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Characteristics and Impact of U.S. Military Blast-Related Mild Traumatic Brain Injury: A Systematic Review

Helen Phipps^{1*}, Stefania Mondello^{2,3*}, Arlington Wilson¹, Travis Dittmer¹, Natalie N. Rohde¹, Paul J. Schroeder¹, Jaime Nichols¹, Camille McGirt¹, Justin Hoffman¹, Kaila Tanksley¹, Mariam Chohan¹, Amanda Heiderman⁴, Hussein Abou Abbass⁵, Firas Kobeissy⁶ and Sidney Hinds⁷

¹ Booz Allen Hamilton, San Antonio, TX, United States, ² Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy, ³ Department of Neurology IC, Oasi Research Institute-IRCCS, Troina, Italy, ⁴ Dell, Round Rock, TX, United States, ⁵ Department of Anatomy, Cell Biology and Physiological Sciences, Faculty of Medicine, American University of Beirut, Beirut, Lebanon, ⁶ Department of Psychiatry, Center for Neuroproteomics and Biomarkers Research, University of Florida, Gainesville, FL, United States, ⁷ Medical Research and Development Command, Ft Detrick, MD, United States

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*Correspondence:

Stefania Mondello
stm_mondello@hotmail.com
Helen Phipps
Phipps_helen@bah.com

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As a result of armed conflict, head trauma from exposure to blasts is an increasing critical health issue, particularly among military service members. Whilst numerous studies examined the burden of blast-related brain injuries on service members', few systematic reviews have been published. This work provides a comprehensive summary of the evidence on blast-related mild traumatic brain injury (mTBI) burden in active U.S. military service members and inactive Veterans, describing characteristics and outcomes. Records published up to April 2017 were identified through a search of PubMed, Web of Science, Scopus, Ovid MEDLINE, and Cochrane Library. Records-based and original research reporting on U.S. military service members and Veterans with mild blast TBI were included. Data on subject characteristics, exposure, diagnostic criterion, and outcomes were extracted from included studies using a standardized extraction form and were presented narratively. Of the 2,290 references identified by the search, 106 studies with a total of 37,515 participants met inclusion criteria for blast-related mTBI. All but nine studies were based out of military or Veteran medical facilities. Unsurprisingly, men were over-represented (75–100%). The criteria used to define blast-related mTBI were consistent; however, the methodology used to ascertain whether individuals met those criteria for diagnosis were inconsistent. The diagnosis, most prevalent among the Army, heavily relied on self-reported histories. Commonly reported adverse outcomes included hearing disturbances and headaches. The most frequently associated comorbidities were post-traumatic stress disorder, depression, anxiety, sleep disorders, attention disorders, and cognitive disorders. The primary objective of this review was to provide a summary of descriptive data on blast-related mTBI in a U.S. military population. Low standardization of the methods for reaching diagnosis and problems in the study reporting emphasize the importance to collect high-quality data to fill knowledge gaps pertaining to blast-related mTBI.

Keywords: blast, mild traumatic brain injury, U.S. military, PTSD, systematic review, epidemiology

INTRODUCTION

Mild traumatic brain injury (mTBI) has been coined as one of the signature wounds of war with blast-related injuries being the most militarily unique (1, 2). Causes of mTBI from blast-related incidents are multifaceted in that the physical wound to the brain may result from direct and/or indirect exposure to over-pressure environments. Improvised explosive devices, occupational training, and heavy munitions firing are common sources of blast injuries incurred during military services (3). Despite more than a decade of research, the etiology, treatment, and recovery from blast-related mTBI remains poorly understood.

The Department of Defense (DoD) defines five mechanisms of blast-related brain injury ranging from primary to quinary and referred to as a taxonomy of injuries from explosive devices as outlined in **Table 1** (5). Owing to its unique outcomes, the entire spectrum of all severities and mechanisms of blast-related brain injury is now recognized as a specific area of focus within the broad spectrum of TBI (6). There are several reasons why this development is gaining momentum: (1) its impact on the readiness of militaries worldwide, (2) its coexistence with secondary through quinary effects (7), and (3) the overlapping symptomology with post-traumatic stress disorder (PTSD). Nevertheless, to date, reliable estimates of the burden of blast-related mTBI are lacking, mainly because of ambiguity about the definition among medical practitioners and researchers, absence of objective tests to make a definitive diagnosis of blast-related mTBI especially in an operational environment, and the potential overlap and co-existence of other neuropathological conditions (e.g., PTSD). In fact, it has been shown that depression and PTSD are major components of the psychological changes that accompany mTBI as shown by Hoge et al. (8) and more recently that suicide is associated with mTBI (9). Thus, there is a need for research to fill the gaps in knowledge about blast-related mTBI.

The direct and indirect costs of the broad spectrum of TBI among Americans, regardless of their military status, were reported as ~\$60 billion annually in 2006 (10) and \$76.5 billion in 2010 (11). Eibner et al. (12) estimated that per case costs of the full spectrum of deployment-related TBI fell between \$96.6 and \$144.4 million using a 2007 price level. While this estimated value included hospital care costs, rehabilitation, death, and lost productivity, other economic factors such as substance abuse and homelessness were not considered. Therefore, the reported estimates probably underestimate the “real” economic burden.

Government-sponsored public reports of the broad spectrum of TBI prevalence rates among U.S. military service members are available. For example, the Defense and Veterans Brain Injury Center (DVBIC), a component of the U.S. Military Health System, provides some summary data on prevalence rates. However, publicly available data from the DVBIC are limited to only totals among branches without consideration for multiple TBIs among individual service members and do not provide detailed data on specific types of injuries, such as blast-related mTBI. They only report the highest severity TBI

sustained per service member which results in underreporting of TBIs (13). Currently the DVBIC assessment is the best publicly available estimate of U.S. military TBI. More specific inquiries require a formal request to the center. According to the DVBIC, the majority of brain injuries are diagnosed in non-deployed settings (14). Other available data focus on the health outcomes of blast-related mTBI among active U.S. military service members and inactive Veterans (15–19). Although assessments of the cost of TBI on military services have been conducted (20), few systematic assessments of the body of evidence surrounding the prevalence and cost of blast-related mTBI among active U.S. military service members and inactive Veterans have been performed. Additional parameters that can only be obtained from a thorough patient record review and expert characterization and analysis of the actual blast event(s) would be needed for the most accurate assessment of the mechanisms causing the physical injury coupled with the alterations in physiology and pathophysiology. These parameters are beyond the scope of most database/diagnosis-centric resources.

Current estimates from DVBIC indicate that between 2000 and 2019, the total number of service members diagnosed with a TBI was 413,858 (21). This value is congruent with prior reports (22, 23). Although exact current estimates of the prevalence of blast-related mTBI are scarce, evidence from records-based studies offer insight into the scope of the issue. For example, one study (24) reported that, between 2006 and 2011, 70% of the 43,852 patients screened for TBI had a blast-related injury. It should be noted that accurate prevalence and incidence rates of service-related injuries are difficult to ascertain. There are several reasons for this: (1) military service members may under-report injuries (25, 26), (2) medical data may have been entered after the injury incident and/or may be incomplete, (3) mTBIs may be misdiagnosed due to overlapping symptoms with other conditions [e.g., PTSD or “breacher’s brain”; (27–29)], (4) differences in how data were analyzed (30), and (5) the reported estimate may be based on data gathered from specific populations (23). Thus, prevalence rates of mTBI among military service members should be interpreted with caution.

The objectives of this study were to review the literature on blast-related mTBI in active U.S. military service members and inactive Veteran populations with the aim of *characterizing the epidemiological patterns of blast-related mTBI and assess clinical outcomes*. More specifically, the goal was to examine trends in reported outcomes from a carefully selected group of published reports on blast-related mTBI. The outcomes of interest included:

- Diagnostic and assessment procedures
- Mechanisms of injury
- Inclusion criteria in the study (e.g., active duty and veteran U.S. military)
- Research design (inclusion of a comparative group)
- Time between injury and study participation
- Service branches of the participants
- Demographics of the participants

TABLE 1 | Taxonomy of injuries from explosive devices per DoD Blast Injury Research Coordinating Office.

Blast injury category	Description	Examples
Primary	Result from the high pressures, or blast overpressure, created by explosions. Blast overpressure can crush the body and cause internal injuries. Primary blast injuries are the only category of blast injuries that are unique to the blast or high pressures that occur.	<ul style="list-style-type: none"> • Blast lung (pulmonary barotrauma) • Tympanic Membrane rupture and middle ear damage • Abdominal hemorrhage and perforation • Globe (eye) rupture • Concussion (mild traumatic brain injury (mTBI) without physical signs of head injury)
Secondary	Result when strong blast winds behind the pressure front propel fragments and debris against the body and cause blunt force and penetrating injuries.	<ul style="list-style-type: none"> • Penetrating ballistic (fragmentation or blunt injuries) • Eye penetration • Closed or open brain injuries
Tertiary	Result from strong blast winds and pressure gradients that can accelerate the body and cause the same types of blunt force injuries that would occur in a car crash, fall, or building collapse.	<ul style="list-style-type: none"> • Bone fractures • Traumatic amputations • Blunt injuries • Crush injuries • Closed or open brain injuries
Quaternary	Result from other explosive products (such as heat and light) and from exposure to toxic substances from fuels, metals, and gases that can cause burns, blindness, and inhalation injuries.	<ul style="list-style-type: none"> • Burns (flash, partial, and full thickness) • Injury or incapacitation from inhaled toxic fumes (breathing problems from dust, smoke, or toxic fumes)
Quinary	Refer to the clinical consequences of post-detonation environmental contaminants, including chemical (e.g., sarin), biological (e.g., anthrax), and radiological (e.g., dirty bombs) substances.	<ul style="list-style-type: none"> • Chemical burns • Radiation exposure • Viral or bacterial infections

Office (4).

- Injury associated with TBI (e.g., cognitive and neurosensory impairments, headaches, etc.)
- Comorbidities
- Brain regions of interest (e.g., white matter, cerebrum, thalamus, etc.)
- The financial and work-related cost of treating injuries as reported by the included studies and/or other referenced sources.

For this systematic review the focus is on the general impact of blast-related mTBI, rather than a concentration on acute and post-acute injuries. Veterans were considered inactive consistent with the legal definition according to Title 38 of the Code of Federal Regulations. Primary outcomes of interest were prevalence and incidence of blast-related mTBI in active U.S. military service members and inactive Veterans. Secondary outcomes of interest were related clinical outcomes and economic costs as well as their patterns and changes over time (i.e., study period). The conclusions drawn from this review are necessary to inform research for prevention, resource allocation, and care of blast-related mTBI.

MATERIALS AND METHODS

Design

In accordance with the published protocol (PROSPERO CRD42017054942), a systematic review of studies reporting epidemiological patterns, burden, and outcomes of blast-related mTBI in active U.S. military service members and inactive Veterans was performed. The current systematic review followed guidelines for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (31) and the Cochrane Handbook (32).

Search Strategy

For this systematic review, blast-related mTBI was defined as any mTBI associated with a blast-related event (e.g., over-pressurization impulse, forced air-flow) and included primary, secondary, tertiary, quaternary, and quinary mechanisms (5, 33, 34). Since the population under consideration was limited to U.S. military it was assumed that a diagnosis of mTBI was consistent with the current Department of Defense (DoD), American Congress of Rehabilitation Medicine (ACRM), or the World Health Organization (WHO) guidance, at the time of diagnosis (Table 2). Consistent with DoD guidance (39), articles that reported the individual and cumulative effects of blast components (e.g., primary, secondary, and other damage associated with overpressure wave, maximal pressure, impacts with debris, or ground) were included in this review.

PubMed, Web of Science, Scopus, Ovid MEDLINE, and Cochrane Library databases were systematically searched from their inception dates to April 2017. With the help of an information specialist, search strategies specific to each database were developed using a combination of broad keywords and subject headings/indexing terms. The full search strategies are provided as **Supplemental Material**.

Study Selection and Eligibility Criteria

The results from the search strategy yielded a total of 2,990 citations, duplicate records were identified and removed (Figure 1). Titles and abstracts of the identified records were screened for relevance. Full text articles of all potentially eligible studies were obtained and evaluated against the inclusion criteria. Studies that were included met the following criteria: (a) the study population was active U.S. military service members and/or inactive Veterans, (b) condition under study included blast-related mTBI and the blast-related mTBI population could be

TABLE 2 | TBI definitions and diagnostic criteria.

Organization	TBI definition	mTBI diagnostic criteria
DoD/VA (35) (36)	A traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force that is indicated by new onset or worsening of at least one of the following clinical signs, immediately following the event: (1) any period of loss of or a decreased level of consciousness (LOC); (2) any loss of memory for events immediately before or after the injury [post-traumatic amnesia (PTA)]; (3) any alteration in mental state at the time of the injury (e.g., confusion, disorientation, slowed thinking, etc.); (4) neurological deficits* (weakness, loss of balance, change in vision, praxis, paresis/plegia, sensory loss, aphasia, etc.) that may or may not be transient.	Imaging: Normal* LOC: 0–30 min AOC: <24 h PTA: <24 h GCS: 13–15 within 24 h**
ACRM (37)	A traumatically induced physiological disruption of brain function, as manifested by at least one of the following: (1) any period of loss of consciousness; (2) any loss of memory for events immediately before or after the accident; (3) any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused); and (4) focal neurological deficit(s) that may or may not be transient; but where the severity of the injury does not exceed the following: LOC of ~30 min or less; after 30 min, an initial Glasgow Coma Scale (GCS) of 13–15; and PTA not >24 h.	LOC: 0–30 min AOC: <24 h PTA: <24 h GCS: 13–15 after 30 min
WHO (38)	An acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include: (1) 1 or more of the following: confusion or disorientation, LOC for 30 min or less, post-traumatic amnesia for <24 h, and/or other transient neurologic abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; (2) GCS score of 13–15 after 30 min post-injury or later upon presentation for health care; (3) These manifestations of MTBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g., systemic injuries, facial injuries, or intubation), caused by other problems (e.g., psychological trauma, language barrier, or coexisting medical conditions), or caused by penetrating craniocerebral injury.	LOC: 0–30 min AOC: <24 h PTA: <24 h GCS: 13–15 after 30 min

*Removed from and/or not indicated for mTBI in the updated DoD definition.

**No longer recommended by the DoD as a TBI diagnostic criteria.

stratified out of other populations included, (c) prevalence, incidence, and/or health outcomes of blast-related mTBI were investigated, and (d) an appropriate study design was used as determined by quality assessment (approach explained below). We excluded studies that: (a) presented mixed populations with a preponderance of moderate or severe blast-related TBI cases that could not be stratified out of the blast-related mTBI cases; and/or (b) condition under study was non-blast TBI (e.g., traditional mechanism TBI).

All languages were included in the searches. Studies with overlapping populations were identified by examining the methodology of each study. Particular attention was paid to the source of the data (e.g., health records, registries, and/or primary research), the time period of the data gathering (if reported), and the location of the data gathering (if reported). Endnote (version X7.5, Thomson Reuters, Toronto, Canada) and a web-based systematic review workflow platform (Covidence, Alfred Health Melbourne, Australia) were used to manage citations.

Data Extraction

Data extraction was performed by at least two reviewers independently using a standardized (i.e., each reviewer used the same extraction form format and associated data element definitions) and piloted extraction form (i.e., the extraction form was beta tested by several reviewers prior to implementing). Discrepancies were resolved through discussion or arbitration by a third reviewer. Extracted data included information about the study design, setting, population characteristics, case ascertainment methods, TBI assessment and diagnostic modalities, diagnostic criteria, number of blast-related mTBI cases and population denominator (Total), and outcomes.

Studies were stratified by three case ascertainment methods: (1) Medical Records, (2) Original Assessments, or (3) Both.

Original assessments included Self-Report, Clinical Assessments, and Imaging as defined below that were administered by the study team. Studies were further analyzed to determine the specific TBI assessment and diagnostic modalities used by researchers. These were categorized as Self-Report, Clinical Assessment, Medical Records, and Imaging as defined below.

- **Self-Report:** Interview or questionnaire using self-reported information
- **Clinical Assessment:** Clinical exams, tests, and neurocognitive assessments performed by a clinician
- **Imaging:** Neuroimaging studies (e.g., MRI or CT)
- **Medical Records:** Data from historical medical records, medical record reviews, or general reference to medical records or medical history.

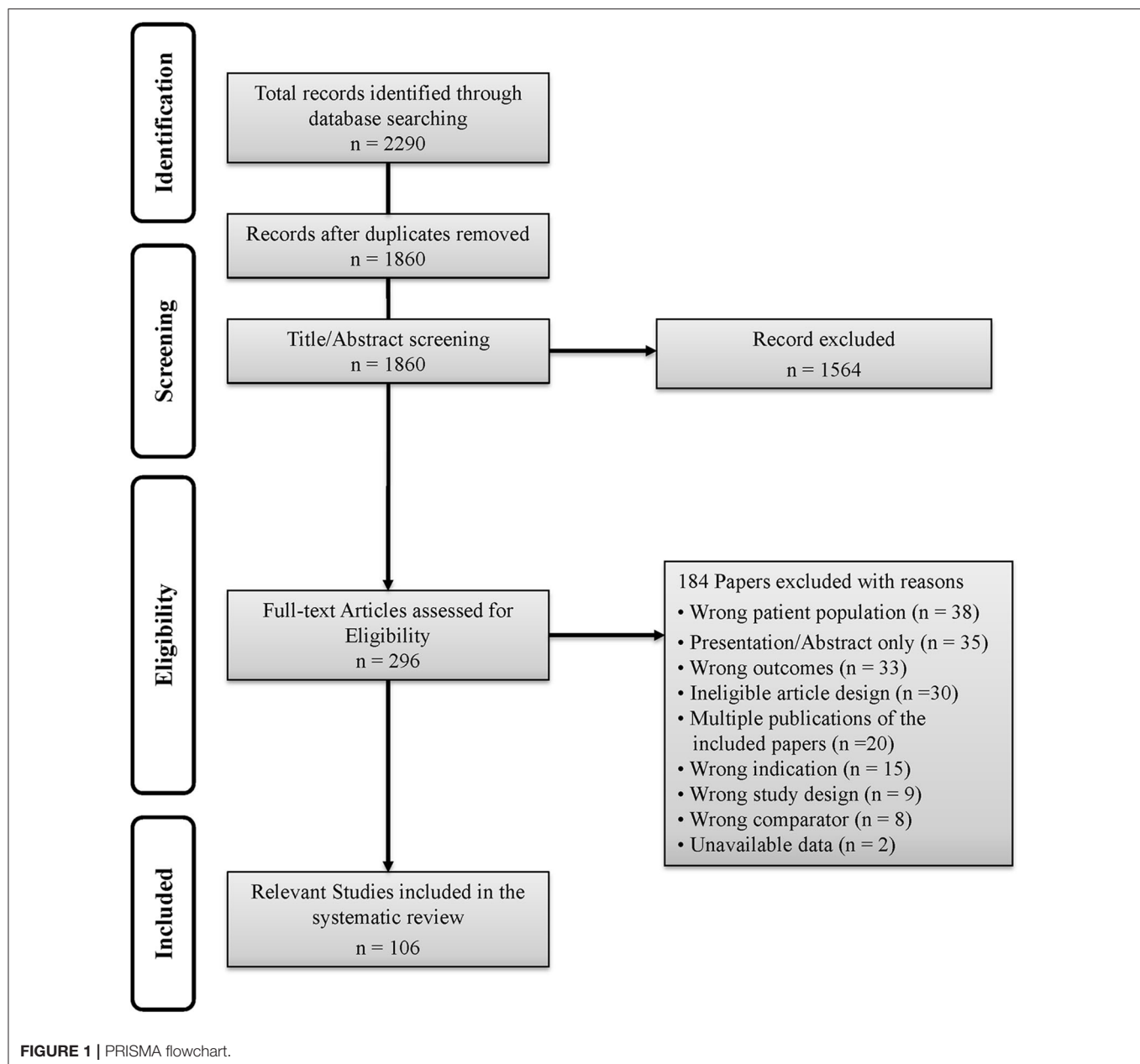
Study settings were grouped as Military, Civilian, VA, or Combination based on the affiliation of the study centers as described below.

- **Military:** Military treatment facility, field hospital, or research facility
- **Civilian:** Civilian medical or research facility
- **VA:** Veterans Affairs medical or community center
- **Combination:** Any combination of the above.

Quality Assessment

The quality of the included studies was assessed according to Weiskopf et al. (40). The guideline provides a 5-item checklist—completeness, correctness, concordance, plausibility, and currency. Two reviewers determined whether each study met the five criteria using five factors. The quality of the included studies is summarized in **Table 3**.

Completeness indicates the presence or absence of key data elements from report i.e., sample size at the start of the study



(excluded for records-based research); study time period; time since injury (i.e., time between injury and data points); control group; age of the study population (or age only reported as greater or less than with no mean, median, or range); and/or sex of the study population. This means that the data element was not reported but does not necessarily indicate whether the element was part of the study but inadvertently excluded from the report. Elements that were not considered key did not influence the indicator of completeness (e.g., branch of service, region TBI sustained, and GCS [since DoD no longer requires GCS for diagnosis]).

Correctness indicates whether there was a control or comparative group reported. If absent, this calls into question the

quality of the data. However, although control or comparative groups were not reported in several studies, the data was in concordance with other high-quality studies (see concordance).

Concordance indicates the consistency of data reported as compared to a gold standard reference when taking currency into account [i.e., structured quantitative data and unstructured qualitative data related to outcomes were compared to those reported in the Veterans Health Administration, 2016 QUERI study; (143)]. Note that imaging outcomes were not reported in the VHA, 2016 QUERI study so imaging outcomes were not used to determine concordance.

Plausibility indicates whether data reported are within logical values. Logical values were considered as realistic

TABLE 3 | Quality assessment of included studies.

#	Study ID	Completeness	Correctness	Concordance	Plausibility	Currency
1	Adam et al. (41)	✓	✓	✓	✓	✓
2	Akin and Murnane (42)	✗	✓	✓	✓	NR
3	Barlow-Ogden et al. (43)	✗	✓	✓	✓	✗
4	Bazarian et al. (44)	✗	✓	✓	✓	✗
5	Belanger et al. (45)	✗	✓	✓	✓	✗
6	Belanger et al. (46)	✗	✓	✓	✓	✗
7	Bell et al. (47)	✗	✓	✓	✓	✓
8	Bjork et al. (48)	✗	✗	✓	✓	✓
9	Bolzenius et al. (49)	✗	✓	✓	✓	✗
10	Verfaellie et al. (50)	✗	✓	✓	✓	✓
11	Brenner et al. (51)	✗	✗	✓	✓	✗
12	Callahan et al. (52)	✗	✓	✓	✓	NR
13	Capo-Aponte et al. (53)	✗	✓	✓	✓	✓
14	Capo-Aponte et al. (54)	✓	✓	✓	✓	✓
15	Chen et al. (55)	✗	✓	✓	✓	✓
16	Connelly et al. (24)	✗	✓	✓	✓	NR
17	Cooper et al. (56)	✓	✓	✓	✓	✗
18	Davenport et al. (57)	✗	✓	✓	✓	✓
19	Davenport et al. (57)	✗	✓	✓	✓	NR
20	Davenport et al. (58)	✗	✓	✓	✓	NR
21	de Lanerolle et al. (59)	✗	✓	✓	✓	✓
22	Dretsch et al. (60)	✓	✓	✓	✓	✓
23	Erickson (61)	✓	✓	✓	✓	✗
24	Farrell-Carnahan et al. (62)	✗	✗	✓	✓	✗
25	Finkel et al. (17)	✗	✓	✓	✓	NR
26	Fischer et al. (63)	✗	✓	✓	✓	✗
27	Franke et al. (17)	✗	✓	✓	✓	✗
28	Gilmore et al. (64)	✗	✓	✓	✓	✗
29	Gilmore et al. (65)	✗	✓	✓	✓	✗
30	Goodrich et al. (66)	✗	✓	✓	✓	✓
31	Han et al. (67)	✓	✓	✓	✓	✓
32	Hayes et al. (68)	✓	✓	✓	✓	NR
33	Heinzelmann et al. (69)	✗	✓	✓	✓	✗
34	Heltemes et al. (70)	✗	✓	✓	✓	✓
35	Hetherington et al. (71)	✗	✓	✓	✓	NR
36	Hoffer et al. (72)	✗	✓	✓	✓	NR
37	Huang et al. (73)	✗	✓	✓	✓	✓
38	Huang et al. (74)	✗	✓	✓	✓	✗
39	Janak et al. (75)	✓	✓	✓	✓	✓
40	Karch et al. (76)	✗	✓	✓	✓	✓
41	Kennedy et al. (77)	✗	✗	✓	✓	✓
42	Kennedy et al. (78)	✓	✓	✓	✓	✓
43	Kennedy et al. (79)	✓	✓	✓	✓	✓
44	Kontos et al. (80)	✗	✓	✓	✓	NR
45	Kontos et al. (81)	✗	✓	✓	✓	✓
46	Kontos et al. (82)	✗	✓	✓	✓	NR
47	Lange et al. (83)	✓	✓	✓	✓	✗
48	Lemke et al. (84)	✗	✗	✓	✓	✓
49	Levin et al. (85)	✗	✓	✓	✓	✗
50	Lew et al. (86)	✗	✓	✓	✓	NR
51	Lew et al. (87)	✗	✗	✓	✓	✗

(Continued)

TABLE 3 | Continued

#	Study ID	Completeness	Correctness	Concordance	Plausibility	Currency
52	Lew et al. (88)	✗	✓	✓	✓	NR
53	Licon et al. (89)	✗	✓	✓	✓	✓
54	Lindquist et al. (90)	✗	✓	✓	✓	NR
55	Lippa et al. (91)	✗	✓	✓	✓	✗
56	Luethcke et al. (92)	✗	✓	✓	✓	✓
57	MacDonald et al. (93)	✓	✓	✓	✓	✓
58	MacDonald et al. (94)	✗	✓	✓	✓	✗
59	MacDonald et al. (95)	✓	✓	✓	✓	✓
60	MacDonald et al. (96)	✓	✓	✓	✓	✓
61	MacDonald et al. (97)	✓	✓	✓	✓	✓
62	MacDonald et al. (98)	✗	✓	✓	✓	✗
63	Macera et al. (99)	✗	✓	✓	✓	NR
64	MacGregor et al. (100)	✗	✓	✓	✓	✓
65	MacGregor et al. (101)	✗	✗	✓	✓	✓
66	Magone et al. (102)	✓	✓	✓	✓	✓
67	Maguen et al. (103)	✓	✓	✓	✓	✗
68	Matthews et al. (104)	✗	✓	✓	✓	✗
69	Mendez et al. (105)	✗	✓	✓	✓	✗
70	Mendez et al. (106)	✗	✓	✓	✓	✗
71	Miller et al. (107)	✗	✓	✓	✓	✗
72	Morey et al. (108)	✗	✓	✓	✓	✗
73	Nathan et al. (109)	✗	✓	✓	✓	✗
74	Neipert et al. (110)	✗	✓	✓	✓	✗
75	Newsome et al. (111)	✗	✓	✓	✓	✗
76	Norris et al. (112)	✗	✗	✓	✓	✓
77	Norris et al. (113)	✗	✗	✓	✓	✓
78	Oleksiak et al. (114)	✗	✓	✓	✓	NR
79	O'Neil et al. (115)	✗	✓	✓	✓	✗
80	Petrie et al. (116)	✗	✓	✓	✓	✗
81	Pogoda et al. (117)	✗	✓	✓	✓	✓
82	Reid et al. (118)	✗	✓	✓	✓	✗
83	Riedy et al. (119)	✓	✓	✓	✓	✗
84	Robinson et al. (120)	✗	✓	✓	✓	✗
85	Ruff et al. (121)	✗	✓	✓	✓	NR
86	Ruff et al. (122)	✗	✗	✓	✓	✗
87	Ryu et al. (123)	✗	✓	✓	✓	✓
88	Saxe et al. (124)	✗	✓	✓	✓	✓
89	Scheibel et al. (125)	✗	✓	✓	✓	NR
90	Storzbach et al. (126)	✓	✓	✓	✓	✗
91	Stout et al. (127)	✗	✓	✓	✓	✗
92	Strigo et al. (128)	✗	✓	✓	✓	✗
93	Tate et al. (129)	✗	✓	✓	✓	✓
94	Trotter et al. (130)	✗	✓	✓	✓	NR
95	Troyanskaya et al. (131)	✗	✓	✓	✓	✗
96	Trudeau et al. (132)	✗	✓	✓	✓	NR
97	Vakhtin et al. (133)	✗	✓	✓	✓	NR
98	Verfaellie et al. (134)	✗	✓	✓	✓	✗
99	Verfaellie et al. (135)	✗	✓	✓	✓	✗
100	Walsh et al. (136)	✗	✓	✓	✓	✓
101	Wares et al. (137)	✗	✓	✓	✓	NR
102	Wilk et al. (138)	✗	✓	✓	✓	✓

(Continued)

TABLE 3 | Continued

#	Study ID	Completeness	Correctness	Concordance	Plausibility	Currency
103	Wilkinson et al. (139)	✗	✓	✓	✓	✗
104	Xydakis et al. (140)	✗	✓	✓	✓	✓
105	Yeh et al. (141)	✗	✓	✓	✓	✓
106	Yeh et al. (142)	✗	✓	✓	✓	✗

✓ Denotes the element was found within the study report. ✗ Denotes that the element was found to be within the study report, but did not meet the criteria (e.g., not complete). NR denotes unknown, unclear, or unreported. This means that the data element was not reported. NR does not necessarily indicate whether the element was part of the study, but inadvertently excluded from the report.

values within possible limits for the methods cited within the study.

Currency indicates the minimum (median or average if minimum was not reported) time from injury (after rounding time reported for the study population which was not necessarily limited to blast-related mTBI) to data collection (if available). Times were reported in months. An average month was considered to be 4 weeks/30 days for conversion purposes where studies reported time in units besides months. Data were rounded up to nearest whole number if decimal over 0.5. NR indicates the data elements were unknown, unclear, or unreported. For records-based research the health records were assumed to be current unless otherwise reported (i.e., it is assumed that health records are reported at the time of or soon after the data are collected from the patient). For original research without use of health records, time since injury to data collection of over 3 months was considered as not current considering there is little evidence to suggest impairment beyond 3 months after a single mTBI (144–146). On occasion some report symptoms out to ~12 months (147). This is not meant to say that blast-related or non-blast-related mTBI cannot cause long-term outcomes, but simply cites that the time between sustaining the TBI and the minimum time to data collection was >3 months.

As shown in **Table 3**, 16% ($n = 17$) of the included studies were judged to be complete, 90% ($n = 95$) were judged to be correct, 100% were judged to be concordant, 100% were judged to be plausible, and 34% ($n = 36$) were judged to have currency. Across the five items, 8% ($n = 9$) of the included studies met all five items, 27% ($n = 29$) met four items, 59% ($n = 63$) met three items, and 5% ($n = 5$) met two items. No studies were judged to have met <1 item. Taken collectively, these figures suggest that the included studies matched with the goals of the current study.

Data Synthesis and Statistical Analysis

Results were reported numerically and narratively to include a descriptive synthesis of the findings from the included studies. To facilitate appropriate comparisons, studies were first grouped according to whether they reported country-level data (derived from national hospital or registries) or field data. Other stratifications—for example, by study design and retrospective/prospective data collection—were also considered.

Findings are described overall, and broken down according to year of publication, military service, diagnostic criteria, age, and sex. Time trends of prevalence and outcomes of blast-related mTBI also are described. Data are presented in tables and figures.

Meta-analysis was not possible owing to the heterogeneity of the studies.

RESULTS

Description of Studies

The search strategy identified 1,860 unique records, of which 296 full text articles were assessed for eligibility. One hundred six of them met the criteria for inclusion in the review (**Figure 1**, PRISMA flowchart). Characteristics of the included studies and demonstration of data quality and epidemiological patterns of blast-related mTBI are summarized in **Tables 3–8**. The majority of studies included were published in 2007 or later with one exception published in 1998. Only 3 studies reported data on inactive Veterans from prior wars, the remaining focused primarily on TBIs sustained in Iraq and Afghanistan. Control or comparative groups were present in over 93% ($n = 99$) of the studies and consisted of healthy participants, with no TBI, with TBIs of varying severity, and/or caused by other mechanisms, and/or with other comorbidities.

All the studies included in this review were from U.S. investigators and utilized various inclusion criteria, case ascertainment sources, and TBI diagnostic and assessment modalities, which precluded comparative analyses. Of the 106 included studies, over 36% (38 studies) were conducted at, or leveraged data from specialty care clinics where brain imaging (e.g., MRI) was utilized to measure the presence and/or effects of blast-related mTBI at military or other medical facilities using self-report measures to analyze outcomes following injury and/or cognitive testing by a physician (**Table 4**). The remaining studies used data collected by physicians at the time of injury, by physicians or other specialists seen at specialty care clinics with a focus on treating patients with these types of injuries, by researchers, or by self-reported measures. All but three of the included studies were based out of Military or Veteran Facilities (**Table 4**).

Table 5 presents the number of publications by year and the design of the studies. There are two noteworthy aspects of **Table 5**. First, among the included studies, 78% ($n = 83$) were published between 2009 and 2015. Within those 6 years, 46% ($n = 38$) were published in 2014 and 2015. Trends in the publication years of the included studies can be traced to two sources: (1) successive increases in VA-sponsored funding for TBI research following the ninth State-of-the-Art (SOTA) conference in 2008, which focused on advances in TBI science

TABLE 4 | Characteristics of included studies.

Study ID	Timeframe	Case ascertainment			Population at start	Blast-related mTBI		Assessment modality				Study setting category
		Medical records	Other assessment	Both		n	%	Self-report	Clinical assessment	Imaging	Medical records	
Adam et al. (41)	3/2012–9/2012		✓		230	95	41%	✓	✓	✓		Military
Akin and Murnane (42)	NR		✓		NR	9		✓	✓			Civilian
Barlow-Ogden et al. (43)	NR		✓		NR	15			✓		✓	VA
Bazarian et al. (44)	8/2008–1/2010		✓		500	31	6%	✓		✓		VA
Belanger et al. (45)	NR			✓	137	38	28%	✓	✓		✓	VA
Belanger et al. (46)	NR			✓	640	298	47%	✓				Combination
Bell et al. (47)	4/2003–4/2008	✓			513	229	45%		✓			Military
Bjork et al. (48)	NR		✓		133	98	74%	✓	✓			VA
Bolzenius et al. (49)	NR			✓	40	12	30%	✓	✓	✓	✓	Civilian
Verfaellie et al. (50)	NR		✓		136	88	65%	✓	✓			Combination
Brenner et al. (51)	NR		✓		49	45	92%	✓	✓			Military
Callahan et al. (52)	NR			✓	87	42	48%	✓			✓	VA
Capo-Aponte et al. (53)	NR	✓			NR	20			✓			Military
Capo-Aponte et al. (54)	1/2008–2/2011	✓			549	343	62%	✓			✓	Military
Chen et al. (55)	10/2007–9/2009	✓			235	13	6%				✓	VA
Connelly et al. (24)	5/2006–7/2011	✓			43,852	1,950	4%		✓		✓	Military
Cooper et al. (56)	1/2008–1/2010	✓			120	32	27%	✓	✓		✓	Military
Davenport et al. (57)	3/2006–7/2007			✓	522	64	12%	✓		✓		Combination
Davenport et al. (57)	NR			✓	522	64	12%	✓		✓		Combination
Davenport et al. (†) (2016)	NR			✓	124	54	44%	✓		✓	✓	Military
de Lanerolle et al. (59)	NR		✓		NR	25			✓	✓		Combination
Dretsch et al. (60)	2009		✓		71	34	48%	✓	✓			Military
Erickson (61)	11/2007–10/2009	✓			170	77	45%		✓			Military
Farrell-Carnahan et al. (62)	2008–2012			✓	424	114	27%	✓			✓	VA
Finkel et al. (17)	8/2008–12/2009	✓			NR	51			✓			Military
Fischer et al. (63)	NR		✓		107	21	20%	✓	✓	✓		VA
Franke et al. (17)	NR		✓		196	66	34%	✓	✓			Combination
Gilmore et al. (64)	NR			✓	127	127	100%	✓		✓	✓	Combination
Gilmore et al. (65)	NR		✓		124	60	48%	✓	✓			Combination
Goodrich et al. (66)	NR	✓			100	50	50%				✓	VA
Han et al. (67)	2008–2009 and 2010–2011		✓		124	103	83%			✓		Combination
Hayes et al. (68)	NR			✓	NR	59		✓	✓	✓		VA
Heinzelmann et al. (69)	NR	✓			117	19	16%	✓	✓		✓	Military

(Continued)

TABLE 4 | Continued

Study ID	Timeframe	Case ascertainment			Population at start	Blast-related mTBI		Assessment modality				Study setting category
		Medical records	Other assessment	Both		n	%	Self-report	Clinical assessment	Imaging	Medical records	
Heltemes et al. (70)	3/2004–3/2008	✓			1,129	473	42%				✓	Military
Hetherington et al. (71)	NR		✓		45	25	56%			✓		VA
Hoffer et al. (72)	NR		✓		127	60	47%	✓	✓			Military
Huang et al. (73)	NR			✓	99	23	23%	✓	✓	✓	✓	Military
Huang et al. (74)	NR		✓		NR	26			✓	✓		Combination
Janak et al. (75)	2008–2013	✓			2,502	159	6%	✓			✓	Military
Karch et al. (76)	1/2008–2/2011	✓			500	303	61%				✓	Military
Kennedy et al. (77)	1/2007–4/2009			✓	NR	274		✓			✓	Military
Kennedy et al. (78)	5/23/2005–8/31/2009	✓			926	586	63%				✓	Military
Kennedy et al. (79)	5/2010–11/2010		✓		377	342	91%		✓			Military
Kontos et al. (80)	11/2009–12/2011	✓			27,169	1,113	4%		✓			Military
Kontos et al. (81)	12/2009–3/2012		✓		276	19	7%		✓			Military
Kontos et al. (82)	NR			✓	50	23	46%		✓	✓		VA
Lange et al. (83)	2/2002–1/2009	✓			662	35	5%		✓			Military
Lemke et al. (84)	12/2006–1/2012	✓			64	60	94%		✓			VA
Levin et al. (85)	NR		✓		236	37	16%	✓		✓		VA
Lew et al. (86)	12/1999–7/2006	✓			NR	42			✓		✓	VA
Lew et al. (87)	12/2004–4/2008	✓			175	62	35%	✓	✓			VA
Lew et al. (88)	10/2007–6/2009	✓			36,919	10,431	28%	✓				VA
Licona et al. (89)	2005–2012			✓	8,293	84	1%	✓			✓	VA
Lindquist et al. (90)	2000–2011		✓		2,937	63	2%	✓				VA
Lippa et al. (91)	NR			✓	529	138	26%	✓			✓	VA
Luethcke et al. (92)	NR			✓	104	40	38%	✓	✓			Military
MacDonald et al. (93)	11/2008–10/2009			✓	122	63	52%			✓		Combination
MacDonald et al. (94)	NR			✓	NR	4		✓	✓	✓		Combination
MacDonald et al. (95)	2010–2013	✓			255	53	21%	✓	✓	✓		Combination
MacDonald et al. (96)	2008–2009			✓	122	63	52%	✓	✓		✓	Combination
MacDonald et al. (97)	3/2012–9/2012			✓	NR	38		✓	✓			Combination
MacDonald et al. (98)	2008–2013		✓		94	46	49%			✓		Combination
Macera et al. (99)	2008–2009	✓			5,5047	1,117	2%	✓				Military
MacGregor et al. (100)	1/2004–4/2008	✓			NR	1,822					✓	Military
MacGregor et al. (101)	2004–2008	✓			14,653	107	1%				✓	Military
Magone et al. (102)	1/1/2009–12/31/2011	✓			192	31	16%		✓			VA
Maguen et al. (103)	4/2007–1/2010	✓			1,713	390	23%	✓				VA

(Continued)

TABLE 4 | Continued

Study ID	Timeframe	Case ascertainment			Population at start	Blast-related mTBI		Assessment modality				Study setting category
		Medical records	Other assessment	Both		n	%	Self-report	Clinical assessment	Imaging	Medical records	
Matthews et al. (104)	NR		✓		NR	22		✓	✓	✓		VA
Mendez et al. (105)	NR		✓		NR	12		✓	✓	✓		VA
Mendez et al. (106)	NR		✓		150	12	8%	✓				VA
Miller et al. (107)	NR		✓		NR	53		✓		✓		Combination
Morey et al. (108)	10/12/2007–5/10/2010		✓		NR	11		✓		✓		Combination
Nathan et al. (109)	NR			✓	NR	186		✓		✓	✓	Military
Neipert et al. (110)	NR		✓		115	20	17%		✓			VA
Newsome et al. (111)	NR		✓		100	25	25%	✓	✓	✓		Combination
Norris et al. (112)	8/2010–3/2012	✓			990	210	21%	✓	✓			Military
Norris et al. (113)	NR	✓			NR	239		✓	✓			Military
Oleksiak et al. (114)	6/2007–7/2009	✓			250	154	62%		✓		✓	VA
O'Neil et al. (115)	9/2008–4/2011		✓		NR	47		✓				VA
Petrie et al. (116)	NR			✓	NR	34		✓	✓	✓		VA
Pogoda et al. (117)	10/1/2007–6/2009	✓			36,214	11,065	31%	✓	✓			VA
Reid et al. (118)	NR	✓			3,205	505	16%	✓			✓	Military
Riedy et al. (119)	8/1/2009–8/30/2014		✓		1,028	688	67%			✓	✓	Military
Robinson et al. (120)	NR		✓		203	20	10%	✓		✓		VA
Ruff et al. (121)	NR		✓		155	126	81%	✓	✓			VA
Ruff et al. (122))	NR		✓		126	74	59%	✓	✓			VA
Ryu et al. (123)	NR		✓		29	6	21%		✓			Combination
Saxe et al. (124)	10/2006–1/2008	✓			477	76	16%	✓			✓	Military
Scheibel et al. (125)	NR		✓		30	15	50%	✓	✓	✓		VA
Storzbach et al. (126)	9/2008–4/2011			✓	132	49	37%	✓	✓		✓	VA
Stout et al. (127)	NR		✓		57	20	35%			✓		Civilian
Strigo et al. (128)	NR		✓		36	18	50%	✓	✓	✓		VA
Tate et al. (129)	NR		✓		23	12	52%	✓		✓		Military
Trotter et al. (130)	NR		✓		350	45	13%	✓		✓		VA
Troyanskaya et al. (131)	NR		✓		97	54	56%		✓			VA
Trudeau et al. (132)	NR		✓		43	27	623%	✓	✓			VA
Vakhtin et al. (133)	NR		✓		67	13	19%	✓	✓	✓		VA
Verfaellie et al. (134)	NR		✓		95	67	71%	✓	✓			VA
Verfaellie et al. (135)	NR		✓		160	105	66%	✓	✓			VA
Walsh et al. (136)	1/2008–2/2011	✓			166	117	70%		✓			Military
Wares et al. (137)	NR		✓		169	86	51%	✓	✓			VA

(Continued)

TABLE 4 | Continued

Study ID	Timeframe	Case ascertainment			Population at start	Blast-related mTBI		Assessment modality			Study setting category
		Medical records	Other assessment	Both		<i>n</i>	%	Self-report	Clinical assessment	Imaging	Medical records
Wilk et al. (138)	2006–2007		✓		7,668	424	6%	✓			Military
Wilkinson et al. (139)	NR	✓			92	26	28%	✓	✓		VA
Xydakis et al. (140)	NR		✓		1,555	136	9%		✓	✓	Military
Yeh et al. (141)	5/2009–6/2011			✓	NR	16		✓		✓	Military
Yeh et al. (142)	NR			✓	269	202	75%		✓	✓	Military

and (2) increased efforts to promote TBI research across scientific funding agencies [e.g., the 2014 National Research Action Plan (NRAP); (148)]. Second, despite increased in publication rates between 2009 and 2015, relative minor variability was observed in the research designs among the published studies. Across the 12-year range of the included studies, the most frequently used study design was prospective cohort ($n = 62$, 58%), followed by retrospective cohort ($n = 37$, 35%), case control ($n = 4$, 4%), and cross-sectional ($n = 3$, 3%).

The study populations consisted of young adults. The lowest reported mean age was 23 years (60) and the highest was 37 years (42). As expected, the reported proportion of males was greater than females, ranging from 75% in an article on imaging patterns in U.S. military service members (94) to 100% (entirely male blast-related mTBI cohorts) in a series of articles ($n = 31$) (49, 55, 56, 61, 69, 70, 73, 74, 77, 81–83, 93, 95, 99, 104–106, 113, 116, 118, 123, 125, 128, 129, 132, 133, 137, 139, 142).

Data Quality

Correctness, completeness, and currency are fundamental factors that describe the core concepts of health record data quality: if data is truthful, available, and the most recent available data (149, 150).

The quality of reporting in the final set of studies was found to be mixed (Table 3). Table 7 summarizes the findings from this review related to the completeness data quality factor. A set of variables were generally well-reported across all studies [e.g., n blast-related mTBI, Population (N) at End Total, Study Setting, Region TBI sustained, age, and sex]. Conversely, other relevant information that was indicative of study rigor (e.g., Time Since blast-related mTBI, Age Range blast-related mTBI, Study Period, and a clearly specified research design) were inconsistently reported in older papers. Reported outcomes are summarized in Table 8.

Analyses of the Reported Outcomes From the Included Studies

Diagnosis and Assessment

This review included varied sources for mTBI diagnosis and assessment (Table 6): roughly 59% ($n = 63$) used clinical assessments; 66% ($n = 70$) used self-report; 36% ($n = 38$) relied on diagnostic imaging; 29% ($n = 31$) relied on reviews of medical charts. The majority ($n = 99$) used a combination of diagnostic and assessment modalities, while the remaining ($n = 7$) used a single modality for their studies.

Mechanism of Injury

The number of blast-related mTBI participants included in the selected studies compared to the starting population ranged from 1 to 100% ($n = 84/8,293$ and $n = 107/14,653$ vs. $n = 127/127$, respectively).

Research Design and Data Collection Methods

Among the included studies that used non-blast TBI as a comparator or had no group for comparison ($n = 35$), ~57% included participants with blast-related mTBI compared to 43% non-blast mechanism participants. Of the studies included in

TABLE 5 | Number of included publications by year and study design.

Publication year	#Pubs	Prospective cohort	Retrospective cohort	Case-control	Cross-sectional
1998	1	1			
2007	1		1		
2008	1	1			
2009	5	3	2		
2010	6	3	3		
2011	9	2	6		1
2012	13	5	8		
2013	12	7	3	1	1
2014	19	10	7	2	
2015	19	16	2	1	
2016	12	9	3		
2017	8	5	2		1
Total	106	62	37	4	3

TABLE 6 | Number and percentage of diagnostic and assessment modalities used in the included articles.

Diagnostic modalities	#	%
Other Assessment	47	44%
Medical Records	34	32%
Both	25	24%
Assessment modalities		
Self-report	70	66%
Clinical assessment	63	59%
Imaging	38	36%
Medical records	31	29%
Diagnostic and assessment modalities summary		
Single modalities	7	7%
Combination of modalities (non-standard)	99	93%

The categories for assessment modalities are not mutually exclusive meaning that the total will not be 100% (e.g., self-report can be combined with clinical assessment). Also, multiple methods may fall within the same modality (e.g., there are multiple methods that are considered imaging).

this review, 54% ($n = 57$) reported the time between injury and study participation/data collection using at least one parameter (e.g., mean, median, or range). The mean time between injury and study participation ranged from the day of injury up to a maximum of 174 months.

Service Branch

In this review, 55% ($n = 58$) of the included studies reported the branch of service for participants. Of all studies, only 26% ($n = 28$) included service members from all branches. In addition, 18% ($n = 18$) of the studies included service members from 2 to 3 branches or components (including one study that had participants from both the National Guard and Army), and 8% ($n = 9$) included service members from the Army only.

TABLE 7 | Data completeness in the included studies.

Data element	# NR	Percent NR
GCS	96	91%
Median age blast-related mTBI	94	89%
Median time since blast-related mTBI	90	85%
Age range blast-related mTBI	84	79%
Time since blast-related mTBI Range	75	71%
SD time since blast-related mTBI	68	64%
Rank	66	62%
Mean time since blast-related mTBI	65	61%
Branch of service	58	55%
Study period	57	54%
SD age blast-related mTBI	48	45%
Mean age blast-related mTBI	43	41%
n Male/Female blast-related mTBI	38	36%
Population (N) at start total	21	20%
Region TBI sustained	7	7%
Study setting	0	0%
Population (N) at end total	0	0%
n blast-related mTBI	0	0%

TABLE 8 | The number of and percentage of major outcomes reported.

Outcome	#Articles	% articles reporting
PTSD	64	60%
Sensory impairments	35	33%
Depression	32	30%
Cognition	27	25%
Headaches	17	16%
Sleep disturbances	15	14%
White matter abnormalities/Functional connectivity	13	12%
Anxiety	6	6%

The categories for outcomes reported are not mutually exclusive meaning that the total will not be 100% (i.e., multiple outcomes were analyzed in most studies).

Demographics

The majority of studies (66%, $n = 70$) reported the age of participants in some capacity (e.g., mean, median, or range, **Supplementary Table 1**). As shown in **Table 7**, most of the included studies (64%, $n = 68$) reported the sex of the participants with blast-related mTBI. While the reported proportion of males with blast-related mTBI was consistently greater than females, the proportion ranged from 75% in an article on imaging patterns in U.S. military service members (94) to 100% (entirely male blast-related mTBI cohorts) in a series of articles ($n = 31$) (49, 55, 56, 61, 69, 70, 73, 74, 77, 81–83, 93, 95, 99, 104–106, 113, 116, 118, 123, 125, 128, 129, 132, 133, 137, 139, 142).

Neurocognitive and Sensory Impairments

Visual deficits were measured in five studies (66, 88, 102, 117, 136). These studies reported visual impairments in 40%–68%

of participants with photosensitivity and decreased visual acuity being the most commonly reported complaints (66, 88, 102, 117). Walsh et al. (136) reported at least one visual field defect (scatter, hemianopia, quadrantanopia, altitudinal, central, and constricted) in 64% of eyes examined in participants with blast-related mTBI (136). Other visual impairments reported include oculomotor dysfunction, floaters, pain, diplopia, and difficulty reading (66, 88, 102, 117).

Headaches

Our analysis included four studies looking specifically at prevalence of headache and seven others that reported headaches as an ancillary outcome. Of these studies of headache prevalence, the majority (over 60%) of participants with mTBI reported headache.

Comorbidities

Increased reports of these comorbidities were recorded for mTBI associated with blast, loss of consciousness, and multiple exposure. Of those observed in this review, PTSD had the highest prevalence with 64 studies reporting the condition, sensory impairments were the second most commonly reported ($n = 35$), and other common blast-related mTBI comorbidities included: depression ($n = 33$), cognitive deficits ($n = 27$), headaches/migraines ($n = 17$), and sleep disturbances ($n = 15$).

DISCUSSION

The primary goal of this review was to characterize the epidemiological patterns of blast-related mTBI and assess clinical outcomes in active U.S. military service members and inactive Veterans. Importantly, rigorous evaluation and confirmation of both mTBI and mechanism of injury (i.e., blast-related) are vital to producing a valid research study and to implement effective management and intervention strategies. However, it was evident from our review that blast-related mTBI studies are plagued by different and inconsistent diagnostic and assessment approaches. This issue has been noted in prior reviews (151), which suggests that it is an ongoing concern for the DoD medical community. Among the studies included in this review, the majority reported using self-report measures and a combination of diagnostic and assessment techniques. It should be noted that, in some cases, use of participants medical history was not possible because the study was conducted outside of the DoD or VA healthcare system or because the records were incomplete.

This analysis included studies that focused on multiple mechanisms of injury as well as some that were solely cohorts of blast-related injured active U.S. military service members and inactive Veterans; isolation of those studies [excluding studies where the Population (N) at the Start were not reported] revealed an average of 13% for blast-related mechanism with mTBI. Recent studies support a higher report rate (80%) in military cohorts with moderate-severe penetrating TBI (152).

Moreover, there was substantial variability of the inclusion criteria among the study samples. For example, we found a remarkable heterogeneity in terms of the number of blast-related

mTBI participants included in the selected studies compared to the starting population. This was primarily due to the outcome measures used which included severity of specific outcomes of blast-related mTBI and prevalence of specific outcomes in mild-severe TBI resulting from various mechanisms of injury. Likewise, the composition of the comparative groups in the studies were also variable. Despite the observed variability in inclusion criteria and group composition, the participants in the included studies tended to be fairly homogenous: recently-deployed active duty participants with PTSD (57), combat Veterans who served in Operation Iraqi/Enduring Freedom (OIF/OEF) (43), and other military service members experiencing blast-related mTBI (43, 112).

That slightly higher than half of the studies reported the time between injury and study participation/data collection is important because the time immediately after injury is when symptoms tend to be most prominent. For example, in cases of acute mTBI, cognitive difficulties tend to diminish 3 months after injury (153).

Discrepancies were also observed in the reporting of the service branches of the participants in the included studies. Reporting participants service branch is important, not only for research purposes, but for policy and decision-making as well. For example, it is used to guide decision making about budget allocation for medical resources, education of service members and providers, research, and other areas. That the Army was prominently represented in the included studies is congruent with current and historical data from the DVBIC website (dvbic.dcoe.mil) which have shown that, among the major armed service branches, reports of TBI were most prevalent among the Army. In the first quarter of fiscal year 2018, 82% of all TBI reports were traced to the Army. The increase in mTBIs reported in other services, as well as the increase in reports among the female military population, is evidence of the spreading concern associated with the broad spectrum of TBIs and mTBIs in particular. A breakdown of the incidence and prevalence across branches of service was not calculated due to the limitations in the reported data.

It should be noted that, although the majority of studies reported the age of participants, the effect of age on the outcomes after any TBI is controversial. Some evidence suggests that younger individuals exhibit better recovery from TBI in general as compared to older adults. A study by Marquez de la Plata et al. (154) found that 16 to 26 year-olds and 27 to 39 year-olds showed better and faster improvement in functional abilities (e.g., following commands, performing daily activities, and engaging in recreational activities) as compared to individuals over 40 years, suggesting that neuroplasticity plays a role in the recovery process. Other research studies report discrepant findings that young adults are disproportionately affected by blast-related mTBIs. A growing body of literature suggests strong evidence from experimental and human studies that there is an association of an early life blast-related mTBI with late-onset neurodegenerative conditions and neuropathologic findings as a result of dynamic and persistent pathobiological processes and microstructural changes in the brain triggered by the injury (155–160). This will be a critical avenue

for future investigation since such work would enhance our understanding of the long-term effects of blast-related concussion and encourage better management, strategic health service plans, and more effective preventive and therapeutic interventions to improve the quality of life of those serving in military conflicts.

Despite that more than half of the studies reported the sex of participants with blast-related mTBI, our analysis revealed inconsistencies in the representation of male and female study participants to the extent that there were males were disproportionately represented as compared with females. These findings are in line with the demographics of the U.S. military population where females make up ~14% across all services (161). This finding is significant for several reasons: (1) It highlights the need for additional research on mTBI in female military service members (162). (2) Women serving in the U.S. Military tend to be more diverse in their demographics, experiences, and health concerns as compared to women in the civilian population and men serving in the military (36). (3) Understanding sex-based differences in mTBI may have implications for recovery. For example, prior research has shown that, relative to male service members, female service members were more likely to report more post-concussion symptoms following mTBI (163–165) and were more likely to meet the criteria for post-concussional disorder (165, 166). Additional research suggests that, in some cases, females with mTBI are more likely than males with mTBI to report somatosensory and vestibular symptoms (167). Thus, the effects of blast-related mTBI on females is an important area for future investigation especially since changes in DoD policies will mean that more females will have been exposed to combat and therefore blast-related mTBI since 2015 (168).

Blast-related mTBI may be associated with impairments in sensory and neurocognitive functions. Studies included in this review focused on the prevalence of comorbidities and/or heightened deficits in one or more of the participants' faculties. The main comorbidities reported in the included studies were perceptual, neurological, and psychological. This finding is consistent with outcomes reported in prior reviews (151). Studies in this review that focused on the prevalence of comorbidities and/or heightened deficits reported high rates of multiple comorbid conditions including auditory and visual impairments, headaches, mental health conditions, and white matter changes and abnormalities. Taken collectively, the findings of this review agree with outcomes from prior research that found associations between blast-related mTBI and impairments in the sensory and cognitive faculties of military service members and Veterans.

Sensory impairments affect military service members readiness for deployment (169), job performance (170), and quality of life (171). The blast-related mTBI participants in these studies had a 100% report rate for some level of hearing disturbance immediately following the blast and symptoms persisted upwards of 6 months post-deployment (87, 88, 114, 117, 138). This finding is consistent with hearing loss being the most commonly compensated complaint among U.S. Veterans Administration beneficiaries (172). Although

each study reported a need for further, more extensive research into blast-related mTBIs impact on vision, the consensus was, without considering other mitigating factors, visual impairments improve over time. Thus, although visual impairments may be a measure of blast-related mTBI recovery and could be useful in the rehabilitation process, blast mechanism does not seem to be predictive of visual difficulties. Some researchers have raised concerns about the lack of ICD-10 codes for specific visual and auditory deficits associated with TBI (173).

Another commonly reported outcome in the included studies was post-traumatic and/or comorbid headaches. As mentioned, four of the included studies focused specifically on headaches and three others reported headaches as an ancillary outcome. One study reported that, among a cohort of 96 active duty service members with mTBI, the most common type of headache was "continuous type with migraine features" ($n = 31$, 18.7%) and the least common was "headaches not otherwise classifiable" ($n = 5$, 3.0%) (93). Frequent headaches are associated with an increased need for medical care (174) and a diminished quality of life (175). However, it should be noted that there was no evidence that blast-related injuries increased the likelihood of headaches (151). Interestingly, sleep was found to have the biggest impact on reduction and recovery of the headaches (17, 121, 122, 174).

Among the included studies that leveraged imaging, the most commonly reported neurological abnormalities were white matter irregularities, cerebellar damage, thalamic network architectural differences, metabolic activation, diffuse axonal injury (DAI), and sensorimotor impairment (68, 93, 94, 107–109, 119, 120, 127, 133). Studies compared imaging outcomes from injured and non-injured participants on a range of abilities including: pain perception (123), cognition (41, 45), personality (57), and symptoms of PTSD (130). Outcomes from these studies can be used to develop better preventive devices and to develop targeted treatments.

Due to the nature and conditions in which the injury occurred (e.g., co-occurring battle wounds, conditions that are a product of injuries to the brain, and experiences surrounding the injury), comorbid conditions are common in military service members with blast-related mTBIs. Research is ongoing and more data is needed to distinguish the contributions of pure blast overpressure and blunt trauma in blast-related TBI. The most commonly reported comorbid and pre-existing conditions associated with blast-related mTBI were mental health conditions, including PTSD, depression, anxiety, sleep disorders, attention disorders, and cognitive disorders (44, 55, 62, 65, 77, 78, 92, 103, 115, 124, 134, 135, 176, 177).

U.S. Veterans Administration beneficiaries with mTBI are likely to have comorbid conditions which can drive up the cost of care (178). To explore and provide recommendations that address blast-related mTBI among U.S. Veterans Administration beneficiaries and services members is beyond the scope of this study; however, recommendations by others included providing greater opportunities for rehabilitation and training services to help injured service members transition to a productive civilian life (179). Future studies could provide additional insight into this topic. Of particular note, future efforts should aim to consistently report the Veteran status of participants. The term

“Veteran” was inconsistently used across studies included in this review thus limiting the comparison of outcomes among active U.S. military service member and inactive Veterans.

While the bulk of studies selected for this review focused on diagnostics, treatment, and technology, few addressed the significant financial impact of brain injuries resulting from blast exposures. A recent study by Dismuke-Greer et al. (180) found that outpatient treatment costs for veterans with blast-related mTBI was significantly higher (\$6,480; 95% CI, \$5,842–\$7,187) than outpatient treatment costs for veterans with non-blast-related mTBI (\$4,901; 95% CI, \$4,392–\$5,468) (180). From an economic perspective, the cost of treating all TBI severities is significant. While estimates vary greatly and are severely limited, the 2008 estimates (using 2007 U.S. dollars) revealed costs per case for 1 year following TBI to be ranging between \$27,259 and \$32,759 for mTBI and up to \$408,519 for moderate and severe TBI with the acute hospital care costs ranging from \$15,144 to \$21,246 for mTBI (181). These cost estimates do not factor in the cost of prevention, protection, pre- and post-deployment screening, or other current and emerging costs associated with mental health conditions. As mentioned previously, TBI in general is often accompanied by other comorbidities such as PTSD that itself is costly to treat. For example, in 2008 the RAND Corporation estimated that baseline cost to treat PTSD alone for 50,000 E-5s (e.g., Army Sergeant) was \$204,691,652 (including lives lost to suicide) and \$119,829,381 (excluding lives lost to suicide) (181). In the same report, they estimated that the total cost to treat deployment-related TBI was between \$554–\$854 million dollars and that 47–57% of the total cost is due to productivity loss (181).

In addition to clinical treatment cost and productivity loss, consideration must be given to the cost to fund research studies to further knowledge of TBI. For example, in 2018 the U.S. government appropriated \$125 million to support the Department of Defense Psychological Health/Traumatic Brain Injury Research Program (CDMRP). The important point is that personal and societal cost of treating all forms of TBI is significant. For comparison, the average cost per year per case of multiple sclerosis is estimated at \$69,000 (Society¹) including productivity loss whereas the cost of cardiovascular disease per year per case is estimated at \$18,953 (182, 183). Using data from 16 European Union states, researchers calculated 374,636 years of life lost due to TBI-related deaths (184).

Limitations

Confounding the limitations inherent in the studies themselves, this review was limited in that raw data were not available from all included studies. Studies reviewed did not conform to one approach for confirming participant's TBI diagnoses. More specifically, the documentation of mechanisms was primarily identified through self-report methods. Therefore, this analysis may include misdiagnosed and miscategorized instances of blast-related mTBI, as reported in the included studies, as well as underreporting of mTBI. The exclusion of portions of demographic data in the studies reviewed to include branch

of service could have created bias. With limited data available to characterize the populations from all studies there is a possibility for overlapping populations to be included in this review. Additional studies are warranted to examine the military occupational specialty (MOS) to allow an analysis of the rates of blast-related mTBI among sub-populations with blast-related mTBI. Accumulative effects should also be addressed in future studies.

Since 2006 there have been several changes to DoD policies related to the broad spectrum of TBI to include changes in the DoD definition of mTBI. Resulting education and training on the new definition may have impacted the reported diagnoses in studies of individuals diagnosed before and after the definition changed.

The most important limiting factors hampering research and clinical care of blast-related mTBI are determining physiological from pathological changes: lack of a dose response curve defining exposure to primary blast to injury (185), and the current inability to distinguish the contributions of the secondary to quinary effects from the primary blast, in the human.

Our systematic review focused on U.S. military service members who experienced blast-related mTBI. Unlike other forms of TBI injury (186, 187), no shift or epidemiological transition of this population has been witnessed over the years, making these participants distinct from civilians affected by TBI. While it should be noted that studies have investigated blast-related injuries in civilian samples (188, 189), the fact that the studies under review are limited to primarily military samples may limit the generalizability and clinical applicability of the findings for civilian populations.

Outlook: Implications for Practice and Research

One implication of the findings of this study pertaining to health care practice and research is related to the standardization of diagnostics and reporting of those diagnoses. First, poor or a lack of documentation (e.g., diagnosis and TBI disability severity rating) impedes service members ability to receive care (190). Second, while all studies entailed some sort of clinical assessment, imaging, records, and/or formal interviews with medical specialists as the major diagnostic means, the tools leveraged to accomplish the diagnoses were highly variable from study-to-study which limited comparison across studies. Applying minimal data management standards for epidemiological studies of blast injury consistent with Bieler et al. would address this issue and facilitate use of a broader range of datasets for longitudinal studies (7).

A related implication of the current study is the need for greater specificity in the diagnostic process. Details about the injuring event, including the proximity of the injured person to the blast and the amount of force experienced (151), could facilitate not only a more precise definition of “blast exposure,” but clinical and medical personnel's ability to assess the extent of the injury. One way to accomplish this would be to focus research and development efforts on outfitting service members' helmets with more robust sensors that are capable of recording

¹ *Financial Burdens for People with MS, their Families, and Society.*

force (191). At the same time, there is also a need for greater understanding of outcomes resulting from acute, chronic, and cumulative blast exposures.

Another implication of the findings of this study, particularly with regard to the prevalence findings, is that health care workers should be informed about the issues and challenges that are unique to military service members so that they can provide appropriate treatment (192). This study also reinforces that service members should be using up-to-date protective headgear because it may reduce mortality and severity of TBI (193). It is interesting to note that, even as the state of art of defense weaponry evolves, there remain significant risks to both the target and operator (194). For example, so-called “non-lethal” weapons (e.g., acoustic weapons, laser weapons), can result in TBI-related injuries (195). Thus, it is imperative that service members are equipped to deal with the advancing state of military weaponry and the shifting conditions in which they are encountered and follow the prescribe usage of both weapon systems and protective/preventative equipment.

Furthermore, the military or combat setting is not the only setting for blast-related mTBI. The importance of these findings is increasingly important to civilians because of the frequency of blast-related accidents and incidents as well as use of explosive devices in terrorist attacks.

AUTHOR CONTRIBUTIONS

HP and SM developed and executed the protocol and search strategy, completed the title and abstract reviews as well as

extracted, and the full texts. HA served as a third reviewer in the case of discrepancies during title, abstract, and full text reviews. AW, CM, JH, KT, MC, AH, and HP extracted data from included articles and assisted in drafting the narrative. NR, JN, and PS validated the extracted data and revised the narrative. PS built the tables. HP, SM, TD, FK, and SH revised the final narrative. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fneur.2020.559318/full#supplementary-material>

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