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Prevalence, Assessment, and Treatment of Mild Traumatic Brain Injury and Posttraumatic Stress Disorder: A Systematic Review of the Evidence

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Background: Iraq and Afghanistan war veterans are returning from combat having sustained traumatic brain injury, most commonly mild traumatic brain injury (mTBI), and experiencing posttraumatic stress disorder (PTSD). Clinical guidelines for mTBI and PTSD do not focus on the co-occurrence of these conditions (mTBI/PTSD). A synthesis of the evidence on prevalence, diagnostic accuracy, and treatment effectiveness for mTBI/PTSD would be of use to clinicians, researchers, and policymakers. **Methods:** We conducted a systematic review of studies identified through PubMed, PsycINFO, REHABDATA, Cochrane Library, pearling, and expert recommendations. Peer-reviewed English language studies published between 1980 and June, 2009 were included if they reported frequencies of traumatic brain injury and PTSD, or diagnostic accuracy or treatment effectiveness specific to mTBI/PTSD. **Results:** Thirty-four studies met inclusion criteria. None evaluated diagnostic accuracy or treatment effectiveness. Studies varied considerably in design. Frequency of mTBI/PTSD ranged from 0% to 89%. However, in 3 large studies evaluating Iraq and Afghanistan war veterans, frequencies of probable mTBI/PTSD were from 5% to 7%; among those with probable mTBI, frequencies of probable PTSD were from 33% to 39%. **Discussion:** The wide range of mTBI/PTSD frequency levels was likely due to variation across study parameters, including aims and assessment methods. Studies using consistent, validated methods to define and measure mTBI history and PTSD are needed. **Keywords:** *blast-related injury*, *comorbidity*, *military*, *postconcussive syndrome*, *posttraumatic stress disorder*, *systematic review*, *traumatic brain injury*, *veterans*

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SOLDIERS serving in the current conflicts in and around Afghanistan (Operation Enduring Freedom) and Iraq (Operation Iraqi Freedom) (OEF/OIF) are at risk of sustaining traumatic brain injury (TBI). *Traumatic brain injury* is defined as trauma to the head that results in an alteration or loss of consciousness or posttraumatic amnesia.[1] Among soldiers, TBI is frequently associated with falls, motor vehicle crashes (MVC), and blasts. Blast-related TBI may result from barotrauma associated with dynamic changes in atmospheric pressure, or from blast forces that cause the head to strike against, or be struck by, penetrating or blunt objects.[2] Blunt force TBI is differentiated by level of severity, with mild, moderate, and severe TBI being the most common categories of classification.

Mild TBI (mTBI) is the most frequent type of TBI among civilians and OEF/OIF soldiers and veterans.[3,4] Research has suggested that up to 23% of OEF/OIF soldiers have experienced a TBI, with the majority being mTBI.[5] Research involving primarily civilian populations indicates that most individuals who sustain mTBI

recover fully within 6 months after the injury but that a minority of individuals can suffer ongoing postconcussive somatic, cognitive, and/or behavioral symptoms that may lead to long-term functional limitations.[6–8] Persistent postconcussive symptoms can be nonspecific; many are identical to symptoms of chronic stress or other mental health disorders, hampering differential diagnosis.[9] Early identification and proper care, if indicated, of veterans who have experienced mTBI are a priority for US Veterans Health Administration (VA) and Department of Defense health care providers.[10–12]

Posttraumatic stress disorder (PTSD) is an anxiety disorder characterized by reexperiencing, avoidance, and hyperarousal symptoms following exposure to a traumatic event.[13] Estimates of PTSD among OEF/OIF soldiers and veterans vary widely but suggest that it is also a prevalent problem in these populations. A recent systematic review summarizing studies of Iraq War veterans reported rates of PTSD from 1.4% to 31%; studies involving those at highest risk for combat exposure (ie, infantry units) reported more consistent rates from 10% to 17%.[14] The VA alone treated more than 100,000 OEF/OIF veterans for PTSD between 2002 and the end of 2008.[15] Detection and treatment of PTSD are crucial, as veterans with this disorder can experience significant impairment in psychosocial functioning and quality of life.[16,17] There are efficacious psychological and pharmacological treatments of PTSD, with the strongest evidence supporting cognitive-behavioral psychotherapies.[18] However, many symptoms associated with PTSD (eg, anxiety, insomnia and fatigue, problems thinking or remembering, and irritability, anger, or aggression) can also occur following mTBI. Thus, the accurate attribution of symptoms to one or the other, or both, conditions can be problematic.[19,20]

Historically, some experts debated whether TBI and PTSD were mutually exclusive, as memory of the traumatic event was presumed necessary for a diagnosis of PTSD but can be absent in the more severe cases of TBI.[19,21] However, evidence has accrued showing that individuals who experience TBI can also develop PTSD, either from the same or from a different traumatic event.[19,22,23] Health care providers are currently treating a large number of OEF/OIF combat veterans with a diagnosis of both TBI and PTSD.[24–26] Although the majority of veterans with a diagnosis of TBI have likely sustained mTBI, the prevalence of comorbid symptomatic mTBI and PTSD is unknown. It is also unknown whether diagnostic or even screening instruments commonly used for assessing history and symptoms of mTBI and PTSD perform accurately whether individuals have both conditions. For example, it has been suggested that screening for mTBI based on retrospective reports of individuals' alterations in consciousness may be invalid or unreliable due, in part, to recall error.[20,26] It is possible that one's memory of a traumatic event in this detail may also be affected by current posttraumatic stress symptoms. And while assessment and diagnosis of PTSD is more straightforward, individuals' reports of current stress symptoms have the potential to be affected by, or confused with, persistent postconcussive symptoms.

It is similarly unknown whether evidence-based treatments of symptomatic mTBI and PTSD alone are effective when the conditions co-occur, or whether unique therapies are necessary for individuals who have both. For example, pharmacologic agents used to treat certain symptoms of PTSD have the potential to exacerbate TBI-related cognitive sequelae.[27] It has also been suggested that cognitive limitations, problems with emotion regulation or impulse control, or pain associated with mTBI may limit patients' ability to engage in, or may decrease effectiveness of, evidence-based treatments of PTSD.[21]

In 2009, the VA convened expert clinicians and researchers in a consensus conference to develop practice recommendations for the treatment of veterans with comorbid mTBI, PTSD, and pain. In addition, the VA commissioned a systematic review through its evidence synthesis program[28] to help inform these practice recommendations. The research team conducted a systematic review of scientific literature addressing prevalence of co-occurring TBI and PTSD (TBI/PTSD). Traumatic brain injury of all severity levels was included to examine whether prevalence of PTSD differs among those with moderate and severe TBI versus those with mTBI (mTBI/PTSD). This review also sought evidence on the accuracy of diagnostic assessments and effectiveness of treatments for mTBI/PTSD. The following 3 questions were investigated:

Question 1. What is the observed prevalence of TBI/PTSD? How does prevalence vary by TBI severity and other key variables?

Question 2. What is the relative accuracy of diagnostic tests used for assessing symptomatic mTBI or PTSD in individuals with mTBI/PTSD?

Question 3. Are there psychosocial or pharmacological therapies used for treatment of mTBI/PTSD? Are therapies for treatment of symptomatic mTBI or PTSD effective in individuals with mTBI/PTSD? Is there evidence of harms?

The purpose of this article is to summarize the findings of the comprehensive report[29] and to suggest directions for future research.

METHODS

The key questions, scope, and work plan for this review were developed and refined in collaboration with a technical advisory panel composed of clinical, research, and health policy experts in TBI and PTSD. We

conducted 2 respective searches of PubMed, PsycINFO, REHABDATA, and Cochrane review databases, using terms relevant to (1) TBI ("brain injury [and variants of injury];" "coma"; "coma, posthead injury"; "Glasgow Coma Scale"; "head injuries, closed"; "postconcussion syndrome"; "brain concussion"; "postconcussive"; and "brain injury, chronic"); and (2) PTSD ("combat disorders [and variants of disorder]"; "posttraumatic stress"; "posttraumatic stress disorder [and variants of disorder]"; "post-traumatic stress disorder [and variants of disorder]"; "stress disorders, posttraumatic"; "anxiety"; and "anxiety disorders"). The results from each search were then merged in an attempt to identify studies that included both TBI and PTSD. The search was limited to English language articles published from January 1980 to June 2009 that involved human subjects and presented primary data. Reference lists from the relevant studies were searched for additional references. Expert recommendations of additional references were also solicited.

Inclusion/exclusion criteria

Traumatic brain injury was operationalized as a history of confusion, disorientation, or loss of consciousness resulting from a force to the head.[2,30] Included studies must have assessed participants for a "probable" history of TBI (identified using self-report screening instruments) or diagnosed TBI history, regardless of the presence of current TBI-related symptoms. As previously noted, for Question 1, we included studies that assessed participants with all levels of TBI severity to examine possible variation in PTSD prevalence by TBI severity level (moderate and severe TBI versus mTBI). For Questions 2 and 3, we included only studies that assessed participants for history of mTBI.

Posttraumatic stress disorder was operationalized as the presence of symptoms consistent with those defined by the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-III*, *DSM-III-R*, *DSM-IV*, or *DSM-IV-TR*).[31–33] Included studies must have assessed participants for *DSM-III* or *DSM-IV* diagnoses of PTSD as determined through clinical diagnoses or interviews or "probable PTSD" based on indicated cutoff scores using self-report inventories or screening measures.

Studies of all design types, except case reports, were considered for inclusion. We excluded studies if they were published prior to 1980, included more than 10% of subjects less than 18 years of age, did not enroll individuals with a probable or diagnosed history of TBI or probable or diagnosed PTSD, or did not present results in a manner that addressed the questions of interest (eg, presented correlation between, but not frequency of, TBI and PTSD). We note that, for Question 1 pertaining to prevalence, studies were included whether or not they were designed to estimate population prevalence of TBI and PTSD as long as they reported frequencies of both within their respective study populations. Data on TBI/PTSD frequency were then considered with study design and overall generalizability in evaluating prevalence of TBI/PTSD.

Data extraction and synthesis

Titles and abstracts, when available, from all references identified in the literature search process were reviewed by a study investigator. This initial screening was designed to identify articles which were related to 1 or more of the key questions. Studies that were included after this initial screening were then reviewed in their entirety to determine whether they met the above inclusion or exclusion criteria. For all studies meeting inclusion criteria, data were abstracted onto standardized forms and results were reviewed with another member of the research team. For each included study, investigators abstracted the number of TBI/PTSD cases and the total number of study participants to calculate frequency of TBI/PTSD. The study setting, target population, participant demographics, method(s) used to ascertain, define, and enumerate TBI and PTSD cases (administrative data; self-report; clinical screening; structured, semistructured or unstructured interview; neuropsychiatric evaluation), severity of TBI (mild, moderate, severe, and how defined by study authors), trauma etiology (eg, military, terror, motor vehicle, assault), and number of traumas and time since trauma(s) were also abstracted. We note that, for simplicity, we refer to the event(s) causing physical injury as well as the event(s) leading to psychological stress simply as "trauma," even though these may be different events and may involve distinct etiologic pathways.

We critically analyzed studies to compare their methods and results and drew conclusions based on qualitative synthesis of the findings. Findings were summarized across key variables (ie, TBI severity, trauma etiology), with an emphasis on the studies with greatest applicability to understanding prevalence, assessment, and treatment of mTBI/PTSD among US OEF/OIF soldiers and veterans. The descriptive and heterogeneous nature of the included studies, in terms of study questions, study design, participant demographic characteristics, trauma etiology, disease/injury definition, and assessment methodology, precluded pooled analysis or the application of a formalized system of rating study quality.

RESULTS

Our combined reference library contained 1,107 citations, of which 749 met exclusion criteria based on titles and abstracts (Fig 1). We reviewed 358 articles at

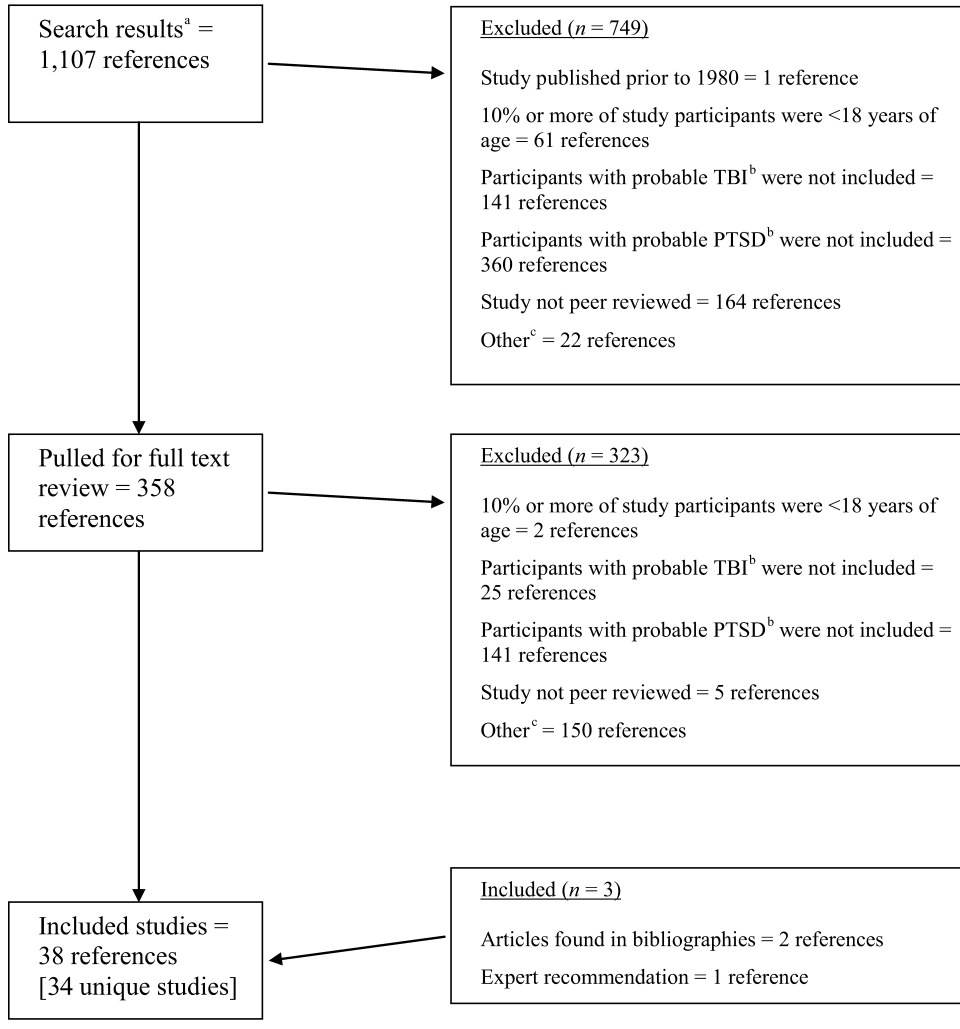

Figure 1. Data search and selection. [a]Search results from PubMed ($n = 700$), PsycInfo ($n = 522$), and REHABDATA ($n = 123$) were combined, removing duplicate entries ($n = 268$.) [b]"Probable" TBI and PTSD cases were those identified through clinical diagnoses, interviews, and positive screens based on indicated cutoff scores on self-report inventories. [c]Other studies were most frequently excluded because they did not present TBI/PTSD data in a manner that addressed the questions of interest.

the full-text level, of which 323 additional studies were found to meet exclusion criteria. Ultimately, 34 unique studies, described in 38 references, met inclusion criteria for this review. Two were identified through bibliographies of other citations and one, a study conducted by the RAND Corporation, was identified via expert recommendation. While the RAND study was not published in a peer-reviewed journal, the report was peer-reviewed, published by RAND, and publicly available on the RAND Web site.[34] Excluded studies were published prior to 1980 ($n = 1$), included more than 10% of participants younger than 18 years ($n = 63$), did not assess participants for probable history of TBI ($n = 166$) or PTSD ($n = 501$), were not peer reviewed ($n = 169$), or were not usable for other reasons ($n = 172$). Most frequently, studies in this last category were excluded because they did not present TBI/PTSD data in a manner that addressed any of our 3 questions of interest.

Question 1: Prevalence of TBI/PTSD

Description of studies

All 34 included studies were used to address Question 1 pertaining to prevalence of TBI/PTSD.[25,34–70] There were 20 studies that reported data on mTBI/PTSD.* A summary of study characteristics and outcomes is presented in Table 1 (SDC content available at http://links.lww.com/JHTR/A45). There was considerable variation in design across studies, including participant characteristics, etiology of participants' trauma,

*References 25, 34–39, 41, 44, 46–48, 53, 55, 60–63,68–70.

and methods and timing of TBI and PTSD assessment. These differences were at least partially due to the distinct study aims. The included studies involved between 10 and 2525 participants; the majority had fewer than 200. Ten studies, including the 3 largest,[25,34,41] involved US military personnel and veterans.[25,34,35,37–41,66,67] Many other studies were single-center studies and reported TBI/PTSD status in patients who had previously been hospitalized or received emergency care subsequent to trauma. Most studies were designed as cohort studies, involving such patients, or were cross-sectional in nature.

Methods of identifying TBI cases in these studies included medical records reviews, clinical interviews, self-reported receipt of treatment for a head injury, or self-report of exposure to a force to the head followed by loss of consciousness or altered mental status. Methods of identifying PTSD cases in the reviewed studies included structured or semistructured clinical interviews, unstructured interviews, self-report checklists, and indication of a clinical diagnosis in participants' medical records. While clinical interviews are considered the gold standard for assessment of both TBI and PTSD, studies frequently used self-report screening measures to identify "probable" TBI or PTSD cases. This included the 3 largest studies that surveyed US military personnel and veterans of OEF/OIF.[25,34,41] Different cutoff scores for self-report PTSD instruments were used across studies. The time since trauma when assessments were conducted was frequently not reported. However, 4 longitudinal studies (described in 5 references) followed TBI patient cohorts over time and assessed individuals for PTSD at various time points since injury.[45,48,51,62,63]

Military-related trauma, from both blast- and nonblast sources, was examined exclusively in 6 of the 10 studies involving US military personnel and veterans[34,37–40,66]; the other studies either did not define *trauma etiology* or included participants who had also experienced nonmilitary trauma.[25,35,41,67] Two Israeli studies also included individuals treated for military-related trauma.[42,43,54] Trauma related to MVC was reported in 22 studies; 5 were exclusive to MVC trauma.[48,53,61–63,65] Assaults and falls were other frequent sources of trauma. Many studies combined participants with different levels of TBI severity; results were stratified by level of TBI severity in some, but not all, of these studies. Twenty-four studies included subjects with a history of mTBI*; 12 studies were exclusive to mTBI.† Three, including the study conducted by the RAND Corporation, did not explicitly report levels of TBI severity.[34,64,65] For purposes of this review, however, we have assumed like other researchers[26] that most participants in the RAND study likely had histories of mTBI. This is justified because the majority of participants who indicated a probable history of TBI had never been medically evaluated for TBI, suggesting mild injuries. The other 2 studies[64,65] involved participants who had sought medical treatment of TBI and thus may have had more severe levels of TBI.

Frequency of TBI/PTSD

Figure 2 displays the range of reported TBI/PTSD frequency levels across study populations, differentiated by population type (US military or veteran vs civilian) and sample size. Note that this figure includes studies in which all participants had a TBI history as well as studies with more heterogeneous study populations in which some participants may not have had a history of TBI. It also includes studies examining all levels of TBI severity. Frequency of TBI/PTSD ranged from 0% to 70% across all studies, although the majority ($n = 23$) reported frequencies of 20% or less.* The few studies reporting TBI/PTSD frequency of 50% or more were relatively small and/or had especially nonrepresentative study samples (eg, case series of patients with obsessive-compulsive disorder).[39,53,66] The 3 large US military or veteran studies each reported probable TBI/PTSD in 5% to 7% of the entire study populations.[25,34,41] We found no discernible patterns in frequency of PTSD over time in participants with TBI who were followed longitudinally and had more than 1 PTSD assessment.[45,48,51,62,63] We also found no discernible differences when comparing studies in which the majority of TBI cases were military-related[25,34,37–40,66] with those in which the majority were not military-related.[42,43,47,48,61–63,65] Among TBI cases, presence of PTSD ranged from 32% to 66% among those with military-related trauma, and from 14% to 56% among those with nonmilitary trauma.

We examined studies to determine whether there were any systematic differences in frequency of TBI/PTSD based on methods of TBI and/or PTSD assessment. We expected that studies utilizing structured interviews to identify TBI and PTSD cases would have reported consistently different values than studies that utilized self-report screening measures. However, there was no clear delineation between studies based on methods of case identification. For example, within studies utilizing structured interviews to assess PTSD, frequency of TBI/PTSD ranged from 3% to 70% across study populations.† Within studies using self-report instruments to assess PTSD, frequency of TBI/PTSD ranged from 5% to 60%.‡

*References 25, 35-39, 41–48, 50, 51, 53, 55–63, 66, 68–70.
†References 25, 38, 39, 41, 46–48, 50, 57–63, 69, 70.

*References 25, 34, 36–38, 41–49, 52, 54–56, 61, 64, 65, 67, 69, 70.
†References 35, 36, 40, 46, 47, 49–51, 53, 55–65,67.
‡References 25, 34, 37–39, 41, 44, 45, 52, 70.

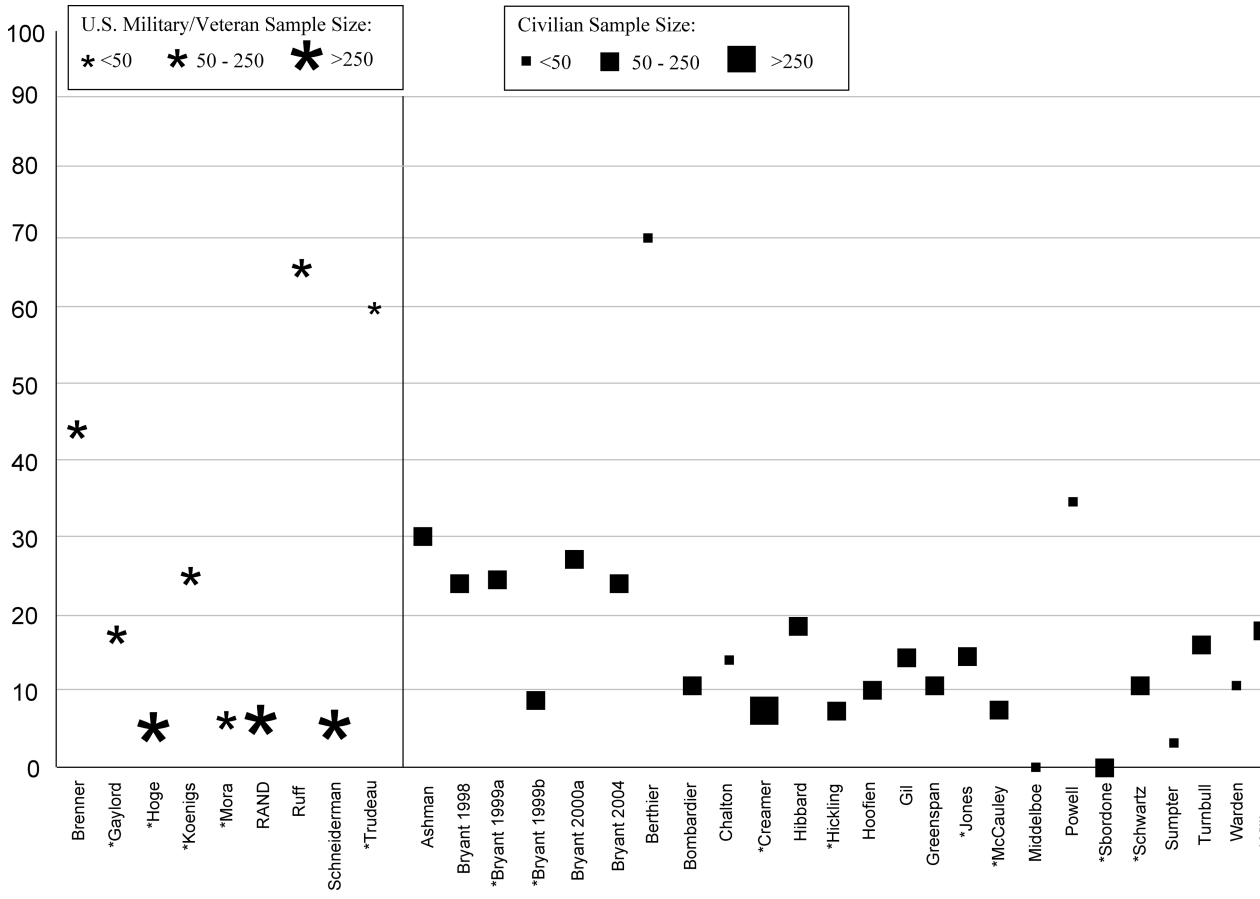

Figure 2. Frequency of traumatic brain injury and posttraumatic stress disorder (TBI/PTSD) across study populations. Sample size indicates the number of participants included in the frequency estimates. Studies with asterisks included participants with and without TBI history. All other studies were exclusive to participants with TBI history. Studies reporting more than 1 TBI/PTSD frequency level over time are presented at the first time point.

Frequency of mTBI/PTSD

To examine the frequency of PTSD specifically among individuals with a history of mTBI, we restricted our analysis to studies that were exclusive to individuals with mTBI or that stratified results for participants with mTBI history.* These studies and resulting data points are presented in Figure 3, again organized by population type (US military or veteran vs civilian) and size of the denominator used in the estimate. For clarity, we highlight the different denominator used in the values reported in Figure 3 (study participants with mTBI) in contrast to Figure 2 (all study participants, *with or without* TBI). Frequency of PTSD in individuals with a positive mTBI history ranged from 0% to 89%, with the majority ($n = 12$) reporting values between 10% and 40%.† The 3 largest studies involving US military personnel or veterans reported that between 33% and 39% of participants with probable history of mTBI also had probable PTSD.[25,34,41] In comparison, the 5 civilian studies with the largest number of participants with mTBI history reported that between 12% and 27% with mTBI also had PTSD.* The methods of assessment tended to differ between the civilian studies and the 3 large US military or veteran studies. The civilian studies tended to utilize structured clinical interviews to assess PTSD among patients specifically treated for TBI in a hospital or clinic. In contrast, the 3 large US military or veteran studies used similar self-report screening measures in telephone[34] or mailed[25,41] surveys to assess both TBI (the Brief Traumatic Brain Injury Screen or questions derived therefrom) and PTSD (the PTSD Checklist).

Question 2: Accuracy of mTBI/PTSD assessment

We found no studies that examined methods of PTSD assessment in individuals with mTBI or methods of mTBI assessment in individuals with PTSD.

*References 25, 34–39, 41, 44, 46–48, 50, 53, 55, 57-63, 68–70.
†References 25, 34, 37, 41, 46–48, 50, 55-63, 68.

*References 46, 47, 50, 55, 57–60, 62, 63.

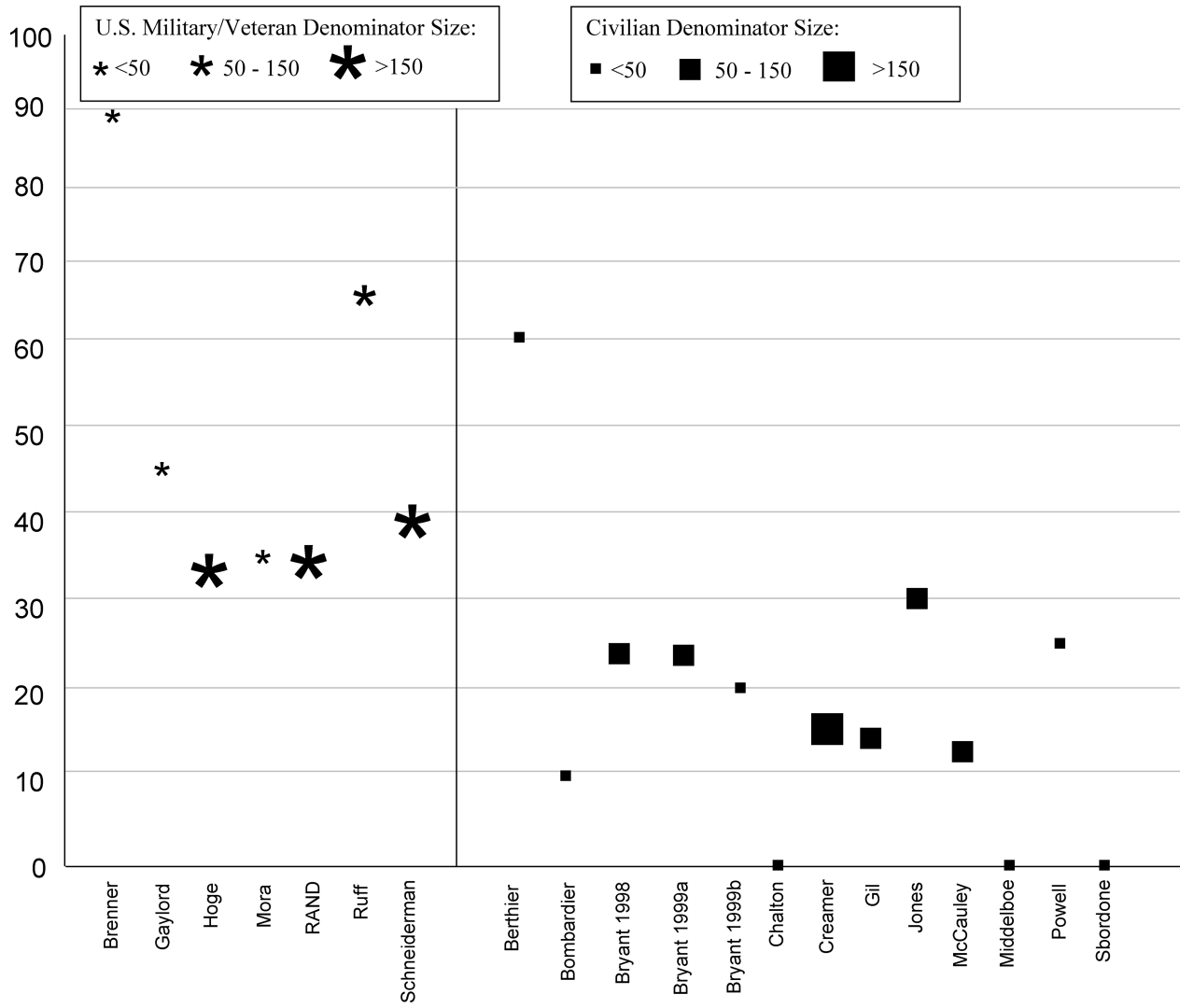

Figure 3. Frequency of PTSD among study participants with mild traumatic brain injury (mTBI) history. Denominator size indicates the number of study participants with mTBI history used in the frequency estimates. Studies reporting more than 1 mTBI/PTSD frequency level over time are presented at the first time point. One study (RAND) did not explicitly report TBI severity but is assumed to have identified primarily mTBI history.

While inclusion criteria were not met, we did identify 1 single-center study that compared the relative accuracy of 4 diagnostic measures of PTSD in a convenience sample of 34 civilians with *severe* TBI (defined as a history of posttraumatic amnesia for more than 1 day).[49] The investigators compared 4 sets of PTSD diagnostic measures or criteria: (1) scores more than 25 on the Impact of Events Scale (IES), a self-report questionnaire; (2) fulfillment of criteria B-F on the Post-Traumatic Diagnostic Scale (PDS), another self-report questionnaire; (3) fulfillment of criteria B-F on the Clinician-Administered PTSD Scale (CAPS), a structured clinical interview; and (4) fulfillment of criteria B-F on the CAPS, plus a clinician's judgment that the endorsed symptoms were valid and indeed related to trauma. The latter was considered the gold standard.

On the basis of the gold standard, only 1 individual (3%) met criteria for PTSD. Six individuals (18%) met criteria based on CAPS without clinical judgment, 15 (44%) met IES criteria, and 20 (59%) met PDS criteria. There were no false-negative cases identified by the IES or PDS; all cases identified by CAPS-without clinical judgment were also identified by these self-report questionnaires. A substudy involving the same group of individuals qualitatively explored reasons for false-positive PTSD diagnoses when using the self-report assessment tools versus the structured clinical interviews.[71] The authors suggested that individuals mistook their severe TBI symptoms for PTSD symptoms on the self-report questionnaires, with these discrepancies becoming clear only during the process of a structured clinical interview.

Question 3: Effectiveness of mTBI/PTSD treatment

We found no studies that examined the effectiveness of evidence-based therapies for treatment of symptomatic mTBI or PTSD in individuals with mTBI/PTSD.

We did identify 1 small but good-quality randomized controlled trial that examined the efficacy of a cognitive-behavioral therapy (CBT) for individuals with acute stress disorder (a posttraumatic stress reaction with symptoms similar to PTSD that occurs within the first month after trauma) and a history of mTBI.[72] This study enrolled 24 civilian men and women who experienced traumatic MVC or nonsexual assaults within the preceding 2 weeks. Participants were randomized to either supportive therapy, involving 5 weekly 90-minute sessions composed of psychoeducation and problem-solving skills, or to 5 weekly 90-minute sessions of CBT composed of psychoeducation, progressive muscle relaxation, imaginal exposure to the traumatic events, cognitive restructuring, and in vivo exposure to avoided stimuli. Results indicated that, immediately posttreatment, PTSD was less frequent in the patients who received CBT (8%; $n = 1$) than the supportive therapy group (58%; $n = 7$). At 6-month follow-up, 17% ($n = 2$) of the CBT group and 58% ($n = 7$) of the supportive therapy group met criteria for PTSD. Furthermore, at posttreatment and 6-month follow-up, patients in the CBT group experienced large, significant decreases in PTSD symptoms (as measured by both the IES and CAPS). The authors concluded that CBT is effective in reducing symptoms and preventing onset of PTSD in patients with ASD and mTBI history.

We also identified 2 *case reports* that described treatment approaches for individuals (1 involving a US military patient) with mTBI/PTSD utilizing empirically supported therapies.[73,74] In both case reports, the therapists used cognitive-behavioral techniques to treat the symptoms of PTSD (cognitive processing therapy; exposure and cognitive restructuring) with few modifications. To manage mTBI-related symptoms, the therapists encouraged the patients to use compensatory strategies (eg, using personal digital assistants, scheduling cognitive breaks). Both reports highlighted the range of problems experienced by the individuals they were treating (eg, anger, depression, substance abuse) and advocated for an idiographic, integrative approach to treatment. These case studies reported a decrease in symptoms of anxiety and depression; however, significant residual symptoms remained.

DISCUSSION

Our systematic review found little consistent evidence on frequency of TBI/PTSD or on variation in frequency levels by TBI severity or other potentially important population or trauma characteristics. We identified no studies that met inclusion criteria and addressed diagnostic accuracy or treatment effectiveness for mTBI and/or PTSD when the conditions co-occur. In the context of the recent and growing awareness of mTBI/PTSD among returning soldiers and veterans, it is clear that further research in this area is urgently needed.

Prior reviews in which rates or prevalence of TBI/PTSD[75] or mTBI/PTSD[22,76] were examined reported similarly diverse findings across studies. This wide range of frequencies reported across studies likely reflects the differences in study objectives, design, and methodology, including methods of defining and assessing both TBI and PTSD cases. Although we were unable to identify any systematic differences in frequency levels by methods of TBI or PTSD assessment, variations in assessment combined with variations in other study parameters (ie, study samples and settings, trauma etiology and severity, number of traumas, and length of time since trauma) may have resulted in the observed heterogeneity. It should be recognized that most studies were not designed to estimate population prevalence of TBI/PTSD but were included in this review because they presented frequency data that could be useful as evidence of prevalence.

Our review included at least 10 new studies, including the 3 large US military or veteran studies,[25,34,41] that were not included in prior systematic reviews. While the overall range in TBI/PTSD frequencies across most of these 10 new studies was as broad as in the prior studies, the results of the 3 large military or veteran studies were strikingly consistent. This consistency was especially remarkable given the different sampling frames and survey methods. Between 5% and 7% of participants in each study responded affirmatively to questions identifying probable mTBI/PTSD.[25,34,41] While the size of these studies and the consistency of their findings strengthen confidence that these values represent the "true" TBI/PTSD prevalence levels for US military or veteran populations, it is important to note that study limitations may have led to biased or inaccurate results. As described previously, all 3 studies were cross-sectional in nature and utilized screening instruments to assess probable history of TBI as well as probable PTSD. Screening instruments may lead to overestimation of TBI and PTSD.[77,78] The Brief Traumatic Brain Injury Screen has been cross-validated with other instruments, but not against a gold standard clinical diagnosis.[79] And while validational studies have shown the PTSD Checklist to have high sensitivity and specificity in some populations (eg, 1.00 and 0.92, respectively), the psychometric properties of this instrument can differ on the basis of both the population and the scoring method

used.[78,80] These and other concerns about the accuracy of current estimates of TBI and PTSD prevalence have recently been described.[78] Not previously noted, however, were the relatively low participation rates in these 3 large studies. Response rates ranged from 34% to 59%, and only 1 of the studies incorporated statistical adjustment in attempt to account for potential response bias.[34] Depending on whether and how respondents and nonrespondents differed systematically, and how representative the study samples were of all deployed military personnel, the figures reported in these studies may actually over- *or* underestimate the true prevalence of mTBI/PTSD among those who have served in Iraq and Afghanistan.

However, even if the population prevalence of TBI/PTSD differs from the estimates reported in the studies included in this review, data across most studies indicate that PTSD is a substantial problem among those with a TBI history. Most studies reported probable or diagnosed PTSD in 10% to 40% of study participants with probable or diagnosed history of TBI. Specific to mTBI, the 3 large US military or veteran studies again had consistent results, reporting probable PTSD in 33% to 39% of respondents who endorsed having experienced a probable mTBI.[25,34,41] While there is debate about the possibility of overestimated mTBI/PTSD prevalence,[26,77,81] it is nonetheless important that clinicians who are screening for or treating veterans with a history of mTBI understand the likelihood and potential implications of co-occurring PTSD. A recent qualitative study identified challenges faced by providers when assessing and treating veterans with both diagnoses.[82] Clinicians expressed a need for comprehensive educational materials as well as enhanced coordination between specialty clinics. The recent evidence suggesting a high prevalence of PTSD among OEF/OIF veterans with a history of mTBI lends urgency to these and other needs expressed by providers.

It was evident from this review that more research needs to be conducted in order to answer key questions pertaining to prevalence, assessment, and treatment of mTBI/PTSD, particularly among OEF/OIF veterans. The internal and external validity of studies making up the current body of evidence were relatively poor. Most studies were small in size, cross-sectional in nature, and/or involved highly selective study populations. Many studies were conducted in a single medical or research center, with participants frequently recruited from among patients who had been hospitalized or had received medical attention specifically for a trauma. Furthermore, assessment methods, timing, and diagnostic criteria (ie, cut-points) used to identify TBI and PTSD cases varied widely, decreasing comparability among studies. To date, no studies based on representative samples have been conducted using gold standard diagnostic interviews.

We acknowledge that many of the studies included in this review were not designed to answer our questions but were included because they provided data on frequency of TBI/PTSD in their respective study populations. We also acknowledge that there are multiple challenges inherent to conducting the high-quality research studies that would most appropriately address the 3 questions posed for this review. We consider many of the current studies to provide important preliminary information on which future work may be based. However, we stress that different methods and thresholds to define disease and injury, as seen in the current body of evidence, can profoundly affect estimates of prevalence, severity, natural history, and response to treatment of a condition. This problem with inconsistency across studies may be exacerbated when individual participants' responses are affected by the potential for financial compensation, as can be the case with both TBI and PTSD sufferers.[26]

Future research

Future efforts are needed to improve the evidence on which assessment and treatment of mTBI/PTSD are based. First and foremost, there is a clear need for the research community to come to consensus about defining and measuring both TBI (particularly mTBI) and PTSD and to then apply these practices consistently across studies. The need to develop standard definitions, study methods, and reporting styles in studies of the epidemiology of TBI was recently described elsewhere.[83] If this suggested level of standardization and consistency were to be met in all future studies of TBI and PTSD, our ability to synthesize data and draw meaningful conclusions from results would be greatly enhanced.

To provide better evidence on the prevalence and outcomes of TBI/PTSD in military and veteran populations, large, prospective epidemiologic studies are needed that recruit and retain the most representative samples possible and utilize standard definitions and measures. This research should be based on methods of collecting the information necessary for assessing the occurrence and severity of TBI near the time of injury without relying on subject recall or hospital records, a charge that is particularly challenging for injuries that occur in a combat setting. Until we have a greater understanding of which individual (eg, demographic; baseline functioning; physical or mental health morbidities) and exposure (eg, trauma etiology; distance from blast or explosion) characteristics can affect prevalence and outcomes of mTBI/PTSD, future efforts, when possible, should collect and report this information consistently.

Stratification of results by clearly defined levels of TBI severity, particularly so that study participants with mTBI history are not combined with those with moderate and severe TBI, is also important. These and other efforts to standardize research methods and reporting will help investigators better synthesize study results in future evidence reviews.

Well-designed studies on diagnostic accuracy and treatment effectiveness are needed to inform the provision and coordination of rehabilitation and mental health services for patients with potential mTBI and PTSD. While there are evidence-based guidelines for assessing and diagnosing mTBI and PTSD in the clinical setting,[84,85] these guidelines do not focus on the co-occurrence of these 2 conditions. Further development in this area is especially important given the frequency of combat-related trauma in OEF/OIF, the potential for financial compensation, the similar presentation between symptomatic mTBI and PTSD, and the length of time between traumatic events, such as blast exposures, and clinical screening and diagnosis. We recommend that researchers examine the negative and positive predictive values of current PTSD assessment methods among veterans with a history of mTBI, similar to the cited study in which the relative validity of 4 PTSD assessment instruments was compared in individuals with severe TBI.[49,71] Future efforts would also benefit from adherence to the Standards for Reporting Diagnostic Accuracy Studies Statement (STARD), which involves a checklist of 25 items by which the external and internal validity of diagnostic accuracy studies may be gauged.[86] In addition, research that develops clinically valid screening or diagnostic tools into valid instruments that can be used with survey-based research would benefit this field.

High-quality (ie, randomized and controlled) studies examining the efficacy and effectiveness versus potential harms of clinical services for individuals with mTBI/PTSD are also needed. Evaluation of the possible effects of PTSD on the outcomes of mTBI rehabilitation, particularly in the domains of social and vocational functioning, which can be strongly affected by PTSD symptoms, is important. It is also imperative to evaluate current evidence-based treatments of PTSD in individuals with history of mTBI, given that mTBI has been an explicit exclusion criterion in PTSD treatment trials.[27] To start, the efficacy of existing empirically supported treatments of PTSD (eg, prolonged exposure therapy, cognitive processing therapy) in individuals with a history of mTBI and, as a subset, those with currently symptomatic mTBI, should be examined. Ideally, participants would be stratified by mTBI status and randomized to either the treatment or control condition, enabling researchers to evaluate differential outcomes between groups based on mTBI status. Such studies should also examine facets of clinical effectiveness, such as treatment adherence, engagement, and tolerability, and should evaluate whether those with mTBI history have more difficulty with tasks related to memory and attention (eg, homework completion, engagement in imaginal exposure) than those with PTSD but no mTBI history. If memory or attentional problems do contribute to differential outcomes, then the development and evaluation of a set of compensatory strategies that could be used in conjunction with existing treatments may prove to be necessary. Finally, if adding compensatory strategies to existing PTSD treatments does not improve outcomes among individuals with mTBI/PTSD, researchers should look to more substantially alter existing evidence-based therapies or begin to develop novel interventions.

CONCLUSION

The reported frequencies of TBI/PTSD, particularly mTBI/PTSD, vary widely, likely because of differences in study aims, samples, and designs. There were no studies on the diagnostic accuracy of commonly used methods to assess history of mTBI or current PTSD when both conditions are present. Similarly, there were no studies evaluating the effectiveness or harms of therapies in adults with mTBI/PTSD. Consensus is needed on the most appropriate instruments and measurement standards for use in identifying history of TBI, particularly mTBI, and PTSD. Long-term prospective studies are needed that use these measures and examine prevalence, accuracy of assessment methods, and effectiveness of therapies for mTBI and PTSD when these conditions co-occur.

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