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Complications of Mild Traumatic Brain Injury in Veterans and Military Personnel: A Systematic Review

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PREFACE

Quality Enhancement Research Initiative's (QUERI) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers, as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout VA.

QUERI provides funding for four ESP Centers and each Center has an active VA affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence,
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of QUERI Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at nicole.floyd@va.gov.

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EVIDENCE REPORT

INTRODUCTION

Traumatic brain injury (TBI) is a common condition, especially among military members. Twelve to 23 percent of service members returning from Operations Enduring Freedom, Iraqi Freedom, and New Dawn (OEF/OIF/OND) experienced a TBI while deployed. Although various criteria are used to define TBI severity, the majority of documented TBI events among OEF/OIF/OND service members may be classified as mild in severity, or mTBI, according to the definition used by the Veterans Health Administration and Department of Defense (VA/DoD).[1]

While some researchers suggest most individuals recover within three months of an mTBI, others estimate that 10 to 20 percent of individuals continue to experience post-concussive symptoms (e.g., headaches, dizziness, balance problems) beyond this time fame.[2] This estimate may be higher among OEF/OIF service members given the frequency of multiple TBI events, concomitant mental health conditions such as depression and posttraumatic stress disorder (PTSD), and other factors unique to combat deployments. As such, deployment-related mTBI is a significant issue for the VA, as patients who report ongoing mTBI symptoms may require the attention from a range of health care professionals.[3] This evidence synthesis review will be used by the VHA TBI Advisory Committee to develop strategies to identify those at-risk for long-term mTBI effects, inform clinical practice, determine resource allocation, and identify future research priorities.

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METHODS

TOPIC DEVELOPMENT

This project was nominated by Dr. Stuart Hoffman, Scientific Program Manager for the Brain Injury portfolio, Rehabilitation Research & Development Service. Operational partners include David X. Cifu, MD, Chair, VHA TBI Advisory Committee and National Director of Physical Medicine and Rehabilitation (PM&R) Program Office; Robert L. Ruff, MD, PhD, National Director for Neurology and Acting-Director of Rehabilitation Research and Development; Joel Scholten, MD, Associate Chief of Staff for Rehabilitation Services, Washington DC VA Medical Center Director of Special Projects, PM&R Program Office, Veterans Affairs Central Office (VACO); and Alexander Ommaya, DSc, Director of Translational Research, Office of Research and Development. We also received input from a technical expert panel.

Anticipated report usage:

The evidence synthesis review will be used by the VHA TBI Advisory Committee to develop strategies to determine which sub-groups are most at risk for long-term effects of mTBI. The review will be used to inform clinical practice and to identify how best to allocate future resources for effective screening for late complications of mTBI. The review will also identify gaps in evidence that warrant further research.

The final key questions are:

Key Question #1. For Veteran/military populations, what is the prevalence of health problems (such as pain, seizure disorders, headaches, migraines, and vertigo), cognitive deficits, functional limitations (such as employment status, changes in marital status/family dynamics), and mental health symptoms (such as PTSD and depression) that develop or persist following mTBI?

Key Question #2. What factors affect outcomes for Veteran/military patients with mTBI? Key Question 2A: For Veteran/military populations, are there pre-injury (premorbid) risk/protective factors (e.g., pre-injury mental health factors, genetic factors, or prior concussions) that affect outcomes for mTBI? Key Question 2B: For Veteran/military populations, are there post-injury risk/protective factors (e.g., PTSD) that affect outcomes for mTBI?

Key Question #3. What is the resource utilization over time for Veteran/military patients with mTBI?

SEARCH STRATEGY

We searched Medline, PsychINFO and Cochrane Register of Controlled Trials (OVID) for observational studies, clinical trials, systematic reviews, and cost studies, from database inception to October 3rd, 2012. We limited the search to articles involving human subjects and published in the English language. We adapted the search strategy developed by the WHO Collaborating Centre for Neurotrauma Prevention, Management and Rehabilitation Task Force for a recent systematic review of prognosis after mTBI, which included the terms 'traumatic brain injury,' 'craniocerebral trauma,' 'prognosis,' and 'recovery of function.'[4] The full details of the search strategy are provided in Appendix A. The preliminary WHO Collaborating Centre for Neurotrauma Prevention, Management and Rehabilitation Task Force search strategy was reviewed by a library scientist and by our team of investigators with clinical expertise in order to assure comprehensiveness of the search. The search was expanded to include additional mTBI search terminology following the discovery of a relevant article which was not identified in the preliminary search. After review, we expanded the WHO Collaborating Centre for Neurotrauma Prevention, Management and Rehabilitation Task Force search with additional TBI terms and also limited the search to Veteran/military population studies by using terms including military, VA, and Veteran (Appendix A). We obtained additional articles from systematic reviews, reference lists of pertinent studies, reviews, editorials, and by consulting clinical and research experts. All citations were imported into an electronic database (EndNote X4).

STUDY SELECTION

We included studies reporting outcomes in Veterans or military personnel who had suffered an mTBI using a case definition consistent with definitions in the VA/DoD Clinical Practice Guideline for Management of Concussion/Mild Traumatic Brain Injury. Abstracts of citations identified from literature searches were reviewed by the PI to assess for relevance to the key questions; a portion of the abstracts were dual reviewed by at least one additional member of the team to assure accuracy and consistency of coding. Full-text articles of potentially relevant abstracts were retrieved for further review, and reviewed by the PI and at least one additional reviewer. Full-text articles for which there was disagreement by two reviewers were reviewed by the team of investigators and included or excluded based on team consensus. Each article was reviewed using the eligibility criteria in Appendix B. A list of excluded studies grouped by reason for exclusion is reported in Appendix F. Eligible articles had English-language abstracts and provided data relevant to the key questions. Articles also had to report outcomes for members of the U.S. armed forces or Veterans.

Diagnostically, to have sustained a TBI one must have experienced an event (e.g., motor vehicle crash, fall) which resulted in a structural injury to the brain or a physiological disruption of brain function (e.g., alteration of consciousness,[5] loss of consciousness [LOC], or post-traumatic amnesia[6]). TBI severity is classified according to the extent of harm to the brain or altered consciousness associated with the injury. Severity of residual symptoms reported or observed should not be used to classify TBI severity. Therefore, to apply consistent criteria to define mTBI and compare similar populations with mTBI, all included studies had to use a definition of mTBI consistent with the VA/Department of Defense (DoD) Clinical Practice Guideline for Management of Concussion/Mild Traumatic Brain Injury described in Appendix C. Articles that described their populations as having mTBI but used definitions of mTBI differing from the VA/DoD criteria were excluded from this evidence synthesis but are described in Appendix D. Due to the frequent lack of reporting or obtaining imaging results (e.g., MRI, CT scan), the only variation from this definition in included studies relates to positive imaging results: we included studies regardless of whether they reported or included participants with positive imaging results as long as the rest of their mTBI inclusion criteria were consistent with the VA/DoD criteria. Finally, we did not limit study eligibility based on number of mTBI incidents or the presence of comorbid conditions.

We published our key questions and abstract online so that they were available for public review. A summary of article inclusion criteria is as follows:

Population(s): Veterans or members of the military who have experienced mTBI. Studies that do not differentiate between adult and child populations, or between Veteran/military and civilian populations, will be excluded. Studies must state a clear case definition for mTBI that falls within the definitions provided by the VA/DoD Clinical Practice Guideline for Management of Concussion/Mild Traumatic Brain Injury (Appendix C).

Intervention(s): Not applicable to the proposed key questions.

Comparator(s): Similar populations that have not been diagnosed with mTBI or concussion; comparison group not required for inclusion.

Outcome(s): Health problems (e.g., pain, seizure disorders, chronic headaches, migraines, vertigo, etc.), cognitive deficits, functional limitations (e.g., employment status, marital status changes/family dynamic changes), mental health symptoms (e.g., diagnosis of PTSD or depression), and cost/resource utilization (ER visits, hospitalizations, outpatient appointments). Outcomes diagnosed post-mortem will be included (e.g., Chronic Traumatic Encephalopathy [CTE]).

Timing: No limitations based on time since injury.

Setting: No limitations based on study setting.

Study design: Systematic reviews, meta-analyses, randomized controlled trials, prospective and retrospective cohort studies, case control studies, case series, and cross-sectional studies.

Sample size: All included studies must include a minimum of 30 mTBI cases, so that a better level of precision and confidence in the results can be achieved.

DATA ABSTRACTION

We abstracted the following data for each included study: sample selection, population characteristics, subject eligibility and exclusion criteria, number of subjects, comparison(s), and outcome(s) (See Table 1 and Appendix E). Data was abstracted by one investigator and reviewed for accuracy by at least one additional investigator.

QUALITY ASSESSMENT

We assessed the quality of included studies pertaining to all of the key questions. We found no randomized trials meeting inclusion criteria, and our entire sample of included studies is comprised of observational studies of various designs, primarily retrospective cohort, case control, and case series. Issues of quality, particularly in observational studies, are often unique to the condition and outcomes of interest. Therefore, though we assessed quality using criteria based on the Newcastle-Ottawa quality assessment tools for observational studies[7] the criteria that specifically related to this body of literature included the following: accurate definition of condition of interest, consecutive sample selection, use of validated assessment tools, blinding of outcome assessors, blinding of patients and assessors to study hypotheses, adjustment for known confounders including mental health condition, comparability of controls, response rate, attrition, and reduced risk of reporting bias. These indicators of study quality and potential for bias were abstracted by one investigator and reviewed for accuracy by at least one additional investigator who was not blinded to the original assessment. In cases of disagreement, the team of investigators reviewed the study and came to consensus on quality assessment. In addition to quality rating of individual studies, we evaluated the overall quality of the evidence for each key question as proposed by the GRADE Working Group.[8]

DATA SYNTHESIS

We constructed evidence tables showing the study characteristics and results for all included studies organized by outcome. We critically analyzed studies to compare their characteristics, methods, and findings. We compiled a summary of findings for each outcome category and key question, and drew conclusions based on qualitative synthesis of the findings. We did not combine the studies in a quantitative manner via meta-analysis because of the heterogeneity of outcomes and study characteristics. The synthesis was conducted by the principal investigator, though all results were reviewed with the team of investigators to review and obtain consensus on the reported findings.

RATING THE BODY OF EVIDENCE

We assessed the overall quality of evidence for outcomes using a method developed by the GRADE Working Group,[8] which classified the grade of evidence across outcomes according to the following criteria:

- High = Further research is very unlikely to change our confidence on the estimate of effect.
- Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very Low = Any estimate of effect is very uncertain.

PEER REVIEW

A draft version of this report was reviewed by 11 technical experts as well as clinical leadership. Their comments and our responses are presented in Appendix G.

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RESULTS

METHODOLOGIC CONSIDERATIONS

The strengths of included studies include using well-validated assessment tools, comparing similar populations with and without mTBI, and applying a clearly reported definition of mTBI consistent with VA/DoD criteria. In spite of these strengths, however, all of the included studies were rated as having high risk of bias for the following reasons: The included studies often did not adequately account for time since injury (the only exception being two studies reporting results from a single population), or other quality factors such as assessor blinding to the presence of mTBI, participant and assessor blinding to study hypotheses, or clearly reporting sampling procedures. This body of observational literature did not, in general, report results in a manner consistent with reduced reporting bias, and it is possible that studies emphasized or only reported statistically significant or otherwise selected results. Because outcomes and risk/protective factors are often described in single studies without replication by other research teams, this body of literature is not strengthened by adequate replication and confirmation of preliminary results. Therefore, the overall body of literature providing evidence on outcomes for those with mTBI is from low quality observational studies, and the overall strength of evidence is low for all outcomes reported in this review. Because all individual studies were rated as having high risk of bias, no studies were differentially weighted based on quality in the data synthesis.

LITERATURE FLOW

We reviewed 2,664 titles and abstracts from the electronic search, and identified an additional 4 studies from reviewing reference lists and conducting manual searches. After applying inclusion/exclusion criteria at the abstract level, 354 full-text articles were reviewed, as shown in Figure 1. Of the full-text articles, we excluded 323 that did not meet inclusion criteria. We grouped the studies by outcome and key question. Figure 1 details the exclusion criteria and the number of references related to each of the key questions. We identified 31 primary studies that addressed the key questions. All studies were conducted in U.S. Veterans or active-duty service members of the U.S. military. Table 1 shows the characteristics of the 31 primary studies, and the following sections detail findings according to symptom category.

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Figure 1. Literature Flow Diagram

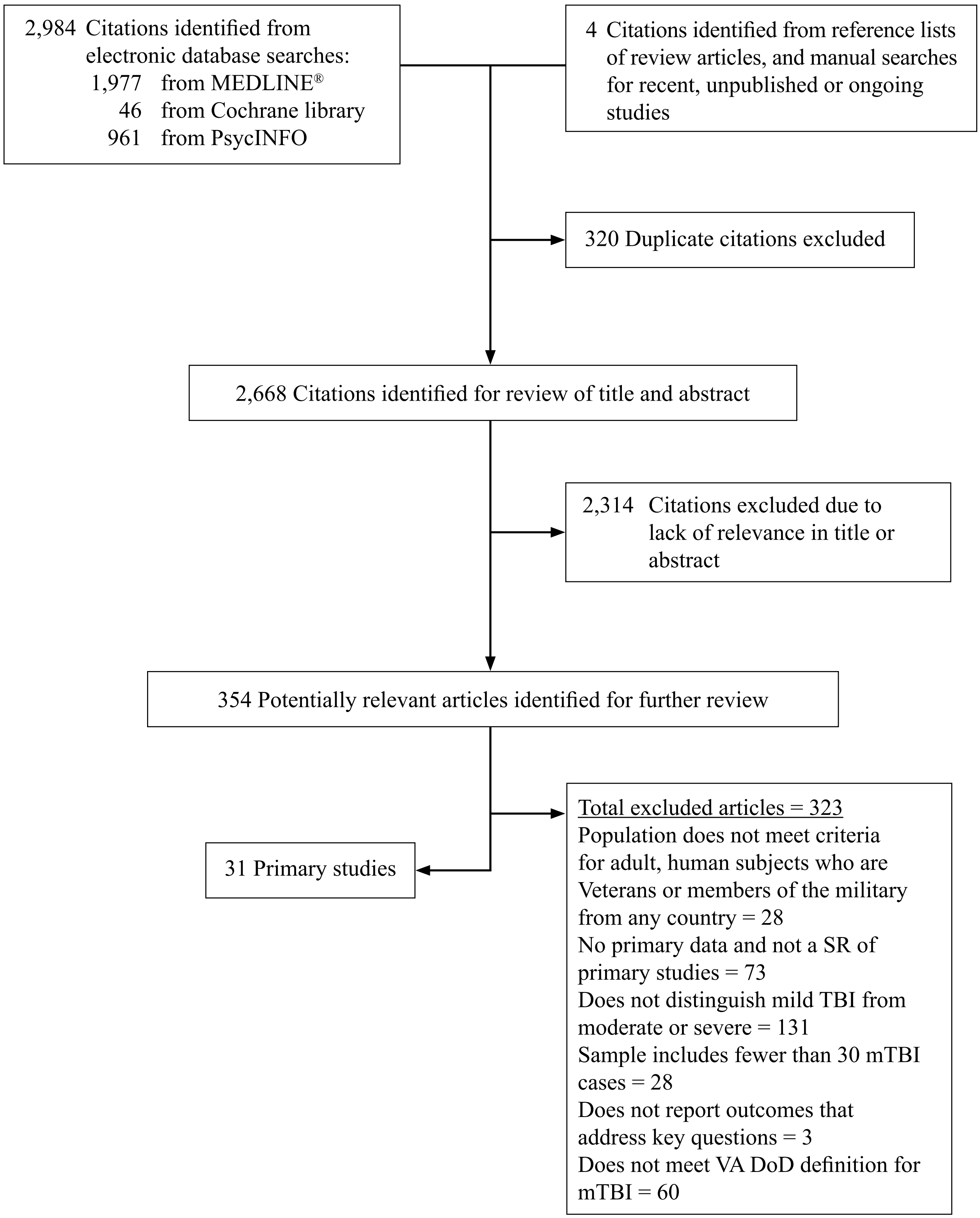

Table 1. Descriptive Characteristics of Studies of U.S. Veterans and Members of the U.S. Military with Mild Traumatic Brain Injury

Author, year	Population and sample selection	mTBI definition and associated citation reported in the study	Sample size: Total, mTBI	Demographics of mTBI group	Time since injury for mTBI group, Mean (SD); Mechanism of injury; Prior TBI
Barnes, Walter, & Chard, 2012[9]	Consecutive referrals for outpatient PTSD treatment between 2006 and 2010 at a Midwestern Veterans Affairs Medical Center. All patients served in OEF and/or OIF and met diagnostic criteria for PTSD due to combat-related trauma. Excluded: LOC >30 mins or PTA >24 hrs.	• Definition: AOC, LOC, PTA. • Positive imaging: NR • Citation: Holm, Cassidy, Carroll, & Borg, 2005 • How assessed: Chart review, clinical interview	92, 46	(data reported only for entire sample) • Age: 30.3 (8.2) • Gender: 100% male • Race/Ethnicity: 93.3% Caucasian, 4.4% African American, 2.2% Native American • Education: NR	• Time since injury: NR • Mechanism of Injury: NR • Prior TBI: NR
Belanger, Kretzmer, Venderploeg, & French, 2010[10]	Patients consecutively admitted to Tampa VAMC or WRAMC; clinics not specified.	• Definition: PTA, LOC • Positive Imaging: Excluded • Citation: Kay et al., 1993 • How assessed: Self report, chart review	225, 134	• Age: 30.7 (9.5) • Gender: 97% male • Race/Ethnicity: NR • Education: NR	• Time since injury: 703.5 (1064.1) days • Mechanism of Injury: 67% blast, 25% MVA, 7% other mechanism of injury • Prior TBI: 14/134 with prior mTBI
Belanger, Kretzmer, Yoash-Gantz, Pickett, & Tupler, 2009[11]	Tampa and Richmond VA consecutive brain injury rehab patients referred for neuropsychological evaluation; Salisbury and Durham VAMC post-deployment and VA outpatients; and "selected research volunteers" from Mid-Atlantic MIRECC. Excluded: poor effort or malingering based on clinical presentation and/or if they failed certain measures of symptom validity; neurological disorders; brain injury due to gunshot.	• Definition: LOC and PTA • Positive Imaging: Included (n = 6 blast, n = 3 non-blast) • Citation: Kay et al., 1993 • How assessed: Self-report, chart review	102, 51	• Age: 30.9 (9.2) • Gender: NR* (4/102 female for entire aggregate sample) • Race/Ethnicity: NR* (76 Caucasian, 16 African American; 8 Hispanic; 2 Other for entire aggregate sample) • Education: 13.1 (2.2) yrs	• Time since injury: 1021.4 (1730.0) days • Mechanism of Injury: For total sample: 49 = blast only; 12 = blast plus MVA; 41 = non-blast • Prior TBI: NR* (n = 20 for entire aggregate sample)
Belanger, Proctor-Weber, Kretzmer, et al. 2011[12]	Tampa and Bay Pines VAMCs and WRAMC. 10% of these participants were included in the Belanger, Kretzmer, Vanderploeg, & French, 2010 analyses.	• Definition: DoD Criteria • Positive Imaging: Excluded • Citation: Kay et al., 1993 • How assessed: Clinical interview chart review	390	• Age: 28.3 (7.9) for blast exposed; 30.0 (9.1) for non-blast exposed • Gender: 94% male • Race/Ethnicity: NR • Education: NR	• Time since injury: 6 months (WRAMC); 52 months (VA) • Mechanism of Injury: 298 = blast, 92 = non-blast cause • Prior TBI: NR
Benge, Pastorek, & Thornton, 2009[13]	Veterans evaluated by the polytrauma team. Excluded: moderate or severe brain injury; skull penetration.	• Definition: Identifying a mechanism of injury and endorsing at least one of the following symptoms: LOC, PTA, or feeling dazed for <24 hrs after the injury. • Positive imaging: NR • Citation: Defense and Veterans Brain Injury Center, 2006 • How assessed: Chart review	345	• Age: 30.4 (7.5) • Gender: 96.2% male • Race/Ethnicity: 11.6% African American, 66.4% White, 18.6% Hispanic, 3.5% other • Education: 55.9% HS diploma or equivalent, 37.1% some college, 5.8% college graduate, 1.2% other	• Time since injury: 3.0 (1.6) yrs (most recent injury) • Mechanism of Injury: 64.6% report at least one blast injury, 29.9 report at least one motor vehicle accident, 25.5 report at least one fall • Prior TBI: NR

Author, year	Population and sample selection	mTBI definition and associated citation reported in the study	Sample size: Total, mTBI	Demographics of mTBI group	Time since injury for mTBI group, Mean (SD); Mechanism of injury; Prior TBI
Coldren, Kelly, Parish, et al., 2010[14]	Jan 11, 2009-Apr 10, 2009, U.S. Army soldiers presenting for medical care within 72 hrs of suffering a concussive event in Iraq. Included: 18-50 years, meeting DoD definition of a concussion, free of psychoactive medication, no significant psychiatric diagnosis requiring ongoing therapy, reporting pain not greater than 7 on a scale of I to 10, consenting to be in the study. Subjects and controls were enrolled from Victory Base Complex, Joint Base Balad, and Mosul. Non-TBI injured controls were patients in the same timeframe. Healthy controls were volunteers located at same base. Excluded: any history of severe TBI, moderate TBI within the previous 3 yrs, or of any concussion within 90 days of current injury.	• Definition: DoD criteria • Positive imaging: NR • Citation: DoD diagnostic criteria, no citation given • How assessed: Clinical interview	237, 71	Cases vs. controls: • Age: 26.5 vs. 27.3 (SD not reported), p = 0.44 • Gender: 96% vs. 88% male, p = 0.07 • Race/Ethnicity: NR • Education (yrs): 12.5 vs. 13.1 (SD not reported), p = 0.02	• Time since injury: within 72 hrs • Mechanism of Injury: NR • Prior TBI: Excluded moderate or severe TBI within 3 yrs, and concussion within 90 days of current injury.
Coldren, Russell, Parish, et al., 2012[15]	US Army soldiers presenting to an outpatient medical facility within 72 hrs of a concussion between January to April, 2009; free of cognition altering medication or severe psychiatric diagnosis requiring ongoing therapy, no pain > 7 on a 1-10 scale, no severe TBI, no moderate TBI within the past 3 yrs, no concussion within the past 90 days.	• Definition: DoD criteria • Positive imaging: NR • Citation: NR • How assessed: NR	235, 69	• Age: 18-20 (9%), 21-25 (45%), 26-30 (26%), 31-40 (17%), 41-55(4%) • Gender: 96% male • Race/Ethnicity: Caucasian (72%), Black (4%), Hispanic (19%), other (4%) • Education: HS (4%), HS graduate (57%), some college (38%), college graduate (0%)	• Time since injury: 0 (2%), 1 (47%), 2 (29%), 3 (22%) days • Mechanism of Injury: blast 45%, blow 26%, mixed 11%, unknown 19% • Prior TBI: none in past 90 days
Cooper, Chau, Armistead-Jehle et al., 2012[16]	Consecutive admissions of OEF/OIF military service members referred to the TBI clinic at BAMC for neuropsychological testing between January 2008 and January 2010. All participants were over 18 years of age, spoke English fluently, and were injured while on active duty. Excluded participants had major body burns, had traumatic amputations, were missing key variable data, or performed below cutoffs indicating suboptimal effort on neuropsychological measures. No psychiatric exclusion criteria were applied.	• Definition: ACRM and VA/DoD criteria • Positive imaging: Excluded • Citation: ACRM, 1993 • How assessed: Clinical interview and chart review	60	Blast exposed vs. non-blast exposed: • Age: 29.5 (7.73) vs. 29.43 (7.95) • Gender: 100% vs. 78.6% male • Race/Ethnicity: NR • Education: NR	Blast exposed vs. non-blast exposed: • Time since injury: 192.29 (167.46), 148.69 (150.98) days • Mechanism of Injury: Blast 53% non-blast 47% • Prior TBI: NR

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Author, year	Population and sample selection	mTBI definition and associated citation reported in the study	Sample size: Total, mTBI	Demographics of mTBI group	Time since injury for mTBI group, Mean (SD); Mechanism of injury; Prior TBI
Cooper, Kennedy, Cullen, et al., 2011[17]	Active duty service members, including activated reservists and members of the National Guard, who were evaluated at a military medical treatment facility in Brooke Army Medical Center (BAMC) following a combat deployment to Iraq or Afghanistan and sustained a concussive injury during their deployment. Subjects were identified for this study through multiple sources including inpatient care, post-deployment primary care clinics, specialty care clinics (e.g. Traumatic Brain Injury Service) and case management. Excluded: did not sustain a TBI, 87 subjects with moderate or severe TBI or penetrating brain injuries; 232 mTBI subjects with PCL-C scores 31–59 from this analysis to maximize the dispersion of the combat stress variable (i.e., excluded medium-combat stress in order to compare low vs. high).	• Definition: ACRM criteria. • Positive imaging: NR • Citation: ACRM, 1993 • How assessed: Clinical interview	240	Low combat stress vs. high combat stress: • Age: 26.4 (6.5) vs. 27.8 (6.9) • Gender: 99.2% vs. 94.4% • Race/Ethnicity: NR • Education: NR	Low combat stress vs. high combat stress: • Time since injury: 3.8 (5.8) vs. 7.3 (11.0) months • Mechanism of Injury: Blast 84% vs. 85% • Prior TBI: NR
Cooper, Mercado-Couch, Richfield, et al., 2010 [18]	194 US military service members with burn injuries due to explosive munitions treated at BAMC between Sep 2005 and Oct 2007. Service members who sustained a blast injury were referred to the Neuropsychology Service as part of routine screening for clinical evaluation and neurocognitive testing. Excluded: 10 participants due to length of PTA suggesting a more severe brain injury than ACRM criteria; 17 subjects because they could not complete the manual portion of neuropsychological testing due to severe bilateral burns and/or amputations.	• Definition: ACRM criteria; and GCS score ≥ 13 • Positive imaging: NR • Citation: ACRM, 1993 • How assessed: Clinical interview and chart review	167, 50	TBI+ (n = 50) vs. TBI- (n = 117): • Age: 25.06 (5.818) vs. 25.67 (5.537), p = 0.524 • Gender: 44 (88.0%) male 114 vs. (97.4%) male, p = 0.013 • Race/Ethnicity: NR • Education (presumably years): 12.54 (1.073) vs. 12.52 (1.454), p = 0.935	TBI+ vs. TBI- • Weeks since injury: 8.12 (7.763) vs. 7.76 (8.181), p = 0.792 • Mechanism of Injury: All subjects had burn injuries due to explosive munitions • Prior TBI: NR
Cooper, Nelson, Armistead-Jehle, et al., 2011[19]	Consecutive referrals to a Brain Injury clinic, including documented or suspected mTBI and neurorehabilitation patients. The sample was primarily composed of active duty service members including activated reservists and members of the National Guard. As part of standard operating procedure, all individuals referred to the clinic completed self- report symptom questionnaires on a computer kiosk prior to their initial encounter with a medical provider. Only subjects completing all three self-report questionnaires. (PCL-M; NSI; mBIAS) were included in the final sample. From an initial archival set of 443 subjects, 40 subjects were excluded for incomplete data on one or more measures of interest.	• Definition: ACRM criteria; GCS score ≥ 13. Consistent with the current DoD guidance … individuals with positive neuroimaging findings, who otherwise met criteria for mTBI, were classified as moderate TBI. • Positive imaging: Excluded • Citation: Casscells, 2007; ACRM, 2003 • How assessed: Clinical interview, chart review	403, 268	• Age: 32 (9) • Gender: 93% male • Race/Ethnicity: NR • Education: NR	• Time since injury: N (%) 1 yr: N = 148 (62%) 1-3 yrs: N = 53 (22%) >3 yrs: N = 35 (15%) • Mechanism of Injury: NR • Prior TBI: NR

Author, year	Population and sample selection	mTBI definition and associated citation reported in the study	Sample size: Total, mTBI	Demographics of mTBI group	Time since injury for mTBI group, Mean (SD); Mechanism of injury; Prior TBI
Drag, Spencer, Walker, et al., 2012[20]	Veterans in TBI clinic at the VA Ann Arbor Healthcare System, consecutive sample. Excluded injuries exceeding a mTBI; C and P evaluation; scored below cutoff on Digit Span; scored below cutoff on the Rey-15; incomplete data; scored below cutoff on the Shipley Vocabulary test.	• Definition: LOC; PTA; "alteration in mental state" at time of injury; focal neurological deficit • Positive imaging: NR • Citation: Kay et al., 1993 • How assessed: Self-report screening tool and structured clinical interview	167	• Age: 29.47 (7.28) • Gender: 163 (M), 4 (F) • Race/Ethnicity: NR • Education: 12.89 (1.63) yrs	• Time since injury: 41.93 (34.06) months • Mechanism of Injury: NR • Prior TBI: NR
Gaylord, Cooper, Mercado, et al., 2008[21]	The population at risk included 360 service members admitted to the USAISR Burn Center for burn and explosion injuries from Aug 2004 to Aug 2006. 146 burned service members treated at the USAISR Burn Center were assessed for PTSD during Sep 2005 through Aug 2006. Of these, 80 were also assessed for TBI. Subjects were included in the study if they sustained both a burn and blast injury and were assessed for both PTSD and TBI (n = 80). Two subjects were diagnosed for moderate and severe TBI and were excluded. Two subjects were excluded because they were not injured in OEF or OIF. Subjects with moderate or severe TBI (as defined by GCS <12 and duration of PTA >24 hrs) were excluded from the current study.	• Definition: ACRM criteria; and a GCS score ≥ 13. • Positive imaging: NR • Citation: ACRM, 1993 • How assessed: Clinical interview	76, 31	• Age: 25.5. (6) mTBI plus PTSD 25, mTBI no PTSD 28.9 • Gender: 96% male mTBI plus PTSD male .93, mTBI no PTSD 1.0 • Race/Ethnicity: NR • Education: NR	• Time since injury: NR, but the admission date for included subjects ranged from Aug 2004-2006, and the sample included subjects assessed for both PTSD and TBI during Sept 2005-Aug 2006. • Mechanism of Injury: Mechanism for burn injury not specified. Blast injury: sustaining a combat injury caused by explosive munitions, such as an IED, RPG, Explosively Formed Projectile (EFP), mortar rounds, VBIED, and conventional grenades. • Prior TBI: NR
Gordon, Fitzpatrick, Hilsabeck, 2011[22]	Veterans who had undergone a neuropsychological evaluation at South Texas Veterans Health Care System; selected from research database. 13/95 excluded based on an invalid TOMM score.	• Definition: LOC; PTA; normal CT and/or MRI • Positive imaging: Excluded; state "uncomplicated." • Citation: Kay et al., 1993 • How assessed: Self-report survey, clinical interview	82	• Age: 49.8 (11.9) • Gender: 88% male • Race/Ethnicity: non-Hispanic White (52%); Hispanic (33%); African Americans (10%); Asian Americans (4%); Native Americans (1%) • Education: 12.9 (2.4) yrs	• Time since injury: 20.1 (14.7) months • MVA (27%); falls (20%); sports injuries (12%); industrial accidents (11%); miscellaneous accidents (11%); assaults (10%); and explosions (9%). "Most (89%) were not sustained during combat." • Prior TBI: NR
Gottshall, Drake, Gray, et al., 2003[23]	From Feb 2000 to Nov 2000, 99 male subjects were evaluated at Camp Pendleton Concussion Clinic (presumably these 99 included 53 cases plus 46 volunteer controls). All subjects were active duty and had no premorbid history of psychiatric or substance abuse disorder. All individuals with mild TBI and a GCS of 14 were included.	• Definition: American Academy of Neurology mTBI definition, • Positive imaging: NR • Citation: Schubert, Herdman, & Tusa, 2001; Kay et al., 1993 • How assessed: Chart review	99, 53	• Age: 22 (SD, NR) • Gender: 100% male • Race/Ethnicity: NR • Education: 98% completed HS; 32% had taken some college-level courses; 4% graduated from college	• Time since injury: mean of 84 hrs post injury (range 2 hrs to 6 days, with the exception of one patient who was not seen until 10 days). • Mechanism of Injury: NR • Prior TBI: NR

Author, year	Population and sample selection	mTBI definition and associated citation reported in the study	Sample size: Total, mTBI	Demographics of mTBI group	Time since injury for mTBI group, Mean (SD); Mechanism of injury; Prior TBI
Kelly, Coldren, Parish, et al., 2012[24]	All U.S. Army soldiers in Iraq presenting for medical care within 72 hrs of a concussive event, from January to April 2009. Inclusion: 18–50, meet DoD criteria for concussion, free of cognition altering medication; have no severe psychiatric diagnosis requiring ongoing therapy (i.e., ongoing medication management by a psychiatrist), report pain not more than 7 of 10, and give consent. Excluded: prior severe TBI, moderate TBI within the previous 3 yrs, or any concussion within the previous 90 days; two cases after demonstrating poor effort on the TOMM; women due to small number of subjects (n = 3).	• Definition: DoD criteria • Positive imaging: NR • Citation: DoD, 2007 • How assessed: Self-report survey, clinical interview	212, 66	Cases (n = 66) vs. controls (n = 146) • Age median (IQR): 25 (22,30) vs. 25 (22,31), p = ns • Gender: 100% male • Race/Ethnicity, (%): p = ns white 74 vs. 70; black 6 vs. 16; Hispanic 17 vs. 8; Asian 0 vs. 1; American Indian 0 vs. 1; Pacific Islander 0 vs. 1; Other 8 vs. 6 • Education (%): p = 0.03; HS: 9 vs. 3; HS graduate 48 vs. 55; Some college 39 vs. 29; College graduate 3 vs. 12	• Time since injury: NR. Cases were admitted within 72 hrs of injury; neuropsych testing administered after a full night's rest. • Mechanism of Injury (%, cases only): Blast: 53%, Blow: 27%, Mixed: 9%, Unknown: 11% • Prior TBI: p<0.01 0: 68 vs. 86; 1: 20 vs. 10; 2: 9 vs. 1
Kennedy, Cullen, Amador, et al., 2010[25]	US military evaluated from Jan 2007-Apr 2009 at Brooke AMC, Ft Sam Houston, Lackland AFB referred to DVBIC. Excluded: moderate, severe, or penetrating TBI; those injured while deployed to OEF; more than 3 OIF deployments; female; non-blast injury mechanism; evaluation more than 12 months after injury.	• Definition: ACRM criteria; and GCS of 13-15 • Positive imaging: NR • Citation: ACRM, 1993 • How assessed: Clinical interview	274	• Age: 28.15 (7.1) mTBI only; 25.40 (5.5) mTBI mTBI plus at least one other AIS coded injury • Gender: 100% male • Race/Ethnicity: NR • Education: NR	• Time since injury: 12.95 (12.9), 12.63(13.4) wks • Mechanism of Injury: Blast or explosion • Prior TBI: NR
Kennedy, Leal, Lewis, et al., 2010[26]	U.S. military service members who were evaluated and diagnosed with mTBI at the San Antonio Military Medical Center from May 23, 2005 to August 31, 2009. Excluded: 97 patients who had incomplete data on the PCL-C; 89 patients with more severe TBI, and 16 with no clear date of injury.	• Definition: ACRM criteria • Positive imaging: NR • Citation: Kay et al., 1993 • How assessed: Clinical interview	724, 586	• Age: 27.9 (7.4) • Gender: 96.7% male • Race/Ethnicity: NR • Education: NR	• Time since injury: Total mTBI sample: 31.3 (47.1) wks; Blast: 30.6 (45.4) wks; Non-blast: 34.1 (54.0) wks • Mechanism of Injury: non-blast mTBI group: deployment-related events such as MVAs, assaults and falls and not as a direct result of a blast explosion. • Prior TBI: NR
Lew, Pogoda Hsu, Cohen, Amick, Baker, Meterko, Vanderploeg, 2010[27]	VA patients (OEF/OIF) who screened positive for symptomatic TBI on 4-item screen, referred to polytrauma outpatient clinic, and completed 2nd level comprehensive TBI evaluation in VA polytrauma outpatient clinic (n = 200) from n = 327 who were seen at the polytrauma network site between 1/1/08 and 04/30/09.	• Definition: Positive 4-item VA TBI screen and subsequently diagnosed with TBI based on 2nd level comprehensive TBI evaluation including severity rating. • Positive imaging: NR • Citation: GAO, 2008 & VHA, 2007 cited for screening; Kay et al., 1993 cited for secondary clinical evaluation. • How assessed: Self-report screen and follow-up clinical evaluation	200, 131	Note: Only age reported for mTBI sample; all other demographics reported for whole sample • Age: 31.02 (9.14) • Gender: 94% male • Race/Ethnicity: NR • Education: pre-military education = 71.7% HS or less	• Time since injury: NR • Mechanism of Injury: NR • Prior TBI: NR

Author, year	Population and sample selection	mTBI definition and associated citation reported in the study	Sample size: Total, mTBI	Demographics of mTBI group	Time since injury for mTBI group, Mean (SD); Mechanism of injury; Prior TBI
Lippa, Pasternik, Benge, & Thornton, 2010[28]	Veterans with current mTBI symptoms referred for evaluation through the VA TBI screening process. Excluded: not meeting mTBI criteria.	• Definition: LOC, or disorientation < 24 hrs • Positive imaging: NR • Citation: CDC, 2003 • How assessed: Self-report	339	• Age: 30.28 (7.59) • Gender: 96.2% male • Race/Ethnicity: 13.3% African American; 62.8% Caucasian; 20.1% Hispanic; 3.8% Other • Education: 55.8% HS Diploma or equivalent; 37.5% some college; 5.6% college graduate; 1.2% other	• Time since injury: 36.72 (19.5) for last reported injury • Mechanism of Injury: Blast (n = 138), non-blast (n = 56), or both (n = 145) • Prior TBI: Some participants had multiple TBIs
Nelson, Hoelzle, Doane, et al., 2012[29]	National Guard soldiers from a Brigade Combat Team n = 41 and OEF/OIF Veterans from VA polytrauma rehabilitation and PTSD clinics n = 61. Excluded: current psychotic disorder, current/past substance abuse/dependence other than alcohol/caffeine/ nicotine, DSM-IV diagnosis prior to deployment, neurologic condition before deployment, current/ pre-deployment unstable medical condition that would likely affect brain functioning, significant risk of suicidal/homicidal behavior, and history of TBI greater than mild in severity, insufficient effort testing.	• Definition: LOC, any loss of memory for events surrounding the event, any alteration in mental state, and focal neurologic deficits, PTA • Positive imaging: NR • Citation: Kay et al., 1993 • How assessed: Participant self-reported symptoms evaluated by psychological consensus team.	104	* 67 participants included in Nelson et al., 2010 • Age: VA = 29.3 (6.3), National Guard = 35.5 (8.7) • Gender: 93.3% male • Race/Ethnicity: 97.1% Caucasian • Education: 14.4 (2.2) yrs	• Time since injury: 177.2 (85.5) weeks since most recent blast exposure • Mechanism of Injury: 84.6% blast exposed overall (regardless of mechanism of mTBI); 50% of overall sample had blast-related concussions • Prior TBI: Included history of mild; 10.5 (21.7) mean number of blast exposures
Nelson, Hoelzle, McGuire, et al., 2010[30]	U.S. Veterans within the Midwestern region of the USA/VISN 23; Research participants were recruited consecutively at the Minneapolis VA Medical Center. Participants required to meet mTBI criteria.	• Definition: ACRM definition • Positive imaging: NR • Citation: Kay et al., 2003 • How assessed: Clinical interview	119	• Age: 35.5 (10.2) • Gender: 93.3% male • Race/Ethnicity: 93.3% Caucasian • Education: 13.7 (2.3) yrs	• Time since injury: 327.0 (425.6) days (most recent concussion) • Mechanism of Injury, n: Forensic or compensation context: OEF/ OIF blast, 19; non-blast, 5; OEF/ OIF non-blast, 1; non-blast n, 11; other, 8; Research context OEF/ OIF blast, 38; OEF/OIF non-blast, 37 • Prior TBI: NR
Patil, St. Andre, Crisan, et al., 2011[31]	Consecutive OEF/OIF combat Veterans with diagnosis of mTBI seen at VA PNS, June 2007-July 2009. Excluded: attending neurology appointment for reasons other than headache; mechanism of injury other than trauma.	• Definition: Based on VA/DoD Consensus-based Classification of Closed TBI Severity • Positive imaging: Included. 45/56 veterans seen in neurology clinic had CT, MR or both. 40% of these with white matter changes, 30% with sinus polyps/cysts, 25% with arachnoid cysts/ vascular malformations/masses, 5% atrophy • Citation: Defense and Veterans Brain Injury Center, 2006 • How assessed: Clinical interview, chart review	n/a, 246	• Age: 27.9 (6.3) • Gender: 92.3% male • Race/Ethnicity: 85% White • Education: >99% completed HS or GED	• Time since injury: NR • Mean time between mTBI event and neurology visit: 3.1 yrs (data missing in 24/56 patients) • Mechanism of Injury: 65% blast-exposure • Prior TBI: NR

Author, year	Population and sample selection	mTBI definition and associated citation reported in the study	Sample size: Total, mTBI	Demographics of mTBI group	Time since injury for mTBI group, Mean (SD); Mechanism of injury; Prior TBI
Ruff, Riechers, Wang, et al., 2012[32]	OEF/OIF veterans; sought care from the VHA, Louis Stokes CVAMC. Excluded: moderate or penetrating TBI. Results reported for three groups: combat veterans with LOC, combat Veterans without LOC, and then Veterans with civilian mTBI.	• Definition: An episode of TBI with LOC, AOC, and/or PTA • Positive imaging: NR • Citation: Malec, Brown, Liebson, et al., 2007 • How assessed: clinical interview	163 *does not include 5 veterans with "probable" mTBI	Combat Veterans with LOC; combat Veterans without LOC; and then Veterans with civilian mTBI. • Age: 29.2 (2.6); 30.0 (1.6); 35.1 (2.2) • Gender: 92.1, 90.5, 90.5% male • Race/Ethnicity: NR • Education: 100% HS graduates; 8.7, 5, 9.5% college graduates	• Time since injury: NR • Mechanism of Injury: Military and civilian incidents • Prior TBI: NR
Ruff, Ruff, & Wang, 2008[33]	OEF/OIF veterans; evaluated at the VHA, Louis Stokes Department of CVAMC. Exclusions: the initial screen was not truly positive because a veteran did not understand a question; the veteran had moderate or severe TBI or had sustained penetrating TBI; TBI was not due to exposure to an explosion; and the veteran did not complete the second-level evaluation.	• Definition: LOC, any alteration in mental state following the TBI < 24 hrs, PTA • Positive imaging: NR • Citation: Ruff, 2005; Malec, Brown, Liebson, et al., 2007; Esselman & Uomoto, 1995; Kay et al., 1993 • How assessed: self-report screening tool and clinical interview	126	• Age: NR • Gender: NR • Race/Ethnicity: NR • Education: NR	• Time since injury: NR • Mechanism of Injury: Explosion • Prior TBI: NR
Ruff, Ruff, & Wang, 2009[34]	OEF/OIF veterans; evaluated at the VHA, Louis Stokes Department of CVAMC. Same exclusions as Ruff, Ruff, & Wang, 2008 above. Included veterans from the previous study who had "abnormalities on neurological examination, neuropsychological testing, or both" as well as headaches."	• Definition: LOC, the duration of any alteration in mental state following the TBI < 24 hrs, PTA • Positive imaging: NR • Citation: Kushner, 1998; Ruff, 2005; Malec, Brown, Liebson, et al., 2007; Esselman & Uomoto, 1995; Kay et al., 1993 • How assessed: self-report screening tool and clinical interview	74	Note: Subpopulation from the Ruff et al., 2008 study also reported • Age: 29.4 (2.9) • Gender: 95% male • Race/Ethnicity: NR • Education: NR	• Time since injury: NR • Mechanism of Injury: Explosion • Prior TBI: NR
Schiehser, Delis, Filoteo, et al., 2011[35]	Active duty noncombat, nondeployed service members with mild TBI. Recruited thru local DVBIC; actual recruitment procedures not specified	• Definition: LOC; GCS score between 13 and 15; and/or PTA • Positive imaging: Excluded (classified as moderate TBI) • Citation: NR • How assessed: "Self-report"	66, 44	Note: mild and moderate TBI populations combined • Age: NR • Gender: NR • Race/Ethnicity: NR • Education: NR	• Time since injury: 38.3 (11.8) days • Mechanism of Injury: Blunt force • Prior TBI: Excluded
Spencer, Drag, Walker, et al., 2010[36]	Referrals to the TBI Clinic at the VA Ann Arbor Health Care System for a more comprehensive medical evaluation which included a neuropsych assessment. Excluded: inconsistent effort on neuropsych testing as evidenced by a score of 8 or below on the Rey 15-item Memory Test; seen as part of a C and P; exceeded criteria for mild TBI	• Definition: screened positive for possible head injury on standard VA clinical reminder consisting of PCS • Positive imaging: NR • Citation: NR • How assessed: Clinical Interview	105	• Age: 29.8 (8.2) • Gender: NR • Race/Ethnicity: NR • Education: 12.9 (1.4) yrs	• Time since injury: NR • Mechanism of Injury: NR • Prior TBI: NR

Author, year	Population and sample selection	mTBI definition and associated citation reported in the study	Sample size: Total, mTBI	Demographics of mTBI group	Time since injury for mTBI group, Mean (SD); Mechanism of injury; Prior TBI
Swick, Honzel, Larsen, et al., 2012[37]	Combat Veterans diagnosed with PTSD. Controls were recruited primarily through advertisements. Excluded: significant medical disease, severe psychiatric problems (such as schizophrenia or bipolar disorder), active substance abuse, visual deficits, or history of other neurological events.	• Definition: VA/DoD Clinical Practice Guidelines • Positive imaging: NR • Citation: The Management of Concussion/mTBI Working Group, 2009 • How assessed: Clinical interview	73, 30	• Age: 32.3 (7.5) • Gender: 97% male • Race/Ethnicity: NR • Education: 13.6 (1.2) yrs	• Time since injury: 3.8 (1.5) yrs postdeployment; time since injury NR • Mechanism of Injury: NR • Prior TBI: Yes, some
Theeler & Erickson, 2009[38]	US Army soldiers who were evaluated between Jan and June 2006 in the Neurology Clinic at Madigan Army Medical Center for chronic headaches following a 12-month combat tour in Iraq. Soldiers were eligible if they experienced headaches during deployment and continued to experience headaches for 3 or more months after returning from Iraq.	• Definition: DVBIC Working Group on the Acute Management of Mild Traumatic Brain Injury in Military Operational Settings criteria • Positive imaging: NR • Citation: DVBIC Working Group on the Acute Management of Mild Traumatic Brain Injury in Military Operational Settings Clinical Practice Guideline and Recommendations, ND • How assessed: Chart review	81, 33	• Age: 29.1 • Gender: 80% male • Race/Ethnicity: NR • Education: NR	• Time since injury: NR • Mechanism of Injury: Of the n = 33 (41%) with head or neck trauma: 15% blunt trauma, 18% other explosive, 67% blast • Prior TBI: Multiple head or neck injuries occurred in 6 soldiers
Toblin, Riviere, Thomas, et al., 2012[39]	Soldiers from 3 U.S. infantry brigade combat teams surveyed 6 months post-deployment during Nov-Dec 2008, deployed to Iraq or Afghanistan for at least one month. 50% of all soldiers from participating units were present during recruitment phase. Excluded: 10 soldiers who reported moderate or severe TBI	• Definition: Combat injury was grouped into no injury, non-mTBI injury, mTBI with AOC but no LOC, and mTBI with LOC. • Positive imaging: NR • Citation: Hoge et al., 2008 • How assessed: Self-report survey	1522, NR	• Age: NR • Gender: NR • Race/Ethnicity: NR • Education: NR	• Time since injury: NR • Mechanism of Injury: NR • Prior TBI: NR

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SUMMARY OF FINDINGS

In general, we found that, though cognitive, physical, and mental health symptoms were frequently reported by Veterans/military members following mTBI, there was little evidence that symptoms were more common in those with mTBI than those without mTBI. However, the evidence base is weakened by inconsistent findings, methodologic shortcomings of many studies, and variation in outcomes considered and outcome measurement approaches. We grouped findings into categories according to our key questions; though some outcomes could have been included in multiple categories (e.g., sleep), we chose to categorize outcomes as commonly reported in the literature, and report specific outcomes within each category individually for clarity. Findings by outcome categories are reported in detail in the following sections.

COGNITIVE FUNCTIONING RESULTS

Summary of Cognitive Functioning Results

We found 17 studies reporting cognitive outcomes for those with mTBI. Overall, few studies found an association between mTBI and cognitive deficits. The strength of evidence is very low because of poor and incomplete reporting of data and sampling procedures, lack of time-since-injury information, and because most studies were unblinded and single-center.

The studies reporting cognitive outcomes reported mean scores rather than proportions of individuals with impaired scores, making estimates of prevalence of cognitive impairment impossible. The best approximation of prevalence of impairment comes from studies reporting standardized scores which can be associated with impairment below certain cutoffs, and cognitive results should ideally be adjusted for pre-morbid functioning since the most accurate assessment of impairment reflects intra-individual change over time. We report estimates of impairment based on mean standardized scores, when available, and none of the included studies provided information on pre-morbid functioning such that change from baseline could be assessed at the intra-individual level. Though the majority of studies reported mean standardized scores within normal limits, the nature of mean score reporting is such that individuals comprising those means may have scored significantly above or below the mean. Therefore, though overall scores may be within normal limits, it is likely that some individuals obtained scores indicative of impairment, and individual variation should be kept in mind when interpreting findings.

There were studies that found mTBI patients had deficits in visuospatial abilities, attention/concentration, and total/cross-domain composite scores as compared to patients without mTBI. However, even within each of these subdomains, findings were inconsistent across studies. In nearly all studies, scores for each of the subscales fell within normal limits, suggesting no clinically significant impairment in the group as a whole. Because studies did not report the proportion of patients scoring below normal range for each of the subscales, it is unclear whether there may have been subgroups of mTBI patients with cognitive deficits. Of note, single studies reported that mTBI patients within 10 days of injury and those undergoing disability evaluation had low processing speed scores.

It is difficult to draw overall conclusions about which factors, in addition to mTBI, are independently associated with cognitive test performance since studies evaluated a variety of different factors and there were inconsistent findings among them. Individual studies suggested that impaired cognitive test performance was associated with comorbid mental health diagnosis, time since injury of less than 10 days, self-reported cognitive complaints, and experiencing loss or alteration of consciousness at the time of injury. One study found that Veterans who participated in a headache intervention demonstrated better overall cognitive functioning post-intervention than those who did not participate in the intervention.

Prevalence estimates of self-reported cognitive complaints were not reported in the included studies. Potential risk factors for more severe self-reported cognitive problems include having an additional injury, LOC or PTA at the time of injury, being service connected, and having an Axis I mental health disorder.

The following table summarizes the evidence on cognitive outcomes, which is then followed by detailed results descriptions for each cognitive domain.

Table 2. Summary of Evidence for Cognitive Functioning Outcomes Associated with mTBI in Veteran and Military Populations

Domain (number of studies)	Key Question 1: Estimates of Prevalence and Impairment (number of studies)	Key Question 1: Statistically Significant Deficits Compared to Controls (number of studies)	Key Question 2: Statistically Significant Potential Risk or Protective Factors (number of studies)
Language Abilities and General Fund of Verbal Knowledge (8)	Mean scores were within normal limits (7)	No (3)	No: Axis I disorder (2) No: Blast exposure (1) No: Disability/C&P Evaluation (1) No: LOC or PTA (1)
Visuospatial Abilities (6)	Mean scores were within normal limits (2)	Yes (1) No (1)	Yes Risk: Axis I disorder (1) No: Axis I disorder (3) No: Blast exposure (1) No: Self-reported cognitive problems (1)
Memory (11)	Mean scores were within normal limits (5)	No (3) Yes (2 studies on same population; differences only significant within 5 days of injury)	Yes Risk: Time since injury 72 hours (1) Yes Risk: Axis I disorder (1) Mixed Risk: Axis I disorder (2) Mixed Risk: Self-reported cognitive problems (1) Mixed Risk: Time since injury 5 days (1) No: Axis I disorder (1) No: Blast exposure (2) No: Disability/C&P Evaluation (1) No: LOC or PTA (1) No: Service connection (1) No: Time since injury 10 days (1)
Attention/Concentration (8)	Mean scores were within normal limits (2)	No (2) Yes (3)	Yes Risk: Time since injury 72 hours (1) Mixed Risk: Axis I disorder (1) No: Axis I disorder (1) No: Blast exposure (1) No: Disability/C&P Evaluation (1) No: LOC or AOC (1) No: Service connection (1) No: Self-reported cognitive problems (1) No: Time since injury 5-10 days (1)

Domain (number of studies)	Key Question 1: Estimates of Prevalence and Impairment (number of studies)	Key Question 1: Statistically Significant Deficits Compared to Controls (number of studies)	Key Question 2: Statistically Significant Potential Risk or Protective Factors (number of studies)
Processing Speed (9)	Mean scores were within normal limits; exceptions were scores below expected limits for some participants evaluated for disability/C&P and < 10 days since injury. (4)	No (5)	Yes Risk: Disability/C&P Evaluation (1) Yes Risk: Time since injury 5 days (1) No: Axis I disorders (3) No: Blast exposure (1) No: LOC or PTA (1) No: Time since injury 10 days (1)
Executive Functioning (7)	Mean scores were within normal limits (4)	No (2)	No: Axis I disorder (3) No: Blast exposure (1) No: Disability/C&P Evaluation (1) No: LOC or PTA (1)
Effort/Motivation (1)	Mean scores were within normal limits (1)	No (1)	Yes Risk: Disability/C&P Evaluation (1)
Total and Cross-Domain Composite Scores (9)	Mean scores were within normal limits (2)	No (2) Yes (1)	Yes Protective: Participation in headache intervention (1) Yes Risk: Disability/C&P Evaluation (1) Yes Risk: LOC or AOC (1) No: Blast exposure (1)
Self-reported Cognitive Deficits (7)	NR	NR	Yes Protective: Additional injury (1) Yes Risk: LOC or PTA (1) Yes Risk: Service Connection (1) Yes Risk: Axis I disorder (4) No: Axis I disorder (1) No: Blast exposure (1)

Note. The impairment summary is based on average scores for groups with mTBI, and does not reflect individual variation in scores which could include some impairment for a certain proportion of participants. "Mixed" results indicate both significant and non-significant results for multiple assessments of the same outcome in a single study.

Language Abilities and General Fund of Verbal Knowledge

Key Question 1: We found eight primary studies that assessed this domain of cognitive functioning using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Language subtest, the Shipley Institute of Living Scale Vocabulary subtest, the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Information subtest, and the Wechsler Adult Test of Adult Reading (WTAR).[10,11,16,18,20,22,29,30] The results abstracted from these studies are found in Appendix E, Table 1a. Three studies examined outcomes compared to a non-TBI group from the same population, describing similar performance across groups.[18,29,30] All of the three studies reported standardized scores, and all of the mean scores fell within normal limits for language abilities and general fund of verbal knowledge, suggesting that, on average, clinically significant impairment in this domain is not associated with mTBI. None of the studies reported proportions of patients who obtained impaired scores on tests of language abilities and general fund of verbal knowledge.

Key Question 2: One study examined differences between Veterans with a history of mTBI who were obtaining testing as part of a C and P evaluation (i.e., a disability evaluation associated with potential financial gain) versus those recruited in a research context, and reported no significant differences between the groups.[30] A study by the same group of authors examined the effect of having an Axis I disorder on two different tests assessing language abilities and general fund of verbal knowledge, and both tests indicated non-significant differences between groups.[29] Similarly, studies examining the possible effect of PTSD diagnosis or mental health diagnosis other than PTSD[22] and LOC and/or PTA at the time of injury (compared to solely experiencing alteration of consciousness)[20] both reported non-significant group differences. One study reported non-significant differences between Veterans with mTBI who were exposed to blast versus those who were not exposed to blast.[16]

Visuospatial Abilities

Key Question 1: Six primary studies reported visuospatial outcomes using the RBANS: Visuospatial/Constructional subscale; Rey Complex Figure Test (RCFT); a study-specific Visual Organization/Processing factor; and the WAIS-III: Block Design subtest (Appendix E, Table 1b).[16,18,20,22,29,36] In the studies that directly compared mTBI with non-TBI participants from the same population, groups performed similarly on two measures of visuospatial abilities (WAIS-III Block Design and RCFT Figure Copy), though the mTBI group performed significantly worse than participants without mTBI on the RBANS Visuospatial/Constructional subscale.[18,29] All of the mean standardized scores reported in these studies are within normal limits for visuospatial abilities.

Key Question 2: Studies examining the effects of Axis I disorders,[29] PTSD diagnosis,[22] or mental health diagnosis other than PTSD[22] reported equivalent results across groups. Contrary to these results, another research group examined the association between mental health variables including PTSD, depression, and anxiety with a visual organization/processing factor score, and reported significant negative correlations between visuospatial abilities and both self-reported PTSD and depression symptoms, but non-significant differences for service connection and LOC or PTA at the time of injury.[20] One study reported non-significant differences based on blast exposure.[16] Finally, a study examining self-reported cognitive deficits found no significant association with objective visuospatial test results.[36]

Memory

Key Question 1: We found 11 primary studies that assessed this domain of cognitive functioning using the Automated Neuropsychological Assessment Metrics (ANAM): Code Substitution Delayed (CDD) and Matching to Sample (MSP) subtests; Brief Visuospatial Memory Test Revised (BVMT-R): Total Recall and Delayed Recall subtests; the California Verbal Learning Test Second Edition (CVLT-II): Trials 1-5, Short Delay Free Recall, and Long Delay Free Recall subscales; a study-specific Memory Composite Score; a study-specific Memory Factor; the RBANS Story Memory Immediate Recall, Story Memory Delayed Recall, Immediate Memory, and Delayed Memory subtests; the RCFT: Immediate Recall and Delayed Recall subtests; and the WAIS-III: Digit Symbol Coding subtest (Appendix E, Table 1c).[11,15,16,18,20,22,24,29,30,35,36] Five studies examined outcomes compared to a non-TBI group from the same population, reporting similar results across groups in most cases.[15,18,24,29,30] The notable exception was from two studies by the same group of authors and the same patient population which reported significant group differences on both 72 hour assessments, one of the two 5 day assessments, and neither of the 10 day assessments.[15,24] In these two studies, the participants were assessed by the ANAM subtests, and the assessments were conducted within 72 hours, 5 days, and 10 days of injury; the rest of the comparisons were between populations with longer time since injury, and using assessment tools other than the ANAM. Of the studies which reported standardized scores on assessments, all of the mean scores fell within normal limits for memory functioning; none of the studies reported proportions of patients who obtained impaired scores on tests of memory.[11,18,20,29,30]

Key Question 2: As noted above, two studies reported ANAM outcomes at specific times following mTBI event; these studies report significant deficits in memory on the majority of ANAM subtests at 72 hours and 5 days following injury.[15,24] These same studies also report comparisons with controls after 10 days following injury, and notably these latter results are both non-significant. One study reported non-significant differences between Veterans with mTBI who were exposed to blast versus those who were not exposed to blast in terms of their immediate and delayed memory test performance.[16] One study examined differences between Veterans with mTBI who were obtaining testing as part of a C and P evaluation versus those recruited in a research context, reporting non-significant differences between groups.[30] A study by the same group of authors examined the effect of having an Axis I disorder on three tests assessing memory, and two out of three assessment results indicated non-significant differences between individuals with mTBI who did and did not have an Axis I disorder.[29] One study examined the effect of mental health diagnosis other than PTSD on memory outcomes, and found similar results across groups.[22] Two studies examined the effect of PTSD on memory outcomes. One of these studies did not report p-values, though results for four out of five memory tests were worse for those with a diagnosis of PTSD.[22] The other study reported a significant negative relationship between scores on a self-report PTSD symptom inventory and a composite memory score.[20] This latter study also reported a non-significant association for self-reported depression and service connection with memory test results, though self-reported anxiety was significantly related to memory functioning.[20] A study examining self-reported cognitive deficits found no significant correlation between memory test results and self-reported cognitive deficits for two out of three tests.[36] One study examined the impact of blast exposure and reported no significant differences between groups.[11] Finally, one study reported similar results across groups based on mTBI with LOC and/or PTA at the time of injury compared to those with mTBI who only reported alteration of consciousness at the time of the mTBI event.[20]

Attention/Concentration

Key Question 1: We found eight primary studies that assessed this domain of cognitive functioning using the ANAM: Mathematical Processing (MTH) subtest; the RBANS: Attention subscale; study-specific Visual and Verbal Attention factor scores; and the WAIS-III and WAIS-IV: Digit Span subtest scores (Appendix E, Table 1d).[15,16,18,20,24,29,30,36] In five studies that compared mTBI directly with non-mTBI controls, findings varied with the metric used. The mTBI group performed similarly to a non-TBI comparison group on the WAIS-IV Digit Span measures of attention in two studies,[29,30] In other studies, participants with mTBI performed worse on the RBANS subtest and on the ANAM subtest, but deficits noted at 72 hours diminished with time.[15,18,24] As with other outcomes, mean scores fell within normal limits for attention/concentration abilities.[29,30]

Key Question 2: Seven studies reported results separately for mTBI groups with and without potential risk or protective factors.[15,16,20,24,29,30,36] As noted with other cognitive outcomes, significant deficits in attention/concentration at 72 hours following injury diminished to non-significant differences 5 and 10 days following injury.[15,24] One study reported non-significant differences in attention based on blast exposure.[16] The study that compared mTBI participants in a research setting with a forensic setting (i.e., a setting in which patients were evaluated for potential compensation) found non-significant differences in attention/concentration, in contrast with other outcomes for which participants in the forensic setting performed worse.[30] Having an Axis I disorder in addition to mTBI did not emerge as a significant factor on attention/concentration outcomes.[29] A study that examined the possible effects of PTSD, anxiety, and depression on attention and concentration outcomes reported significant associations between worse visual, but not verbal attention for depression and anxiety, and significant negative associations between both visual and verbal attention for PTSD.[20] Service connection was non-significantly associated with verbal and visual attention.[20] Participants with LOC and/or PTA following TBI had similar results on attention/concentration compared with those who did not have these immediate sequelae.[20] WAIS-IV Digit Span test results were not significantly correlated with self-reported cognitive deficits in one study.[36]

Processing Speed

Key Question 1: We found nine primary studies that assessed processing using the ANAM: Code Substitution (CDS), Procedural Reaction Time (PRT) subtest, and Simple Reaction Time (SRT) subtest; reaction time on a Go/NoGo task; Stroop Color & Word Test: Color and Word subtests; the Trail Making Test Part A; and the WAIS-III: Digit Symbol Coding subtest (Appendix E, Table 1e).[11,15,20,22,24,29,30,36,37] Five studies examined outcomes compared to a non-TBI group from the same population.[15,24,29,30,37] In three of these studies, the mTBI group performed similarly to a non-TBI comparison group on multiple measures of processing speed.[29,30,37] By contrast, two studies conducted in the same patient population using the ANAM observed processing speed deficits soon after injury (72 hours and 5 days), although statistically significant differences between cases and controls were not detected upon longer term follow-up (10 days after injury).[15,24]

Key Question 2: As noted above, two studies report significant deficits in processing speed on the majority of ANAM subtests at 72 hours and 5 days following injury, but non-significant differences 10 days after injury.[15,24] One study examined differences between Veterans with mTBI who were obtaining testing as part of a C and P evaluation compared with Veterans with mTBI who were recruited in a research context, describing worse processing speed performance on all four tests examined by those obtaining a C & P evaluation.[30] Studies examining Axis I disorders,[29] PTSD diagnosis,[22] mental health problems other than PTSD,[22] self-reported cognitive deficits,[36] blast exposure,[11] and LOC and/or PTA[20] all reported equivalent results across compared groups.

Executive Functioning

Key Question 1: We found seven primary studies that assessed this domain of cognitive functioning using the Controlled Oral Word Association (COWA) test, the Stroop Color and Word Test Color-Word subscale, the Trail Making Test Part B, and an Executive Functioning Composite test score (Appendix E, Table 1f).[11,20,22,29,35,36] Two studies by the same group of authors examined outcomes compared to a non-TBI group from the same population.[29,30] In these studies, the mTBI group performed similarly to a non-TBI comparison group on multiple measures of executive functioning. Of the four studies reporting standardized scores, all of the mean scores fell within normal limits for executive functioning; none of the studies reported proportions of patients who obtained impaired scores on tests of executive functioning.

Key Question 2: One study examined differences between mTBI Veterans who were obtaining testing as part of a C and P evaluation (i.e., a disability evaluation associated with potential financial gain) versus those recruited in a research context, reporting no significant differences between groups.[30] One study examined the effect of having an Axis I disorder, and all results were non-significant.[29] Similarly, another study examined the possible effect of PTSD diagnosis or mental health diagnosis other than PTSD on executive functioning outcomes, and found non-significant differences between groups.[22] A study examining self-reported cognitive deficits found no significant association with executive functioning test results.[36] One study on blast exposure reported no significant group differences.[11] Finally, one study reported non-significant group differences based on mTBI with LOC and/or PTA at time of injury compared to those with mTBI who did not have these immediate sequelae.[20]

Effort/Motivation

Key Question 1: We found one primary study that assessed effort and motivation on cognitive tests using the CVLT-II: Forced Choice subtest, an Effort Failures composite; the Rey 15 Item test (Rey FIT): Combination test, the Victoria Symptom Validity Test (VSVT); and the WAIS-III: Reliable Digit Span subtest (Appendix E, Table 1g).[30] This study did not report comparisons between those with and without mTBI (Appendix E, Table 1g).[30]

Key Question 2: The same study also examined differences between Veterans with mTBI who were obtaining testing as part of a C and P evaluation (i.e., a disability evaluation associated with potential financial gain; n = 24) versus those with mTBI who were recruited in a research context (n = 38).[30] Veterans tested in the context of a disability evaluation scored worse on every measure of effort and motivation administered, and five out of the seven outcomes reported were statistically significant.[30]

Total and Cross-Domain Composite Scores

Key Question 1: We found nine primary studies that assessed cognitive functioning across domains using an Attention/Processing Speed composite score; "positive neurological and/or neuropsychological findings," Montreal Cognitive Assessment (MOCA); Overall Test Battery Mean; RBANS: Total Score; WAIS-III: Vocabulary, Information, Matrix Reasoning, Block Design Subscales; and WAIS-IV: all subtests (Appendix E, Table 1h).[16,18,22,29,30,32-35] Three studies examined outcomes compared to a non-TBI group.[18,29,30] In two of these studies,[29,30] there were no significant differences between mTBI and non-mTBI participants on Overall Test Battery Mean scores, though one study[18] reported significantly lower RBANS total scores for mTBI participants. Of the two studies reporting standardized scores on assessments, all of the mean scores fell within normal limits for cognitive functioning; none of the studies reported proportions of patients who obtained total or composite scores indicative of impaired cognitive functioning.[29,30]

Key Question 2: One study reported non-significant differences in RBANS total score between Veterans with mTBI who were exposed to blast versus those who were not exposed to blast.[16] One study examined differences between Veterans with mTBI who were obtaining testing as part of a C and P evaluation (i.e., a disability evaluation associated with potential financial gain) versus those with mTBI who were recruited in a research context, reporting significantly lower Overall Test Battery Mean scores for evaluations linked to potential financial gain.[30] A study by the same group of authors examined the effect of having an Axis I disorder, and results indicated non-significant differences between the groups.[29] Similarly, another group of authors investigated the effect of having PTSD or a mental health diagnosis other than PTSD, and reported similar cognitive functioning across groups.[22] Another study examined the possible effects of a headache intervention involving sleep hygiene, Prazosin, headache and pain education, and group therapy.[34] This study indicated that completion of the intervention was associated with significantly higher MOCA scores. The same group of authors also reported that MOCA scores were significantly lower for Veterans who experienced LOC compared to those who did not experience LOC.[32] Finally, another study by this same groups of authors reported a significant association between obtaining positive neurological or neuropsychological test results and the number of blast exposures resulting in LOC, as well as an association with the number of blast exposures resulting in either LOC or AOC.[33]

Self-Reported Cognitive Problems

Key Question 1: Seven primary studies examined self-reported cognitive problems including self-reported blackouts; confusion; Frontal Systems Behavioral Scale (FrSBe): Subjective Executive Dysfunction pre- to post-injury change; memory problems; and Neurobehavioral Symptom Inventory (NSI): concentration, decision-making, memory, and slowed thinking/organization items and cognitive cluster score (Appendix E, Table 1i).[12,13,17,20,25,29,35] We found no studies reporting prevalence estimates or comparisons with a non-mTBI control group.

Key Question 2: One study examining the effects of Axis I disorders reported non-significant differences between groups,[29] and another described non-significant differences for those with and without blast exposure.[12] Four studies examined self-reported cognitive problems on the NSI and their relationship to anxiety,[20] depression,[20] PTSD,[12,17,20] service connection,[20] and presence of LOC and/or PTA at the time of injury,[20] and all describe significantly worse symptoms reported by participants with mTBI with these potential risk factors. Finally, one study described having an additional injury being significantly correlated with fewer self-reported cognitive complaints.[25]

PHYSICAL HEALTH RESULTS

Summary of Physical Health Results

We found 17 studies reporting physical health outcomes for those with mTBI. Low strength evidence suggests that self-reported physical symptoms are associated with mTBI. This body of evidence is comprised entirely of low quality studies generally limited by poor and incomplete reporting of data and sampling procedures, lack of time-since-injury information, and lack of blinding of those conducting outcomes assessments; most studies were also single-center.

Studies included in this report suggest that symptoms reported by those with mTBI include headaches, pain, vestibular symptoms, hearing and vision problems, nausea or loss of appetite, and neurologic symptoms. One study reported that the prevalence of neurology referrals for headaches was 33.3% for Veterans with mTBI, though no other physical health studies reported prevalence estimates for these outcomes. It is also unclear whether mTBI directly contributes to the prevalence or severity of physical health symptoms, as only two studies included a comparison group of participants without mTBI. Self-reported symptom severity ranges widely across individuals and many of the reported physical health outcomes are based solely on responses to an individual item from the NSI, a general post-concussive symptom inventory. Additionally, inconsistent information on risk and protective factors provides insufficient evidence to make strong conclusions about potentially moderating factors for self-reported physical health outcomes.

The following table summarizes the evidence on physical health outcomes, which is then followed by detailed results descriptions for each physical health domain.

Table 3. Summary of Evidence for Physical Health Outcomes Associated with mTBI in Veteran and Military Populations

Domain (number of studies)	Key Question 1: Estimates of Prevalence and Impairment (number of studies)	Key Question 1: Statistically Significant Deficits Compared to Controls (number of studies)	Key Question 2: Statistically Significant Potential Risk or Protective Factors (number of studies)
Headaches (10)	Prevalence of neurology referrals for headache = 33.3%. (1) Average self-reported headache severity = "moderate-severe" (1) Average headache pain = 4.33 on a scale of 0-10 (1)	NR	Yes Protective: Additional injury (1) Yes Protective: Headache intervention (1) Mixed Risk: Axis I disorder (2) No: Blast exposure (2) Yes Risk: Positive neurological or neuropsychological findings (1) Yes Risk: Referral to neurology clinic for headaches (1)
Pain (2)	Median pain = 3.5 on a scale of 0-10 (1)	Yes: Average pain severity (1)	NR
Vestibular (6)	Average vestibular symptom severity = mild-moderate (1)	Mixed (1)	Yes Risk: 1-3 weeks following injury (1) Mixed Risk: 4 weeks following injury (1) Mixed Risk: Axis I disorders (2) Yes Protective: Additional injury (1) No: Blast exposure (1)
Vision (5)	Average vision-related symptom severity = mild-moderate (1)	NR	Mixed Risk: Axis I disorders (3) Yes Protective: Additional injury (1) No: Blast exposure (1)
Hearing (5)	Average hearing-related symptom severity = moderate (1)	NR	Mixed Risk: Axis I disorders (3) Mixed Protective: Additional injury (1) Mixed Risk: Blast exposure (1)
Nausea/Appetite (5)	Average appetite/ nausea-related symptom severity = mild-moderate (1)	NR	Mixed Risk: Axis I disorders (3) Mixed Protective: Additional injury (1) No: Blast exposure (1)
Neurological (5)	Average numbness or tingling severity = mild-moderate (1)	NR	Yes Risk: PTSD (2) No: Additional injury (1) No: Blast exposure (1) Yes Risk: LOC (1)

Note. The impairment summary is based on average scores for groups with mTBI, and does not reflect individual variation in scores which could include some impairment for a certain proportion of participants. "Mixed" results indicate both significant and non-significant results for multiple assessments of the same outcome in a single study.

Headaches

Key Question 1: We found 10 primary studies that reported headache outcomes for Veterans and members of the military including self-reported headaches, headache days per month, headache duration, headache frequency, headache pain level or severity, headache type, time since injury of initiation of headaches, worsening of pre-trauma headaches, headache referral, headache medication overuse, Migraine Disability Assessment Score (MIDAS), Headache Impact Test (HIT-6) score, and NSI: Headache item (Appendix E, Table 2a).[12,13,16,17,25,29,31,33,34,38] One study without a comparison group reported prevalence of neurology referrals for headache in an mTBI population was 33.3%.[31] Another study reported an average NSI headache item scores between 1.45-2.71, corresponding to a self-report of headache severity in the moderate range.[25] Finally, one study reported average headache pain of 4.33 on a scale of 0-10 for Veterans with mTBI.[33] All other prevalence estimates and comparisons with a non-mTBI population reported in the included studies were based on populations selected because they experienced headaches, and therefore prevalence estimates are not accurate for a general mTBI population.

Key Question 2: A study comparing a similar population of Veterans with history of mTBI who also had at least one additional injury reported that additional injury is, in fact, a protective factor for experiencing headaches, reporting that those with additional injuries reported significantly lower NSI headache item severity than those without.[25] Another study investigating the effects of a headache intervention found that following completion of this intervention, Veterans reported decreased headache frequency and severity compared to a comparison group who did not complete the intervention.[34] One study reported non-significant differences in headache impact based on blast exposure.[16] One study reported a non-significant relationship between Axis I disorder and headaches.[29] All other studies investigating possible risk and protective factors reported statistically significant risk associated with blast exposure,[12] PTSD,[12,17] positive neurological or neuropsychological findings,[33] and referral to neurology clinic for headaches.[31]

Pain

Key Question 1: We found only two studies documenting outcomes related to pain using self-reported pain in the past 30 days, and self-reported pain on a 0-10 scale (Appendix E, Table 2b).[9,27] Only one study compared pain to a non-mTBI population, describing statistically significant differences in median pain scores of 3.5/10 for the participants with mTBI and 2.0/10 for those without mTBI.[9]

Key Question 2: Neither included study provided data related to this key question.

Vestibular

Key Question 1: We found six primary studies reporting vestibular outcomes including disorientation, dizziness, Dizziness Handicap Inventory (DHI) scores, Dynamic Visual Acuity Test (DVAT) scores, imbalance, and NSI: Feeling Dizzy, Loss of Balance, and Poor Coordination item scores (Appendix E, Table 2c).[12,13,17,23,25,29] Ranges of mean scores on vestibular NSI items ranged from 1.32-1.47 for mTBI populations, corresponding to mild-moderate symptom severity.[13] One study compared DHI and DVAT scores to non-mTBI populations, reporting significantly more vestibular symptoms in mTBI groups at 1, 2, 3, and 4 weeks following injury for DHI and 1 week but not 4 weeks following injury for DVAT.[23]

Key Question 2: As noted above, one study reported that significantly worse DVAT scores for the mTBI group became non-significantly different from those of non-mTBI controls after 4 weeks following injury.[23] Two studies reported non-significant differences in vestibular outcomes for those with Axis I disorders[29] or blast exposure.[12] Three studies reported that PTSD[12,17] and additional injury were significantly associated with worse self-reported vestibular symptoms in Veterans with mTBI.

Vision

Key Question 1: We found five primary studies reporting vision-related outcomes including "photophobia" and NSI: Vision Problems and Sensitivity to Light item scores (Appendix E, Table 2d).[12,13,17,25,29] Ranges of mean scores on vision-related NSI items ranged from 1.51-1.72 for mTBI populations, corresponding to mild-moderate symptom severity.[13] No studies compared mTBI to non-mTBI populations.

Key Question 2: Two studies reported non-significant differences for those exposed to blast,[12] and those with Axis I disorders.[29] Four studies reported significantly worse self-reported vision-related outcomes for those with PTSD[12,17] and additional injury.[25]

Hearing

Key Question 1: We found five primary studies reporting hearing-related outcomes including tinnitus, "phonophobia," and NSI: Hearing Difficulty and Sensitivity to Noise item scores (Appendix E, Table 2e).[12,13,17,25,29] Average self-reported hearing difficulty and sensitivity to noise were in the moderate range.[13] No studies compared mTBI to non-mTBI populations.

Key Question 2: Two studies investigating the association of blast exposure[12] and additional injury[25] with hearing-related outcomes reported significant findings for sensitivity to noise, but not for hearing difficulty. One study reported non-significant differences for those with Axis I disorders.[29] Two studies reported significantly worse self-reported hearing-related outcomes for those with PTSD.[12,17]

Neurological

Key Question 1: We found five primary studies reporting neurological outcomes including neurological deficits based on examination, and NSI: Numbness or Tingling item score (Appendix E, Table 2f).[12,13,17,25,32] Average self-reported numbness or tingling was of mild-moderate severity.[13] No studies compared populations with mTBI to those without mTBI.

Key Question 2: One study investigating the association of blast exposure with the NSI item score described non-significant group differences,[12] as did a study on presence of additional injury.[25] Two studies reported significantly worse NSI numbness or tingling score for those with PTSD.[12,17] Finally, one study reported that Veterans with LOC at the time of injury were significantly more likely to obtain positive neurological exam findings than those without LOC.[32]

Nausea/Appetite

Key Question 1: We found five primary studies reporting outcomes related to appetite and nausea including self-reported nausea, and NSI: Loss of Appetite, Change in Taste or Smell, and Nausea item scores (Appendix E, Table 2g).[12,13,17,25,29] Average self-reported change in taste or smell, nausea, and loss of appetite ranged from mild to moderate in severity.[13] No studies compared populations with mTBI to those without mTBI.

Key Question 2: One study reported that having an additional injury was a protective factor on two NSI items, but non-significantly related to the NSI item assessing change in taste or smell.[25] Two studies investigating the association of blast exposure[12] and presence of an Axis I disorder reported non-significant group differences for items assessing nausea, appetite, and changes in taste and smell.[29] Two studies reported significantly worse self-reported appetite and nausea-related outcomes for those with PTSD.[12,17]

MENTAL HEALTH RESULTS

Summary of Mental Health Results

Twenty studies reported mental health outcomes for Veterans or members of the military with mTBI. Mental health outcomes varied greatly in terms of methods of assessment, ranging from lengthy clinical interviews based on diagnostic criteria, to single-item, self-report screeners. Overall, this body of literature provides low strength evidence, as it is based on studies with many methodological limitations.

Studies included in this review suggest that there are high rates of comorbid mental health disorders and symptoms for those with mTBI. Notably, studies examined different, sometimes overlapping mental health outcomes (e.g., some studies examined only PTSD, while others reported combined mental health outcomes such as “any Axis I disorder.” Rates of Axis I disorders ranged from 50-78% in two studies; single studies reported that reported that the rate of PTSD was 45%, alcohol abuse/dependence was 28%, drug abuse/dependence was 9% suicidal ideation was 25%, suicidal intent was 7%, and past suicide attempts was 4% for Veterans with mTBI. Notably, however, the majority of included studies suggest that there are few, if any, significant differences in mental health outcomes for those with mTBI compared to Veteran/military participants without mTBI). Finally, though many individual studies investigated potential moderating factors for mental health outcomes, no clear risk or protective factors were identified; however, studies often reported an association multiple mental health outcomes (e.g., depression, anxiety, and PTSD symptoms were reported to be significantly correlated for those with and without mTBI).

The following table summarizes the evidence on mental health outcomes, which is then followed by detailed results descriptions for specific areas of mental health.

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Table 4. Summary of Evidence for Mental Health Outcomes Associated with mTBI in Veteran and Military Populations

Domain (number of studies)	Key Question 1: Estimates of Prevalence and Impairment (number of studies)	Key Question 1: Statistically Significant Deficits Compared to Controls (number of studies)	Key Question 2: Statistically Significant Potential Risk or Protective Factors (number of studies)
PTSD (17)	Yes: Mean scores indicated impairment (4); No: (1) Proportion with PTSD = 45% (1)	Mixed (1) No (3)	Yes Protective: Additional injury (1) Yes Risk: Anxiety (1) Yes Risk: Blast exposure (2) Yes Risk: Depression (1) Yes Risk: LOC and/or AOC or PTA (3) Yes Risk: Positive neurological or neuropsychological assessment results (1) Yes Risk: Self-reported cognitive complaints (1) No: Referral to neurology clinic for headaches (1) No: Blast exposure (1)
Anxiety (6)	Average anxiety = “moderate-severe” (1) Yes: Mean scores indicated impairment (2)	NR	Yes Protective: Additional injury (1) Yes Risk: Depression (1) Yes Risk: LOC and/or PTA (1) Yes Risk: PTSD (2) Yes Risk: Self-reported cognitive complaints (1) No: Blast exposure (1)
Depression (8)	Mixed: Mean scores indicated impairment (2)	No (2)	Yes Risk: LOC and/or PTA (1) Yes Risk: PTSD (2) Yes Risk: Self-reported cognitive complaints (1) No: Additional injury (1) No: Blast exposure (1)
Substance Use Disorders (2)	Prevalence of alcohol abuse/dependence = 28% (2) Prevalence of drug abuse/dependence = 9% (1)	No (2)	Yes Risk: Axis I disorder (1)
Suicide (1)	Prevalence of suicidal ideation = 25% (1) Prevalence of suicidal intent = 7% (1) Prevalence of past suicide attempts = 4% (1)	No (1)	NR
Other (6)	Prevalence of Axis I disorder = 50-78% (2) Self-reported irritability/ frustration = “moderate-severe” (2)	Yes: Any Axis I disorder (1) No: Any Axis I disorder (1)	Yes Protective: Additional injury (1) Yes Risk: PTSD (2) No: Blast exposure (1)

Note. The impairment summary is based on average scores for groups with mTBI, and does not reflect individual variation in scores which could include some impairment for a certain proportion of participants. “Mixed” results indicate both significant and non-significant results for multiple assessments of the same outcome in a single study.

PTSD

Key Question 1: There were 17 studies that met inclusion criteria and reported PTSD outcomes (Appendix E, Table 3a).[9-13,16,19-21,25,27,28,31-33,36,38] These studies used the following assessment tools to measure PTSD: Clinician Administered PTSD Scale (CAPS): Total Score and Re-experiencing subscale; PTSD diagnosis; PTSD Checklist - Civilian Version (PCL-C) Total Score, Avoidance subscale, Hyper-Arousal subscale, Re-experiencing subscale, and individual item scores; PTSD Checklist - Military Version (PCL-M); and the PTSD Checklist - Stressor Specific Version (PCL-S). Mean scores on the PCL measures for those with mTBI ranged from 34.6[38] to 61.9,[9] suggesting clinically significant impairment for many with mTBI. Similarly, the one study reporting proportion of patients obtaining scores indicative of clinically significant impairment reported that 45% of individuals with mTBI obtained such scores.[21] Of the studies comparing PTSD in those with mTBI to similar populations without, three reported non-significant differences between groups,[19,21,38] and one provided mixed results.[9]

Key Question 2: One study examined individual items on the PCL-C, and found that all but one (the item asking about disturbing memories) were significantly lower for those who had at least one additional injury.[25] The same study examined the association between PTSD and blast exposure for those with LOC or AOC at the time of injury, describing non-significant findings for all PCL symptom clusters and total scores with the one exception of higher scores on the PCL re-experiencing cluster.[25] Three additional studies examined the association with blast exposure, reporting significantly worse symptoms for those with blast exposure in two of the studies[12,28] and non-significant differences in one study.[16] One study reported significant, positive associations among PTSD, depression, and anxiety symptoms.[20] Two studies reported significantly worse PTSD symptom reports by those with LOC at the time of injury[32] and LOC and/or PTA.[20] One study reported a significant association between PTSD and obtaining positive neurological or neuropsychological test results.[33] One study reported non-significant differences in PTSD between those who were and were not referred to neurology clinics for headache treatment.[31] Finally, one study reported a significant association between self-reported cognitive complaints and PTSD symptoms.[36]

Anxiety

Key Question 1: We found six primary studies reporting anxiety outcomes including the Hospital Anxiety and Depression Scale (HADS): Anxiety assessment and the NSI: Feeling Anxious item score (Appendix E, Table 3b).[12,13,17,20,25,36] Average self-reported anxiety symptoms were in the moderate-severe range on the NSI and in the clinically significant range on the HADS.[13,36] No studies compared mTBI to non-mTBI populations.

Key Question 2: One study investigating the association of blast exposure with self-reported anxiety resulted in non-significant findings.[12] Four studies reported significantly worse self-reported anxiety for those with PTSD,[12,17] LOC and/or PTA immediate sequelae,[20] self-reported depression, [20] and self-reported slowed thinking, attention deficits, and memory deficits. [36] One study reported that having at least one additional injury was negatively associated with self-reported anxiety.[25]

Depression

Key Question 1: We found eight primary studies reporting depression outcomes including Beck Depression Inventory 2nd Edition (BDI-II) score, a single-item hopelessness assessment, Hospital Anxiety and Depression Scale (HADS): Depression subscale score, Neurobehavioral Symptom Inventory (NSI): Depression item score, and Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I): Major Depressive Disorder diagnosis (Appendix E, Table 3c).[9,12,13,17,20,25,36,37] Average self-reported depression severity was in the moderate range on the NSI,[13] though average scores did not fall within the clinically significant range on the HADS.[36] Of the two studies comparing depression symptoms for those with and without mTBI,[9,37] neither reported significantly worse depression symptoms for mTBI participants.

Key Question 2: Two studies investigating the association of blast exposure[12] and additional injury[25] with depression reported non-significant findings. One study investigated presence of LOC and/or PTA[20], two studies investigated PTSD,[12,17] and one study investigated self-reported cognitive problems[36]; all reported that these were statistically significantly associated with worse depression in those with mTBI.

Substance Use Disorders

Key Question 1: We found only two primary studies reporting substance use outcomes, both using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) to establish drug or alcohol use/dependence (Appendix E, Table 3d).[9,29] The studies reported that the prevalence of substance use disorders in this population ranged from 9% for drug abuse/dependence[9] to 28% for alcohol abuse/dependence.[9,29] Both studies reported non-significant differences in prevalence compared to controls.

Key Question 2: One of the studies described having another Axis I disorder as significantly associated with increased prevalence of alcohol abuse/dependence.[29]

Suicide

Key Question 1: We found only one primary study reporting outcomes related to suicide (Appendix E, Table 3e).[9] This study used the following single item assessments of suicide-related outcomes: Suicidal Ideation (Have you had thoughts about death or about killing yourself?), Suicidal Intent (Have you ever intended to commit suicide?), and Past Suicide Attempts (Have you ever attempted suicide?). This single study reported that the prevalence of suicidal ideation in this population was 25%, suicidal intent was 7%, and past suicide attempts was 4%. The authors report non-significant differences when comparing these outcomes to results from non-mTBI controls.

Key Question 2: We did not find any evidence related to this key question.

Other Mental Health Outcomes

Key Question 1: We found six primary studies reporting other mental health outcomes and summary scores (Appendix E, Table 3f).[9,12,13,18,25,35] The outcomes investigated in these studies included Frontal Systems Behavioral Scale (FrSBe): Apathy pre- to post-injury change and Behavioral Disinhibition pre- to post-injury change subscales, Neurobehavioral Symptom

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Inventory (NSI): Affective Cluster, Neurobehavioral Symptom Inventory (NSI): Irritability and Frustration items, Psychiatric Diagnosis, and Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I): Axis I Disorder diagnosis. The prevalence of Axis I disorder in mTBI populations was reported to range from 50-78% based on two studies, though these same studies report mixed results in terms of whether these prevalence estimates are significantly higher compared to non-mTBI controls.[9,18] Self-reported irritability and frustration were both within the moderate to severe range as assessed by the NSI in one study.[13]

Key Question 2: One study reported a non-significant association between blast exposure and frustration severity.[12] One study reported a significant negative association between having an additional injury and NSI affective cluster, frustration, and irritability scores. [25] Finally, two studies reported that PTSD was significantly associated with poor NSI frustration and irritability item scores[12,18] as well as the NSI affective cluster score.[18]

FUNCTIONAL/SOCIAL OUTCOME RESULTS

Summary of Functional/Social Outcome Results

We found 12 studies, all low quality, reporting functional/social outcomes for Veterans or members of the military with mTBI. Due to methodologic limitations as well as small sample size and inadequate reporting of and accounting for time since injury, the strength of evidence for this group of studies is low. One study reported that approximately 20% of Veterans with mTBI experience unemployment. One of two studies comparing participants with mTBI to participants without mTBI found higher unemployment among those with mTBI. Another study found that 26% of those with mTBI had difficulties with interpersonal relationships, though this was not significantly different in comparison to individuals without mTBI. Ten studies examined sleep disturbance: two found an overall prevalence of 13-23% in those with a history of mTBI, and seven found that sleep disturbances, when present, were moderate to severe. One of two studies found that sleep disturbance was more common in those with mTBI compared to those without a history of mTBI. No clear patterns of risk or protective factors emerged from studies examining potential moderators of mTBI history for functional or social outcomes.

The following table summarizes the evidence on functional/social outcomes, which is then followed by detailed results descriptions for each functional/social domain.

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Table 5. Summary of Evidence for Functional/Social Outcomes Associated with mTBI in Veteran and Military Populations

Domain (number of studies)	Key Question 1: Estimates of Prevalence and Impairment (number of studies)	Key Question 1: Statistically Significant Deficits Compared to Controls (number of studies)	Key Question 2: Statistically Significant Potential Risk or Protective Factors (number of studies)
Employment (2)	Prevalence of unemployment = 20% (1)	Yes (1) No (1)	No: LOC (1)
Sleep (10)	Mixed results related to impairment: Mean self-reported sleep disturbance and fatigue ranged from approximately "mild" to "very severe." (7) Prevalence < 4 hours of sleep per night: 13% (1) Prevalence of > 2 hours sleep loss per night: 23% (1)	Yes (1) No (1)	Yes Protective: Additional injury (1) No: Blast exposure (1) Yes Risk: PTSD (2) Yes Risk: Positive neurological or neuropsychological findings (1) Yes Protective: Participation in a headache intervention (1) No: Referral to neurology clinic for headaches(1)
Relationships (1)	Prevalence of lack of emotional support = 26% (1)	No (1)	NR

Note. The impairment summary is based on average scores for groups with mTBI, and does not reflect individual variation in scores which could include some impairment for a certain proportion of participants. "Mixed" results indicate both significant and non-significant results for multiple assessments of the same outcome in a single study.

Employment

Key Question 1: We found only two studies documenting outcomes related to employment status using self-reported unemployment, two or more missed workdays in the past month, difficulty carrying a heavy load in past month, and difficulty performing physical training in past month as indicators of employment outcomes (Appendix E, Table 4a).[9,39] One study described a non-significant comparison to a non-mTBI population, and reported that the rate of unemployment for the mTBI population was 20%.[9] Another study reported that the odds of missing more than 2 days of work ranged from 1.4-1.8, odds of difficulty carrying a heavy load in past month ranged from 2.2-3.0, and odds of difficulty performing physical training in the past month as indicators of employment outcomes ranged from 1.6-1.9 when compared to a non-mTBI reference group.[39]

Key Question 2: One study examined the potential impact of LOC on employment outcomes for Veterans with mTBI, and reported equivalent results across groups for all outcomes assessed. [39]

Sleep

Key Question 1: We found 10 primary studies that reported sleep outcomes for Veterans and members of the military including the Epworth Sleepiness Scale (ESS); Neurobehavioral Symptom Inventory (NSI): Fatigue and Sleep items; hours per night of sleep; hours per night of sleep lost; and sleep disturbance in the past 30 days.[12,13,15,17,24,25,27,31,33,34] Of the two studies comparing participants with and without mTBI, three out of six sleep outcomes were significantly worse for those with mTBI, and the others were approximately equivalent across groups.[15,24] Only one study reported prevalence of sleep disturbance, estimated at 13% (less than four hours of sleep per night) to 23% (more than 2 hours sleep loss per night) for active duty military personnel within 10 days of injury.[15] Notably, self-reported sleep disturbance and fatigue on the NSI ranged from approximately "mild" (0.86) to approximately "very severe" (3.45) depending on the sub-population with mTBI (e.g., those with and without PTSD), indicating clinically significant impaired sleep for at least some Veterans and members of the military with mTBI.[12,13,17,25,31,33,34]

Key Question 2: One study examining differences between Veterans referred to the neurology clinic for headaches versus those not referred noted non-significant differences between groups on mean NSI sleep item score.[31] Studies examining additional injury,[25] blast exposure,[12] PTSD,[12,17] and positive neurological or neuropsychological findings[33] all suggest that participants with mTBI with these potential risk factors endorse significantly worse sleep disturbance than those without these factors. Similarly, a study investigating a headache intervention described significantly less sleep disturbance endorsed by participants with mTBI who were randomly assigned to the intervention condition compared to the control group of participants with mTBI who were not offered the intervention.[34]

Social

Key Question 1: We found only one study reporting social outcomes as indicated by lack of emotional support and marital status (Appendix E, Table 4b).[9] This study reported non-significant differences between mTBI compared to non-mTBI participants for both outcomes. The prevalence of lack of emotional support was reported to be 26% for Veterans with mTBI.

Key Question 2: No studies addressed this key question related to social outcomes.

SERVICE UTILIZATION/COSTS RESULTS

Summary of Service Utilization/Costs Results

We found seven studies that described service utilization by Veterans with mTBI, and no studies reported costs associated with mTBI. The overall strength of evidence was low because of the small number and methodologic shortcomings of studies. The available literature suggests that there are few differences in service utilization for those with mTBI compared to similar controls, and no significant associations with potential risk or protective factors were identified. The following table summarizes the evidence on service utilization/cost outcomes, which is then followed by a detailed results description of results.

Table 6. Summary of Evidence for Service Utilization/Costs Associated with mTBI in Veteran and Military Populations

Domain (number of studies)	Key Question 1: Estimates of Prevalence and Impairment (number of studies)	Key Question 1: Statistically Significant Deficits Compared to Controls (number of studies)	Key Question 2: Statistically Significant Potential Risk or Protective Factors (number of studies)
Service Utilization (7)	No mean scores indicating impairment (e.g., diagnosis), with the exception of a broad range of results reported for number of prescribed medications. (2) Prevalence of current counseling = 4-6%. (1) Prevalence of current mental health medications = 4-5%. (1)	No (4)	No: LOC (1)
Costs (0)	NR	NR	NR

Note. The impairment summary is based on average scores for groups with mTBI, and does not reflect individual variation in scores which could include some impairment for a certain proportion of participants.

Service Utilization/Costs

Key Question 1: Table 6 describes the seven primary studies reporting service utilization by Veterans and members of the military including current counseling, current mental health medication, current pain medication, narcotic pain medication, number of medications overall, length of hospital stay, length of intensive care unit stay, and medical utilization as indicated by more than two sick calls within the past month.[10,15,18,21,24,37,39] None of the studies comparing participants with mTBI to those without mTBI[15,18,21,24] or to those with moderate/severe TBI[10] reported statistically significant differences on any service utilization outcomes. One study which did not report a *p*-value, however, reported that participants with mTBI were prescribed an average of 18 medications, compared to a control group without mTBI, who were prescribed an average of five medications.[37] Prevalence of current counseling by those with mTBI was reported to be approximately 4-6% and current mental health medication was 4-5% in two studies of the same population.[15,24]

Key Question 2: One study examined whether or not LOC at the time of injury was related to having two or more sick call visits in the past month, and reported similar odds ratios for mTBI participants with and without LOC.

SUMMARY AND DISCUSSION

SUMMARY OF EVIDENCE

We found 31 studies examining the effects of mTBI in Veteran and military populations. In general, though cognitive, physical, and mental health symptoms were commonly reported by Veterans and members of the military following an mTBI, there was little evidence that symptoms were more commonly reported by study participants with mTBI than similar participants without mTBI. However, the evidence base is weakened by inconsistent findings, methodologic shortcomings of many studies, and variation in outcomes considered and outcome measurement approaches. Therefore, conclusions drawn from this body of literature are uncertain, likely to change given additional research in the future, and should be interpreted with caution.

Mental health problems are a serious concern for Veterans and members of the military with mTBI, though the extent to which these outcomes are uniquely related to mTBI versus other deployment-related illnesses are not clear. Posttraumatic stress disorder (PTSD) is one of the most common mental health disorders among Veterans of wartime service, affecting approximately 15% of Veterans of all eras.[40] A recent systematic review estimated the overall prevalence of comorbid TBI and PTSD among OIF/OEF Veterans at 5-7%,[41] and among Veterans with histories of TBI, rates of PTSD range from 33-65%.[41-44] Furthermore, having both PTSD and TBI may adversely affect functionality more than suffering from either disorder alone.[45]

The high prevalence of comorbid PTSD and mTBI are likely related to both event-related factors and neuropsychiatric symptom overlap between disorders.[46] Modern warfare involving multiple deployments and high rates of blast exposure has greatly increased service members' risk of TBI and PTSD.[47] In addition, there is evidence from neuroimaging studies that PTSD and TBI affect similar areas of the brain, including the prefrontal cortex, hippocampus, and amygdala.[47,48] Regardless of etiology, the overlap in the presentation of mTBI and PTSD can be accounted for at least in part by shared symptoms. In particular, core symptoms of both PTSD and postconcussive syndrome include problems with concentration/attention and memory, sleep disturbance, and irritability.[49,50] Moreover, cognitive complaints and objective neurocognitive deficits are common among individuals with PTSD, even in the absence of a history of TBI,[48,51-54] including problems with memory, concentration/attention, and problem-solving.

We found a very limited evidence base examining functional and social outcomes suggesting that one fifth to one quarter of Veterans with mTBI experienced unemployment, sleep disturbance, or lack of emotional support. Whereas more severe levels of TBI are identified immediately post-trauma, cases of mTBI are often unidentified and untreated until after military discharge, at which point Veterans may begin to recognize problems like trouble reintegrating into work or school or difficulties maintaining familial or social relationships. Longitudinal studies have found impairments ranging from difficulty maintaining leisure interests and friendships, to vocational instability, poor life satisfaction, and poor quality of life among individuals who have incurred mTBI.[55,56] Individuals' social and physical environments can either help or hinder recovery of full functional capacity after mTBI. Research has found factors like social support, family adjustment and cohesion, life stressors, and receipt of compensation for disability to be associated with functional outcomes among individuals with mTBI.[57]

The VA will be providing life-long care for a large number of OEF/OIF/OND Veterans who have sustained mTBI. In some cases, the VA will also provide care for the Veterans' informal/family caregivers.[58] The long-term resource needs of OEF/OIF/OND Veterans are likely substantial; however, these resource needs are possibly related to a variety of factors including comorbid conditions and other consequences of deployment and not uniquely related to having experienced an mTBI. The majority of data on costs and resource utilization of individuals with TBI comes from civilian studies and examines those with moderate-to-severe TBI, for which follow-up care and rehabilitation needs are great and disability is common. Little is known about long-term costs and needs for those with mTBI, particularly military members or Veterans with deployment-related mTBI. Although most outcomes studies of civilians have found that symptoms and sequelae of mTBI resolve within one year after the injury,[59] different contextual factors including mechanism of injury provide only indirect comparisons to Veteran/military outcomes. It is likely that complicating deployment-related factors such as repeat mTBI events or concomitant mental health disorders such as PTSD could result in very different long-term outcomes and resource utilization for this population.

Findings from Civilian Populations

Though the overall strength of evidence evaluating outcomes following mTBI in Veteran or military populations is low, it is noteworthy that the findings are remarkably consistent with higher quality civilian literature.[59] Both bodies of research suggest that many health consequences resolve within the first few months following injury, if not sooner.

A systematic review of literature in children and adults found objective cognitive deficits associated with mTBI resolve within 2-3 months and the physical consequences of mTBI are likely limited to those which resolve within the first few days following injury.[59] The authors note that though objective cognitive impairment resolves quickly, subjective cognitive complaints may linger for years for some individuals who experience mTBI. They also found that litigation or evaluation for compensation was a risk factor for worse cognitive test performance, a finding echoed by another review.[60]

Other systematic reviews reported similar findings. One review described insufficient and inadequate evidence for any cognitive effects of mTBI greater than 6 months following injury.[61] A meta-analysis of sports-related concussion suggests that though some impairment in memory and global cognitive functioning may be present for individuals with mTBI within a week of injury, these effects are no longer present after 7 days post-injury.[60] These authors also found cognitive deficits were no longer present by 3 months after injury in unselected, consecutive samples.[60]

A systematic review of civilian literature related to functional impairment suggests that there is not a significant impact for children with mTBI, and most functional impairment resolves within a month for adults with mTBI.[59] However, this review also points out that self-reported functional impairment may last longer, up to years, in some instances, particularly when individuals are involved in litigation or compensation related to the mTBI, and when individuals experience the mTBI event as psychologically traumatic.

Pertab and colleagues conducted a re-analysis of studies included in earlier meta-analyses. This group of authors suggests that time since injury and the use of different cognitive assessment tools may have a potentially moderating effect on cognitive outcomes.[62] The authors describe a range in summary effect sizes based on cognitive domain and time since injury, suggesting the possibility that some subgroups of those with mTBI may experience some objective cognitive deficits for a limited period of time following injury.

Of note, the WHO Collaborating Centre for Neurotrauma Prevention, Management and Rehabilitation Task Force has recently completed an updated systematic review examining the effects of mTBI in civilian populations. Results are likely to be reported within the next year and should further add to our understanding.

Even though the strength of evidence in civilian populations is higher, there is not enough information in that body of literature either to identify how factors such as time since injury, mechanism of injury, or number of mTBIs influence long-term outcomes.

Use of Imaging and Biomarkers in mTBI Research

Although beyond the scope of this review, since imaging and biomarker technologies are a rapidly evolving area of research of interest to stakeholders, we will briefly summarize recent relevant research here.

Although biomarkers are increasingly being used as prognostic tools among those with moderate or severe TBI, research among those with less severe injuries has been limited.[63] Efforts are focused on evaluating serum and cerebral spinal fluid during different stages of the brain injury cascade (e.g., inflammation, neuronal injury).[64] As no single biomarker with discriminative characteristics has been indentified, Sharma and Laskowitz (2012) suggest that combining biomarkers may increase sensitivity and specificity.[64] For further information regarding biomarkers and mTBI see Jeter et al. (2012), and Sharma and Laskowitz (2012).[64,65]

Recent interest has emerged regarding the possibility that returning military personnel with a history of TBI are at risk for developing chronic traumatic encephalopathy (CTE).[66] CTE refers to persistent cognitive and neuropsychiatric symptoms (e.g., executive dysfunction, memory impairment, depression, poor impulse control, and dementia) secondary to chronic neurodegeneration thought to be caused at least in part by multiple TBIs.[67] At present, CTE can only be identified by direct tissue examination; as such, full autopsies and immunohistochemical brain analyses are necessary for definitive diagnosis. Despite much speculation regarding blast exposed individuals being at risk for CTE, limited data currently exists in support of this relationship. Current efforts pertaining to increasing understanding regarding CTE include: creating clinical diagnostic criteria, identifying objective biomarkers, and increasing understanding regarding additional risk factors and underlying mechanisms.[68]

Recent literature reviews of neuroimaging in mTBI including DTI, functional,[69] and metabolic imaging,[70] have examined the association of imaging findings with neuropathology.[71] Although brain changes resulting from mTBI are often not discernible with conventional clinical structural CT and MRI, there is a growing body of evidence that they are more readily detectible with advanced research imaging technologies, particularly DTI,[72] which measures the functional integrity of white matter interconnections within the brain. A rapidly growing body of DTI investigation indicates that DTI is more sensitive to white matter injury than conventional MRI and CT, with DTI consistently detecting more abnormalities than conventional CT or MRI across multiple mTBI studies. As would be expected from the animal model and neurocognitive assessment literature,[71] acute and subacute structural and functional imaging changes are demonstrated. However, abnormalities have also been demonstrated at chronic stages, suggesting that some patients experience long-term brain changes as well. The most common abnormalities have been shown for long association pathways including the corticospinal tract, corpus callosum, corona radiata, internal capsule, uncinate fasciculus, and the superior longitudinal fasciculus. Further, in some studies, DTI abnormalities correlate with cognitive performance in patients with mTBI, with general aggregate DTI abnormality correlated with executive function, memory, and cognitive processing speed. Locally specific structure-function relationships have sometimes been observed in mTBI, with damage to frontal white matter associated with executive function and attentional performance, and temporal tract changes associated with decreases in memory performance. Some more recent imaging studies support the notion of persistent postconcussive symptoms (PCS), with observable pathophysiological findings correlated with PCS. Supportive of these DTI findings, many fMRI studies found activation differences between individuals with mTBI and individuals in the control group during cognitive and behavioral tasks consistent with DTI findings, although many studies failed to show associated significant differences in task performance.[69] The various metabolic imaging techniques are less well investigated in mTBI, but initial results suggest that these techniques show promise as investigative and diagnostic tools.[70]

Although rapidly growing, there remain several limitations for mTBI neuroimaging research. It is largely made up of cross-sectional studies with small samples, and there is a great deal of method and design variability with respect to such factors as time period of scanning post-injury, brain regions examined, magnet strength, non-imaging outcome variables, and methods of analyses, resulting in differences across studies in both anatomical location of observed brain alterations and the nature of these alterations. Despite considerable consistency in its main findings, this body of research is still relatively new and there remain as-yet unresolved discrepancies. For instance, some DTI studies show increased fractional anisotropy (FA), while others show decreased FA. Also, many fMRI studies failed to show associated significant differences in task performance associated with significant task-related activation differences between patients and control participants.[69] Imaging studies nonetheless are consistent in providing evidence of small and subtle brain injuries in mTBI that are often, although not always, associated with symptoms and cognitive performance. This evidence would not be possible if conventional MRI and CT scans alone were used to establish and characterize brain injury; it requires more advanced and sophisticated imaging methods such as DTI and fMRI that are sensitive to the effects of diffuse axonal injury and altered metabolic function to delineate these abnormalities.

Clinical Considerations

The best available evidence, which is of low quality, suggests that many symptoms that patients ascribe to mTBI may be related to comorbid mental or physical health concerns, or to other factors such as readjustment to civilian life following deployment or injury beliefs and perceptions.[73] Difficulties related to post-deployment adjustment underscores the need to engage recently returned Veterans and members of the military quickly in efforts to identify physical and mental health problems and provide appropriate re-integration services. Patients should be encouraged to engage in treatment for these comorbid concerns with the best available evidence-based treatments (e.g., evidence-based psychotherapy to treat PTSD).

Administrators setting policy for treatment of military-related mTBI should be cautioned to treat the available evidence as limited and subject to change depending on findings from future, more methodologically rigorous studies. Policy based on the best available evidence should likely encourage the treatment of comorbid conditions that commonly occur for Veterans and members of the military who have experienced deployment (e.g., treatment for PTSD, substance use disorders, headaches, sleep disorders, and other post-deployment concerns).

Given the lack of large, good-quality observational studies with adequate follow-up it is very difficult to estimate the long-term cognitive effects of mTBI. However, the current evidence base suggests that cognitive deficits are not common, particularly more than three months after injury. Therefore, should individuals with mTBI continue to experience ongoing cognitive deficits following first-line treatment for co-occurring symptoms and disorders such as PTSD, further testing such as neuropsychological or neurological evaluations or imaging might be warranted.

LIMITATIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

The available literature reporting consequences of mTBI in Veteran and military populations is based on low quality observational studies and provides low strength evidence for the associations synthesized in this systematic review. Notably, not all outcomes of potential interest to stakeholders were found in the literature base (e.g., costs). There is insufficient data to determine the presence or absence of an effect for these outcomes, and further research is warranted.

One of the major limitations of this literature is the inadequate reporting of and accounting for time since injury among Veterans and military members, and therefore it is not possible to construct an accurate picture of mTBI consequences over time for this population. This body of literature is also likely subject to participant recall bias due to the cross-sectional, retrospective nature of almost all included studies. Participants are likely unable to accurately recall symptoms and timeframes so long after one (or more) mTBI events. Future research should take advantage of available VA and DoD databases that have time since injury information and include this variable in the analysis of mTBI consequences on an individual participant level. Similarly, such databases should be used to examine the possible effect of multiple mTBI events as this is a common occurrence for many individuals who were part of OEF/OIF conflicts. Additionally, a large prospective cohort study would be better able to identify factors associated with outcomes in mTBI populations.

A related limitation of the body of literature relates to how data is presented in included studies. Very few studies reported the actual prevalence of symptoms or conditions; most studies simply reported mean scores for the entire study group. This latter approach can provide useful information for determining whether there is a unique contribution of mTBI versus outcomes being affected by more general deployment or combat exposure factors. However, a lack of prevalence estimates limits an accurate description of the population, particularly when a goal of stakeholders is to estimate numbers of Veterans who will be affected by specific outcomes and utilize related treatment services. Future research should not only report mean scores for subgroups, but also report proportions of individuals with clinically significant impairment for each outcome. This recommendation is particularly relevant to the body of research on cognitive outcomes, as the vast majority of this literature describes differences based on means rather than reporting the proportion of individuals who obtain scores indicating impaired functioning. For cognitive outcomes in particular, impairment is ideally determined not only by standardized scores within a certain range, but also by comparison to pre-injury (baseline) functioning. Studies should report this intra-individual change as part of any cognitive findings so that accurate estimates of mTBI-related cognitive impairment are reported.

Few studies presented data on all outcomes of interest to the stakeholders of this review, and few studies reported their outcome reporting rationale. Most studies relied on clinical datasets, which are generally not maintained for research purposes, rather than research databases or registries. The use of these datasets can be efficient relative to primary data collection but typically do not contain all variables of interest in a given scientific inquiry. It is likely that many studies only included outcomes of relevance to the authors' particular study questions, though it is impossible to know whether some studies did not report outcomes given a lack of association with mTBI. There is a pressing need for large cohort studies of Veterans with and without mTBI that prospectively collect data on all risk and protective factors, and all outcomes of interest. Such studies would be relatively costly but would result in higher-quality evidence on which more definitive conclusions could be based.

Although a strength of this review was that many of the included studies relied on well-validated measures commonly used with Veteran/military populations, many of the clinical outcomes relied solely on self-reported outcomes, often obtained from single questionnaire items. Self-report data is often the only way to assess certain outcomes such as pain. However, some notable results from this review and a review of the civilian literature[59] suggest that self-reported deficits are more likely to be reported by individuals with mTBI. Assessment for mTBI is often associated with potential financial compensation, which in turn has been commonly associated with worse outcomes. Because participants are not often blinded to study hypotheses, self-reported outcomes should be interpreted with greater caution than objective findings evaluated by blinded outcome assessors. Thus, future research should consider using objective and validated assessments, blinded outcome assessors, patient blinding to study hypotheses, and accounting for compensation factors whenever possible in order to reduce bias associated with outcome assessment.

Additionally, future research should employ commonly used outcome assessment tools in order to facilitate the combination of results across studies for meta-analytic purposes. One of the limitations of this body of literature was the wide variety of tools used to assess each outcome. Though we reported statistically significant results from included studies, it is possible that combining studies mathematically would increase power, and effects could be detected in aggregate which were not apparent at the individual study level. In the case of this review, diversity in outcome assessment tools precluded mathematical combination of results.[74]

A final strength of this review was the use of clear criteria for defining mTBI. However, because the majority of studies did not assess or report imaging results, and those that did were inconsistent in their inclusion of participants with positive imaging results, we were not able to apply exclusion criteria based on positive imaging as is recommended by the VA/DoD definition of mTBI. Additionally, because of our reliance on stringent definitional criteria, we excluded many studies that purported to study mTBI populations, but did not meet the criteria for this report. The scope of this report focused explicitly on OEF/OIF/OND Veterans and members of the military meeting VA/DoD mTBI criteria; consequently, this report provides a narrow window of information on mTBI and should not be viewed as comprehensive. Findings from other systematic reviews on mTBI in civilian populations should be considered for a more complete understanding of mTBI consequences. Future primary research should clearly report criteria used to define mTBI, including assessment and reporting of imaging results. Future research should investigate the possible impact of number of mTBI events, as many studies noted that Veterans experienced multiple mTBIs, though few examined this variable as a possible moderator of outcomes. Additionally, future reviews should consider examination of differences in outcomes based on definitional criteria for mTBI, as it is possible that less stringent criteria could be associated with different results.

CONCLUSIONS

Overall, given the low strength of evidence, it is difficult to draw firm conclusions about the effects of mTBI in Veteran and military populations. The literature reviewed here is relatively consistent with findings from the more methodologically rigorous, prospective, longitudinal studies conducted in civilian populations. Both bodies of literature suggest that though some negative outcomes occur for a significant portion of individuals who have mTBI, most objective results (e.g., objective cognitive test results) are not significantly different from control participants, and deficits that are present shortly following injury most often resolve within days to months. The literature on Veterans and members of the military suggests that many have physical and mental health symptoms, but it is not clear that those with mTBI experience more or higher severity symptoms than those without mTBI suggesting that outcomes may be influenced by other deployment-related conditions such as PTSD. The studies included in this report were low quality, cross sectional studies which did not provide consistent evidence for potential moderators of mTBI outcomes.

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