diagnoses or interviews or "probable PTSD" based on indicated cutoff scores using self-report inventories or screening measures in not less than 3 months after injury. (4) Results were sufficient to allow calculation of effect sizes. (5) Results were not reported elsewhere.

Data collection

Titles and abstracts from all references identified in the literature search process were reviewed by two independent study investigators. For each study included in the meta-analysis, the author, date of publication, country and assessment tools for PTSD were summarized in Table 1. Several sample characteristics were also noted, including sample size, mean age, mean education, sex, CT examination, and severity of injury as measured by Injury Severity Score (ISS) for patients and control samples when available. Results were reviewed with another member of the research team. Studies included in the meta-analysis were assessed for risk of bias using Newcastle-Ottawa score (NOS) [34]. The score assigns a study a maximum of 9 points, with higher scores indicating a lower risk of bias.

Statistical analysis

The effect of mTBI on the development of PTSD was assessed with odds ratio (or) with 95% confidence intervals (CIs). A subgroup analysis was carried out based on education, mean age, NOS, follow-up, ISS and country. Egger's test was applied to check the potential publication bias. The statistical estimates of effect were derived using a random-effects model with Mantel-Haenszel statistics. Heterogeneity of mTBI effect on the development of PTSD between studies was investigated visually by scatter plot analysis and statistically by the heterogeneity I^2 statistic. I^2 statistic of 0%-40% indicates unimportant heterogeneity, 30%-60% indicates moderate heterogeneity, 50-90% indicates substantial heterogeneity, and 75%-100% indicates considerable heterogeneity. P values were calculated by χ^2 tests. All the reported P values are two-sided and value of P less than 0.05 was regarded as statistically significant for all included studies. All analyses were calculated using STATA (version 10.0).

Results

We identified 853 potentially relevant studies from our combined database, of which 734 were excluded after a preliminary review. The remaining 75 studies were retrieved for detailed assessment. Ultimately, 7 prospective cohort studies met the inclusion criteria (Figure 1). For the study from Bryant et al. [26], outcomes at 3-months and 12-months follow up were both included for analyses. A total of 1222 mTBI patients and 1468 general trauma participants were included. There was no evidence of publication bias for the development of PTSD after mild traumatic brain injury (P value for Egger's test, 0.38). Five high quality studies were judged by a NOS score of 7 or above. The baseline characteristics of the participants and the design of the studies were summarized in the Table 1.

The pooled data consisted of 2690 individuals with 304 PTSD patients. 14 % of mTBI patients reported PTSD, and 9% of general trauma patients developed PTSD. As shown in Figure 2, OR of the pooled studies indicates a 61% increase in the prevalence of PTSD in mTBI patients when compared with general trauma participants, suggesting that mTBI might increase the risk of development of PTSD in civilian settings (OR 1.61, 95% CI 1.25-2.06, p=0.0002, I^2=0%) (Figure 2). In order to evaluate the effect of time after injury on development of PTSD in mTBI populations, the pooled data were classified into 3 subgroups (3-months, 6-months and 12-months follow up groups). There was no significant difference among subgroups (p=0.28) (Figure 2). A sensitivity analysis shows the results are affected by sequential exclusion of study reported by Bryant et al. [26] When Bryant's research was removed, OR of the other six studies demonstrates that

Source	mTBI group		control group		follow up (month)	sex (male)	mean age (year)	ISS	education (year)	CT examination	Newcastle-Ottawa score	country	diagnosis of TBI	screening tools for PTSD
	PTSD	total	PTSD	total										
Levin HS [21] (2001)	8	60	6	52	3	71%	36	5.13	10.84	-/+	6	USA	ACRM	SCID
Jones C [23] (2005)	10	58	11	61	3	40%	37	3.22	N/A	N/A	4	UK	ACRM	PSS
Bryant RA [24] (2010)	48	377	43	555	3	73%	38	10.42	N/A	N/A	7	Australia	ACRM	CAPS
Ponford J [26] (2011)	7	90	3	80	3	70%	35	ND	13.87	-	7	Australia	ACRM	PCL-C
Bryant RA[19] (1999)	15	63	18	71	6	68%	32	6.82	N/A	N/A	7	Australia	ACRM	CIDI
Friedland JF [20] (2001)	17	64	7	35	7	64%	33	20.06	N/A	N/A	7	Canada	ACRM	IES+GHQ
Creamer M [22] (2005)	24	189	8	118	12	76%	37	13.67	N/A	N/A	7	Australia	ACRM	CAPS
Bryant RA [24] (2010)	43	321	36	496	12	73%	38	10.42	N/A	N/A	7	Australia	ACRM	CAPS

N/A, not available; ACRM, American Congress of Rehabilitation Medicine; CIDI, Composite International Diagnostic Interview; PCL-C, PTSD Checklist-civilian version; CAPS, Clinician-Administered PTSD Scale; SCID, structured clinical interview for DSM-IV; PSS, PTSD symptom scale; -/+, negative/positive; IES, Impact of Event Scale; GHQ, General Health Questionaire; CT, computed tomography.

Table 1: Design and patient characteristics for studies included in the meta analysis.

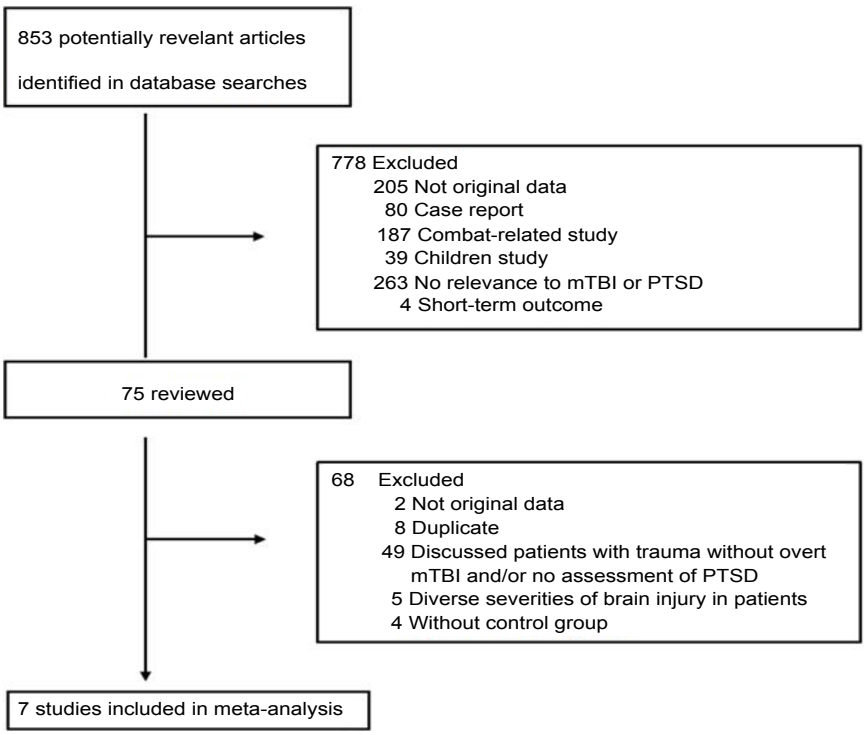

Figure 1: Flow diagram of the literature search and studies selection process.

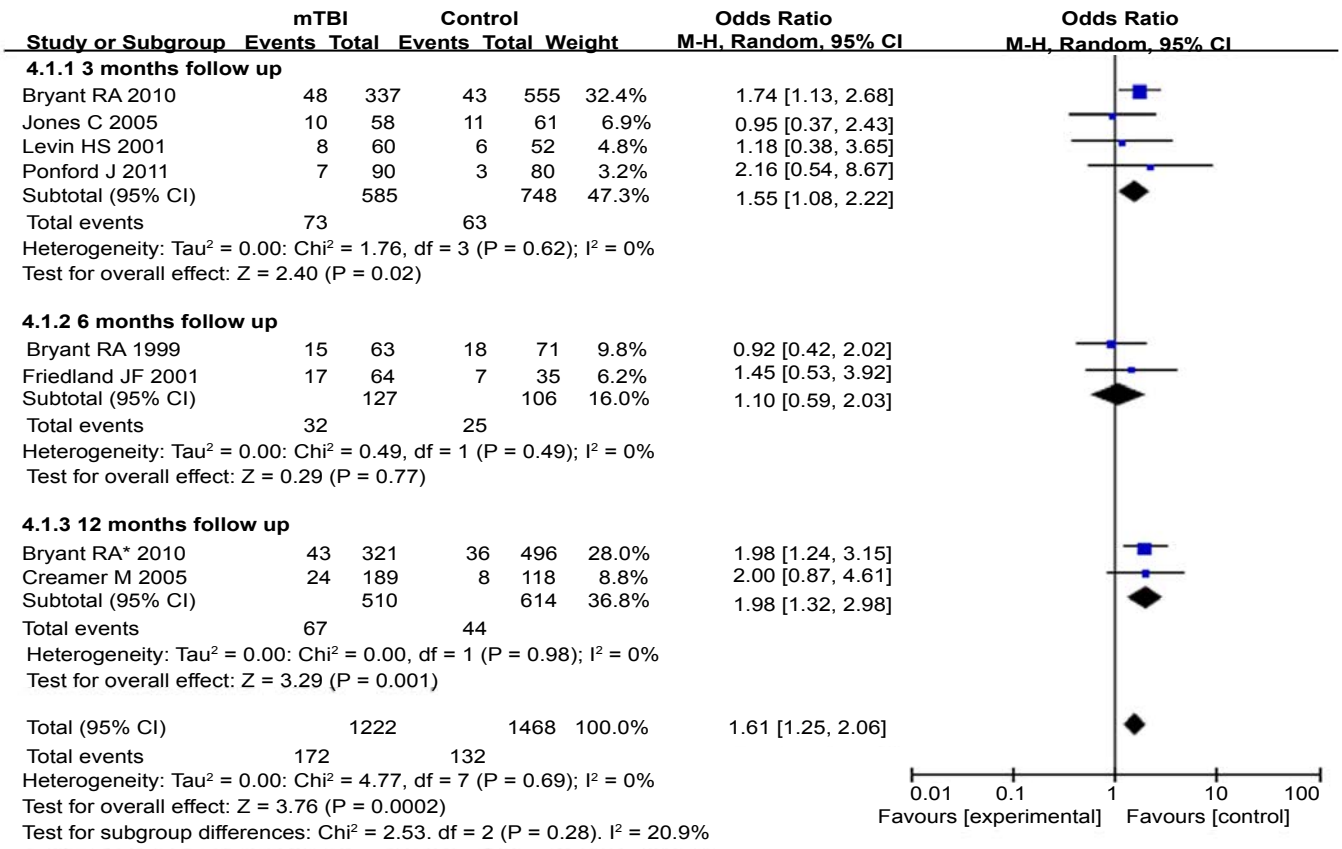

Figure 2: Effect of mTBI on the risk of development of PTSD in civilian populations. * Outcomes at 3-months and 12-months follow up were both included for analyses.

the prevalence of PTSD in mTBI and general trauma groups doesn't significantly differ (OR 1.30, 95% CI 0.88-1.93, p=0.19, I^2=0%). The study from Bryant et al. [26] contributed 57% of patients to overall data, which was derived from four levels I trauma centers across three states in Australia.

Subgroup analyses were carried out based on education, mean age, NOS, follow-up, ISS and country (Table 2). Outcomes at 12-months follow up were included for subgroup analyses in the study from Bryant et al. [26], with the exception of education, mTBI attributed to an increase in the prevalence of PTSD in the other five subgroup analyses, where Bryant's study contributed an overwhelming portion to overall data due to its huge sample size. It is possible that statistical significant difference might come out of contribution of specific study rather than subset factors.

Discussion

Our study is aimed at identifying whether mTBI contributes to a increased risk of PTSD in civilian populations as it happens in the service members. In this review, we surveyed 804 publications related to mTBI and PTSD and 7 studies were finally included in our meta-analysis. The overall incidence of PTSD is 14% in the mTBI patients in a civilian sample. The military or veteran studies reported probable PTSD in 33% to 39% of respondents who endorsed having experienced a probable mTBI [17,35,36]. Since a substantial number of mTBI survivors in the military is the result of non-combat-related injuries (i.e., sports injuries, assaults, motor vehicle accidents), comparison between civilian studies and military studies helps assess how often PTSD is due to the stress of combat/military life. The meta-analysis demonstrates that patients suffering mTBI are at higher risk of PTSD development compared to general trauma patients in the civilian populations. Some literature on PTSD following TBI has shown that PTSD symptoms decrease significantly over time within a year post injury [37-38]. However, quite a quantity of studies disputes the opinion because of the fact that the rates of PTSD don't drop over a year after TBI [26,39,40] Our stratified analyses showed that the prevalence of PTSD at 3-months, 6-months and 12-months follow up didn't differ, supporting the idea that the occurrence of PTSD may be maintained or even increase over time after injury.

Hesdorffer *et al.* [20] reported their systematic review on the long-term psychiatric outcomes following traumatic brain injury in 2009. They concluded, on the basis of their evaluation, that there is inadequate/insufficient evidence to determine whether an association exists between mTBI and PTSD in civilian populations [20]. Of note, they drew their conclusion mainly depending on the study reported by Creame, which was derived from one trauma center in Australia including 189 mTBI patients and 118 general trauma patients. In the present review, we included 2690 individuals in 7 studies with a broad range of baseline characteristics. We argue that the insufficient data might lead to the uncertainty about the relationship between PTSD and mTBI in Hesdorffer *et al.* [20] research.

There are several important limitations in the review. The major limitation is the quality of studies involved. Of the 7 studies, 71% (n=5) were from centers in Australia. Although all the studies are prospective investigation, only the study reported by Bryant, *et al.* [26] is a multisite design with a big sample size of more than 300 mTBI participants. The numbers of mTBI patients vary across the other six studies from 58 to 189. The meta-analysis demonstrates that patients suffering mTBI are at higher risk of PTSD development compared to general trauma patients in the civilian populations, which is in accordance with findings from Bryant *et al.* [26]. However, when the data were removed, a meta-analysis of the other six small studies does not predict the effect of mTBI on the development of PTSD. In some cases, a meta-analysis of several small studies may fail to predict the results of a single large study although it is now widely used to provide evidence to support clinical strategies [41]. The heterogeneity of sample sizes may partially account for the divergence in our study. When divergences are seen between meta-analysis and a large study, few will disagree that the value of the large and well designed studies is of more guidance to clinical practice than meta-analyses. Thus, more large researches of high quality will help us come to a consistent conclusion in the future.

Another limitation is the inconsistent assessment tools of PTSD applied in the studies, consisting of clinical interview and self-reported

Group	PTSD event/total patients		Odds Ratios (OR) and 95%CI	P value	heterogeneity	P value for heterogeneity
	mTBI	GT				
Education (years)						
≥ 12	7/90	3/80	2.16 [0.54, 8.67]	0.28	-	-
<12	8/60	6/52	1.18 [0.38, 3.65]	0.77	-	-
Mean age						
≥ 35	92/718	64/807	1.72 [1.22, 2.43]	0.002	0	0.64
<35	32/127	25/106	1.10 [0.59, 2.03]	0.77	0	0.49
NOS						
≥ 7	106/727	72/800	1.68 [1.21, 2.34]	0.002	0	0.54
<7	18/118	17/113	1.04 [0.50, 2.14]	0.92	0	0.77
Follow-up						
≥ 6	99/637	69/720	1.66 [1.18, 2.33]	0.004	0	0.40
<6	28/208	20/193	1.21 [0.64, 2.31]	0.55	0	0.63
ISS						
>10	60/385	43/531	1.87 [1.22, 2.85]	0.004	0	0.58
<10	33/181	35/184	0.98 [0.58, 1.67]	0.95	0	0.94
Country						
Australia	89/663	65/765	1.71 [1.21, 2.43]	0.003	0	0.39
Other	35/182	24/148	1.16 [0.65, 2.09]	0.61	0	0.83
Overall	124/845	89/913	1.55 [1.15, 2.09]	0.004	0	0.60

Table 2: Subgroup analyses based on education, mean age, NOS, follow-up, ISS and country.

questionnaires. Clinician-Administered PTSD Scale-IV (CAPS), a structured clinical interview with good sensitivity and specificity relative to the Structured Clinical Interview for DSM-IV (SCID), as well as sound test-retest reliability, was utilized to assess PTSD in the studies of Bryant and Creamer Compared to CAPS, self-reported questionnaires could interfere with the ascertainment of PTSD in the studies. Three of the studies used self-reported questionnaires to diagnose probable PTSD. The inclusion of such articles could elevate the estimated incidence of PTSD in the participants.

An additional limitation of the review is the classification of mTBI. All the studies categorized TBI patients according to Glasgow Coma Scale (GCS), widely used to assess the level of consciousness after TBI. GCS score ranges from 3 (most severely impaired) to 15 (no neurologic impairment). GCS 13-15 is often employed as one of criteria to define mTBI. However, GCS score doesn't accord with severity of brain damage all the time. Mild traumatic brain injury can be classified into two categories-complicated and uncomplicated mTBI, in which complicated mTBI means presence of an intracranial abnormality on neuroimaging. Almost all the studies included in our meta-analysis didn't discriminate complicated mTBI from uncomplicated mTBI. Data by Smits *et al.* [42] indicated that complicated mTBI was significantly associated with worse outcome [42]. Grouping all mTBI participants into a single category may oversimplify the complex characteristics of brain injury and obscure important differences related to mTBI severity [43]. In future study, it is necessary to clarify whether injury in the specific sites of brain tissue might confer the risk of development of PTSD following mTBI.

mTBI patients develop post concussion symptoms (PCS), a constellation of physical, cognitive and emotional symptoms. The presence of persistent PCS complicates the diagnosis of PTSD after mTBI because many of the complaints are similar, including irritability, depressive symptoms, sleep disturbance and cognitive difficulties. The issue that PCS are a result of organic or psychological factors, or an interaction between the two has been long debated. The facts that PCS is frequently encountered among healthy adults [44-45] and clinical groups without a history of mTBI [46] indicate that PCS might be nonspecific to mTBI. Recent studies show that PCS complaints after mTBI are more likely to be ascribed to psychological factors, such as anxiety, depression or PTSD rather than mTBI [47-50]. Apart from PTSD, mTBI could be associated with other psychiatric disorders, such as depression, generalized anxiety disorder, obsessive-compulsive disorder and substance abuse. It is a well-studied fact that PTSD patients have high rates of psychiatric comorbidity. Apparently, public health concerns are needed to address the huge health burden caused by the psychiatric effects of mTBI. New approaches that ease early identification of psychiatric disorders and prompt early interventions to prevent psychiatric condition might facilitate optimal recovery from mTBI.

Conclusion

This meta-analysis represents synthesis of the available data on the development of PTSD after mTBI in civilian populations. The overall incidence of PTSD is 14% in mTBI patients and 9% in general trauma patients among the civilian populations. Our data indicate that mTBI patients are more prone to develop PTSD than general trauma patients without mTBI in civilian settings.

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