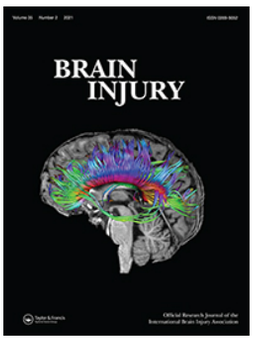

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Factors Increasing Risk of Suicide after Traumatic Brain Injury: A State-of-the-Science Review of Military and Civilian Studies

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ABSTRACT

Primary Objective: Survey TBI literature to identify evidence of risk for post-injury suicide.
Literature Selection: Search terms ((traumatic brain injury OR TBI) AND (suicidality OR suicidal behaviour OR suicidal ideation)) entered in PubMed, OVID Medline, PsychInfo, and Web of Science for papers published in print 01/01/1997 to 06/30/2019.
Analysis of Literature: Authors screened abstracts, excluding duplicates and articles not meeting inclusion/exclusion criteria. Full papers were reviewed to make final exclusions. Data were extracted from 40 papers included co- and premorbid disorders, demographics, injury-related and psychological factors.
Results: Persons with TBI have a higher risk for suicide than the general population. Reviewed articles reported comorbid depression and/or PTSD as risk factors for post-TBI suicide. Co- or premorbid substance misuse, sex, and sleep disturbance moderate risk. Quality of the literature was limited by sample size, the predominance of male participants, and inconsistency in reporting of findings.
Conclusions: Comorbid depression and PTSD are significant post-TBI risk factors for suicide. Several variables combine to moderate or mediate TBI's connection with suicide. Civilian and military clinician cross-talk and consistent reporting of results from reproducible studies of post-TBI suicide risk factors could improve prevention and treatment efforts in veterans and civilians.

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Traumatic brain injury; depression; suicidal ideation; suicidal behaviour

Introduction

Despite media, health services agency and provider attention, suicide remains a leading (10th highest) cause of death in the general population of adults in the United States (US), and the risk is increasing (1). In addition to their multiple challenges, people with traumatic brain injury (TBI) are at three to four times higher risk for death by suicide than uninjured persons, even after concussion (2–5). Fazel found this three-fold increase in risk present as much as five years after injury (6). Harrison-Felix et al. reported similar results in a four-decade study (7). This is clearly a persistent problem highlighting that TBI, a chronic health disorder (8), is in and of itself a foundational risk for suicidal ideation and suicidal behaviour over the lifespan (3,4,9–18). TBI investigators repeatedly link this population to the risk of multiple psychiatric disorders, including depression and suicidal behaviours. All are recommending increased mental health and rehabilitation clinician and provider attention to risk factors and their moderators to improve suicide awareness, prevention, and effective treatment development focused on persons with TBI (10–19).

Comorbid and premorbid psychological disorders, especially depression, have been identified as risk factors for suicide, both in non-injured Americans and those with TBI (1–4). However, given the heterogeneity of cognitive and neurobehavioural symptom profiles and recovery trajectories of persons with TBI, predictive importance of the history of psychiatric disorders may be different as compared to non-injured persons and moderate their influence (19). There are, furthermore, recent research initiatives and priorities that underscore a need to improve knowledge and understanding of these complexities. First, the Precision Medicine initiative has focussed on improving the individualized characterization of patient needs and targeting treatments specifically to meet these needs (20). Second, recent guidance from NIH to treat sex as a biological variable in all phases of research has resulted in important discoveries of sex-based differences for men and women in response to and recovery from TBI (21). Given the well-recognized greater risk for depression among women as opposed to men, these findings urged a more focused study of potential sex-based risk factors for post-TBI depression and suicide risk (22). Third, recent study and characterization of TBI as a chronic disorder (23) emphasizes the need for ongoing attention to depression and other common TBI comorbidities throughout the life span. Finally, failure of multiple TBI treatment trials has increased investigator recognition of and need to delve deeper into reasons for the heterogeneity of TBI profiles

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Table 1. Study inclusions and exclusions.

Inclusions	Exclusions
Published between 01/01/1997 and 06/30/2019	Published before 01/01/1997 or after 06/30/2019
TBI	Mixed brain injury or neurological conditions
Participants ≥ 16 years old	Participants less than 16 years old
Articles in English	Pediatric studies
Descriptive study	Case studies
Only neurological condition is TBI	Reviews
Human participants	Editorials, letters
Sample size ≥15	Meeting proceedings or abstracts
	Book chapters/books
	Commentaries
	Animal studies
	Sample size < 15
	Off Topic, i.e., medications, trials, Not TBI
	White papers
	Outside of date range
	Foreign language
	Prevalence

and outcomes and design studies with careful controls of potential confounders (24,25). In summary, the recent US epidemic of suicide after TBI, even in persons with a concussion or mild TBI (5,12,13,26), tells us it is critical to identify the complexity of variables contributing to suicidal ideation and behaviour in this population such that focused attempts toward improving preventive interventions can be initiated. The objective of this review was to survey the literature to identify evidence of factors increasing the risk of suicide after TBI, with a target audience of mental health and rehabilitation providers.

Materials and methods

Search terms and databases were chosen as the best potential paths for answering the research question: What evidence is there of factors that increase suicide risk after TBI? The search terms of ((traumatic brain injury OR TBI) AND (suicidal behaviour OR suicidality or suicidal ideation)) were entered into PubMed, OVID Medline, Psychinfo, Google Scholar, and Web of Science. In 2018, the term "suicidality' was deemed an unacceptable term by the Center for Disease Control (CDC) in 2019 because it refers simultaneously to suicidal thoughts and behaviours, vastly different descriptors that need separate attention (27). We report and discuss our findings using CDC uniform definitions for suicide terminology (4,27) in this review. These definitions include the terms "Suicidal ideation" (SI)", "Suicide attempts (SA)", and "Suicidal Behavior (SB)". Suicidal ideation (SI) is defined as thinking about, considering, or planning suicide. Suicide attempts/Non-fatal suicidal self-directed violence (SA) is defined as a non-fatal, self-directed, potentially injurious behaviour with an intent to die as a result of the behaviour; it may or may not result in injury. Suicidal behaviour (SB) can include both suicide attempt/non-fatal suicidal self-directed violence as well as death by suicide/fatal suicidal self-directed violence (4,27). However, in the interest of obtaining information from papers using the term "suicidality" published prior to the creation of the CDC uniform definitions, we included this term in our search.

After first hits and removal of duplicates, abstracts were divided among seven reviewer dyads according to the database searched. Independent reviewer dyads were utilized throughout the screening and data extraction processes to reduce bias. The review process occurred in two stages. First, each individual within the dyads independently reviewed the same assigned abstracts against the study inclusion/exclusion criteria. Inclusion and exclusion criteria are presented in Table 1.

Once each reviewer in each of the dyads completed their separate reviews of their assigned abstracts, they met and compared their included and excluded abstract choices. If they disagreed on any choices the reviewers in each dyad discussed these choices toward resolution. If no agreement could be reached, the reviewers in that dyad asked a separate reviewer to assist them toward resolution. Second, following all dyads' completion of the abstract review, the author group met to tally the final inclusions and exclusions to reach the total number of articles for the full paper screening. Duplicates were once again removed. Full unique papers were reviewed to ensure they met every inclusion criterion and none of the exclusion criteria. Reviewers again discussed and decided upon the final included articles. Data were then extracted from the included articles and analyzed using the data extraction form. The focus of data extraction was TBI population, deployment history if military, the severity of the injury, other brain- or injury-related characteristics, presence or absence of psychological characteristics or constructs like hopelessness, premorbid or comorbid psychological conditions; demographic information including age, sex, ethnicity, marital status; suicide measures used, and study sample characteristics.

Results

Search terms yielded 2,099 initial hits. After removing 839 duplicates, reviewer dyads screened 1,269 abstracts. Dyads excluded 1,147 abstracts using inclusion/exclusion criteria, leaving 113 papers to be the screen for eligibility for full paper inclusion. During the full paper review, 73 were excluded for being duplicates or for not meeting inclusion/exclusion criteria. Forty papers met criteria for inclusion in our review. Figure 1 presents the screening process flow chart, including reasons for exclusions of both abstracts and full papers reviewed.

Study samples

Age. The average age in years of reviewed study participant samples in reviewed papers ranged from 18 to 57.96. Some studies treated age as a categorical variable and some as a continuous variable.

Sex. The percentage of women with TBI enrolled ranged from 0 to 69% in civilian studies and from 0 to 55% in military studies. Four military (26,28–30) and four civilian study authors (10,13,15,31) did not report the percentage of men and women in their TBI samples or subsamples. Civilian investigators reported enrollments of men with TBI ranging from 31% (32) to 86.6% (33); military researchers from 45.8% (34) to 100% men with TBI (35–39). Twenty-three (57.5%) of included papers were reporting findings of studies enrolling

Table 2. Risk factors for Suicidal Ideation (SI), Suicide Attempts (SB), completed suicides after traumatic brain injury, in order of sample size.

1st Author, Year	Population	Sample Size	% TBI	Study design	Objective – to determine or explore	% of Males in TBI sample	Age Mean, (SD)/or Range	Severity	Summary of SI and SB Risk Findings
Brenner, Ignacio, 2011	Veterans using VA facilities	7, 859, 472	.632%	Retrospective data analysis	Rates of completed suicide in TBI	100%	57.96 (16.43)	Concussion, Cranial Fx, Contusion/ ICH	Suicide completion rate higher in TBI, with somewhat larger effects based on concussion/cranial fracture than cerebral contusion/traumatic intracranial hemorrhage
Fralick, 2016	Persons with concussion, Canada	235, 110	100%	Retrospective, longitudinal cohort analysis	Determine long-term risk of suicide associated with weekday vs. weekend concussion	52%	41 (range 18–65+)	Mild	Increased risk of suicide death with concussion, with each successive concussion, and if concussion occurred on weekend vs. weekday
Finley, 2015	US Veterans, OIF/ OEF	211, 652	Not reported as isolated TBI	Retrospective data analysis	Assoc. of PTSD/TBI/Chronic Pain with SB	Not reported as isolated TBI	18–56+	Not reported	TBI did not increase risk of SI or SB beyond effect of PTSD
Teasdale, 2001	Danish civilians, hospitalized 1979–93	145, 530	100%	Retrospective data analysis	Rates of completed suicide in TBI	70.5%	21–60+	126, 114 (87%)	concussions 7650 (5%) Cranial Fx 11, 766 (9%) contusion/ICH
Odds of death by suicide higher in all TBI categories than in general public. Higher risk for females than males but lower for those injured before age 21 or after age 60									
Phillips, 2017	Enlisted US marines with basic training, deployed/not deployed	108, 930	3.63%	Retrospective data analysis	Risk factors for completed suicides	100%	19.82 (1.88)	Not reported	TBI associated with higher suicide completion
Maguen, 2015	US Veterans deployed OIF/ OEF screened and tested positive on hopelessness on suicide scale	45,741 (4.3% endorsed SI and Plan, 1829.64)	9.23%	Retrospective data analysis	Risk for having SI and a Plan	88%	33.9 (8.66)	Not reported	TBI not associated with SI and plan
Collet, 2016	US OIF/OEF veteran VHA users with use of CNS polypharmacy	25,546	33.6%	Retrospective data analysis	Assoc. of CNS polypharmacy and overdose, SB	85.8%	35.91 (9.17)	Not reported	History of TBI alone did not influence use of CNS polypharmacy unless combined with PTSD and MDD, which increased use. Polypharmacy use was independently associated with SB

(*Continued*)

Table 2. (Continued).

1st Author, Year	Population	Sample Size	% TBI	Study design	Objective – to determine or explore	% of Males in TBI sample	Age Mean, (SD)/or Range	Severity	Summary of SI and SB Risk Findings
Anstey, 2004	Persons reporting history of TBI, Australia	7,485	5.7%	Prospective cohort survey study	Compared level of psychiatric symptoms, SA risk, psychologic well-being in persons self-reporting TBI vs. persons with no TBI	20–24, 72.2% 40–44, 67.61% 60–64, 73.9%	3 age groups 20–24, 40–44, 60–64	Not reported	Suicidal ideation higher among youngest and middle-age groups of women with TBI than same-age controls
Silver, 2001	General population in Connecticut	5,034	7.17	Prospective survey study	Identify association between TBI Hx and psychiatric diagnoses, SB	61.9%	18–65+	Not reported	TBI associated with higher rates of suicide attempts
Kesinger, 2016	Persons with Mod to severe TBI	3,575	100%	Retrospective cohort repeated measures	Determine assoc. of extracranial injury (ECI) + TBI and SI or SB	71.4%	24–56+	Moderate and severe	Extracranial injury severity and drug use at time of injury associated with higher likelihood of SI
Vanderploeg, 2015	US National Guard service members	3,098 (1,443 Deployed 1, 655 never deployed)	11.8%	Prospective case-controlled survey study	Explore risk and protective factors, SI	not reported for TBI subsample 88.99% in overall sample	18–65+	Mild	In deployed individuals, deployment-related mild TBI associated with SI
Ahmedani, 2017	Persons who completed suicide within MH system	2,674	6.4%	Retrospective case-controlled study	Explore physical conditions as risk factors for suicide	not reported for TBI subsample,7.5% in overall sample	49.9 (19.0) in overall sample	Not reported	Odds of death by suicide higher in TBI than in the general public
Gradus, 2015	Veterans of OIF/ OEF, Women oversampled	1,921 overall 288 TBI	14.99%	Prospective survey study, random sample from prior veteran roster	Examine TBI and SI relationship with association of PTSD and MDD Regression with path analysis	45.8%	35.82 (9.39)	Not reported	For men VHA users, TBI associated with SI after controlling for depression
Mainio, 2007	Finnish persons who committed suicide	1877	5.5% (20% lesion, 80% concussion)	Retrospective, case-controlled observational study	Explore TBI prevalence among persons who committed suicide, association psychiatric disorders/ TBI severity/suicide	79.1%	Medians = 49 Lesion 29 concussion	19% Mod to severe, 81% mild	In people who committed suicide, those with TBI more likely to have had a psychiatric disorder or alcohol-related disorder
Wisco, 2014	Veterans of OIF/ OEF/OND seeking VA MH services	1650	55.8%	Prospective case-controlled survey study	Associations with Hx TBI, lifetime PTSD, and current SI	not reported for TBI subsample, 50.1% in overall sample	37.49 (9.88)	17.8% mod to severe, 82.2% mild	People with TBI at increased risk for SI, with multiple TBIs increasing that risk
Bethune, 2016	Persons with concussion presenting at ED, Canada	871	100%	Retrospective case-controlled, followed by prospective interviews at 3 and 6 months FU	Determine risk factors for SI after concussion	Not reported	18–60	Mild	After mild TBI, SI associated with speaking English as a second language, being a motor vehicle passenger at injury, and history of depression
Shura, 2019	US Veterans deployed, and nondeployed	835	50%	Prospective observational survey study	Determine risk for SI exploring lifetime TBI history, Psychiatric variables, sleep problems after TBI	80.5%	37.05 (9.98)	Mild to moderate	SI risk factors include poor sleep quality, MDD, PTSD. Multiple TBIs did not increase risk after controlling for these factors.

(*Continued*)

Table 2. (Continued).

1st Author, Year	Population	Sample Size	% TBI	Study design	Objective – to determine or explore	% of Males in TBI sample	Age Mean, (SD)/or Range	Severity	Summary of SI and SB Risk Findings
Mackelprang, 2014	Persons with TBI	559	100%	Prospective cohort survey, repeated measures – at 1, 6, 8, 10, 12 months	Determine if demographic characteristics, preinjury psychiatric Hx, or injury-related factors predicted SI during the first year after TBI	71.6%	42.5 (17.9)	52% Mild, 48% mod and severe	Strongest predictor of SI was first PHQ-8 score after injury. Increased ideation if history of prior suicide attempt, history of bipolar disorder, and less than a high school education.
Gunter, 2013	Persons previously incarcerated	419	22%	Prospective cohort survey study	Identify association with presence of SI and SB	not reported for TBI subsample 70% in overall sample	33.5 (9.6)	Not reported	Compared to a no TBI group, persons with TBI with prior incarceration were at greater risk for both SI and SB
Tsaousides, 2011	Community-dwelling persons with TBI	356	100%	Retrospective secondary analysis of data	Identify rates of SI in adults with TBI and associated variables	52.2%	44.45 (15.2)	Mild 37.6%, Mod-severe 62.4%	SI in persons with TBI associated with meeting criteria for depression, anxiety, or PTSD, lower psychosocial functioning, and preinjury SUD
Oquendo, 2004	Psychiatric inpatients with depression and mTBI	325	34%	Prospective cohort survey study	Identify relationship between mTBI and risk factors for SB during MDD episode	51%	39 (13)	Mild	Individuals with TBI more likely to have attempted suicide. Those with TBI who had attempted had higher aggression, more hostility, and higher likelihood of history of substance abuse
Crocker, 2019	OIF/OEF veterans seeking outpatient services with mTBI	282	100%	Prospective cohort, survey study	Determine whether lifetime mTBI moderates relationships between cognitive functioning and SI/SB	93%	33 (8.41)	mTBI	Greater post-concussive symptoms and worse memory performance associated with SI
Wood, 2010	Outpatients at head injury clinic	179 105 TBI, 74 controls	59%	Prospective case-controlled survey study	Relationship of alexithymia and TBI to SI	65%	37.52, (15.21)	Mild to severe	Worthlessness and alexithymia associated with SI in TBI group
Simpson, 2002	Outpatients with TBI, England	172	100%	Prospective, cohort survey study	Explore links between TBI, pre- and post-injury SB and psychological disturbance, hopelessness, and SUD	86.6%	30.81 (12.09)	.Mild to severe	Hopelessness associated with SI. Post-injury emotional/psychiatric disturbance associated with post-injury SB
Bryan, Clemans, 2013	Deployed military outpatients	161	89%	Prospective cohort survey study	Elucidate cumulative association of multiple lifetime TBIs and suicide risk	93.2%	27.4 (7.1)	mild	Increased incidence of lifetime SI (and in past year) or SB positively associated with number of TBIs. Presence of depression exacerbates this effect.
Bryan, 2013	Deployed military outpatients, Iraq	158	85.4%	Prospective cohort survey study	Identify clinical variables associated with suicidality in military personnel with mTBI while deployed	93.0%	27.86 (7.24)	Mild	SI associated with number of mild TBI symptoms, depression, PTSD, shorter LOC, and insomnia severity.
Breshears, 2010	US veterans (1954–2005) with TBI	154	100%	Retrospective cohort survey study	Determine sensitivity/specificity of Personality Assessment (PAI) Inventory Suicide Potential (SPI) and Suicide Ideation Index (SUI) scores to predict SI/SB 2 years post PAI baseline	96.8%	44.94 (11.08)	Mild to severe	SB history most predictive of occurrence of SB during two years before follow-up. Suicide Potential Index and Suicide Ideation scale incrementally contributed to the prediction of post-Personality Assessment Inventory (PAI) SB above and beyond pre-PAI SB alone

(*Continued*)

Table 2. (Continued).

1st Author, Year	Population	Sample Size	% TBI	Study design	Objective – to determine or explore	% of Males in TBI sample	Age Mean, (SD)/or Range	Severity	Summary of SI and SB Risk Findings
Stanley, 2016	Military personnel and 2 civilian contractors, patients at TBI clinic Iraq for eval/treat, 2009	149	84.6%	Prospective cohort survey study	Determine if relationship between mild TBI and suicide risk is accounted for by anger and MDD	92.6%	27.9 (7.2)	Mild	Increased anger and depression mediated the association between mild TBI and suicide risk
DeBeer, 2017	OIF/OEF veterans	139	46.1%	Retrospective cohort survey study	Determine whether sleep mediates the association between TBI and SI	not reported for TBI subsample, 84.6% in overall sample	38.0 (10.76)	Not reported	Sleep quality mediated relationship between TBI and current SI
Brenner, 2015	Veterans–2010-2014 VHA inpatient, outpatient settings, larger community	133	55.0%	Observational 2 × 2 factorial design	Explore relationship between executive dysfunction (lab-based decision-making, impulsivity, anger expression and concept formation) and SB.	89.0%	52.1 (9.6)	Mod to severe	Individuals with prior SB and moderate/severe TBI did not show evidence of learning on a decision-making task
Palladino, 2017	Veterans who used homeless outreach services 2010–2011	103	100%	Prospective case-controlled survey study	associations between suicide risk and physical, psychological, social, and military characteristics among veterans with TBI	100%	53.73 (7.07)	Not reported other than 82.5% of TBI group reported LOC	High risk for suicide for those with PTSD, who were previously married, having difficulty with memory/problem-solving, and with seizures
Barnes, 2012	Two groups of military personnel or veterans OIF/OEF – PTSD, mTBI + PTSD	92	50%	Prospective cohort survey study	Relationship between PTSD and potential added risk of suicide with mTBI + PTSD	100%	30.3 (8.2)	Mild	No differences in suicide risk between PTSD alone or PTSD and a history of mTBI
Juengst, 2014	Adults with acute, mod to severe TBI	89	83.1%	Prospective repeated measures observational study	Association between tumor necrosis TNF-a and disinhibition and SI/SB after TBI	77.75%	34.63 (15.53)	Mod to severe	Acute CSF TNF-a associated with suicidal endorsement at 12 months
Bryson, 2017	College students	84	50%	Retrospective case-controlled survey study	Association between TBI and SB	31%	19 (SD not reported)	Not reported	TBI associated with increased suicide risk in college students
Brenner, Bethauser 2011	Veterans from archival clin data base who had Hx SB between 10/04 and 2/06	81	30%	Retrospective cohort survey study	Association between SB history and PTSD and/or TBI	83%	48.1 (11.2)	Not reported	TBI did not increase risk of suicide attempt beyond effect of PTSD
Lopez-Larson, 2013	Veterans from VA medical center, community healthy controls	74	80%	Prospective cohort imaging and survey study	Thalamic and anterior thalamic radiations (ATR) in a group of veterans to determine if thalamic abnormalities were associated with increased risk of SB.	100%	36.37 (9.13)	Mild	Veterans with TBI+SB had enlarged thalamic volumes as compared to both TBI-SB and healthy controls

(*Continued*)

Table 2. (Continued).

1st Author, Year	Population	Sample Size	% TBI	Study design	Objective – to determine or explore	% of Males in TBI sample	Age Mean, (SD)/or Range	Severity	Summary of SI and SB Risk Findings
Brickell, 2014	Military service members recovering from OIF/OEF deployment-related mild to severe TBI	52	100%	Prospective repeated measures cohort study	Prospective tracking of neurobehavioural symptoms and QOL over 3 years after TBI	94.2% male	27.8 (6.2)	Mild to severe	A trend toward increased consideration of suicide over time (from 12 to 24 to 36 months post injury) is concerning but variability of reporting over the 3 assessments, small sample size, and wide range of injury severity diminishes confidence in quality of evidence
Homaifar, 2012	Veterans with TBI with or without Hx SB	47	100%	Prospective cohort survey study	Explore relationship between executive dysfunction and SB	94%	51.2 (9.8)	Mild to severe	Only Wisconsin Card Sort Test Perseverative Errors score worse for persons with TBI and SB relative to those with TBI but no SB suggesting poor problem solving
Yurgelun-Todd, 2011	Veterans with TBI, veterans–healthy controls	32	47%	Prospective cohort imaging study (MRI, DTI)	Determine association with the white matter microstructural alterations after TBI, clinical features and SB	100%	34.93 (9.71)	Mild to severe	Reduction in fractional anisotropy in frontal white matter tracts in veterans with mild TBI associated with SB
Simpson, 2011	Adults with severe TBI 1 year post-injury	17	100%	Prospective pilot trial to reduce hopelessness	Evaluate efficacy of a psychological treatment to reduce hopelessness after severe TBI	Not reported	41.75 (12.08)	Mod to severe	Hopelessness significantly associated with SI

Legend, Abbreviations:
ED – Emergency department
Fx – fracture
FU – Follow-Up
Hx – History
LOC – Loss of consciousness
MDD – Major depressive disorder
MH – Mental health
MRI – Magnetic resonance imaging
mTBI – Mild traumatic brain injury
SB (Attempts) – Suicidal behaviour
SD – Standard deviation
SI – Suicidal Ideation
SUD – Substance use disorder
US – United States
VA – Veteran's administration
VHA – Veteran's hospital administration

active duty military or veteran samples. Seventeen (42.5%) of full papers reviewed reported on studies enrolling civilian adults. Sample sizes ranged from 17 (31) to 7,859,472 (36). Table 2 contains study enrollment numbers for included papers.

Study design and methodology

Sixty percent of included papers reported on prospective observational studies, while 40% of the articles reported results of retrospective data analysis studies. Twenty percent of studies enrolling civilians with TBI were retrospective while 80% of military studies were retrospective.

Range of study measures

Multiple measures, mostly self-report, were used in the reviewed studies. The Beck Depression, Suicide Risk Scale, Hopelessness Scales, the Structured Clinical Interview for the Diagnostic and Statistical Manual IV (DSM-IV), or SCID, and medical records review were most commonly used in civilian studies. Military investigators tended to use a wider range and larger numbers of assessment measures as well as the unique use of measures of PTSD. Civilian investigators did not assess participants for PTSD. Some studies reported associations with findings of impairment on neuropsychological testing and increased suicide risk, especially tests of memory, processing speed (40) and executive function (41,42).

Findings of risk factors for post-injury suicide

Comorbid depression

Thirty-two percent of all authors of papers in the review reported comorbid depression as most significant risk factor for suicide after TBI within their enrolled populations (13,14,16,33,34,40,43–49). However, the findings were complex. Additional variables were reported as significant risk factors for suicidal ideation, behaviour and completed suicide following TBI, either singly or in combination with depression. These moderators and mediators of risk are detailed by variable type below, and in the Discussion. Table 2 presents summaries of findings for all reviewed papers.

Comorbid substance use disorder

Approximately 30% of the combined military- and civilian-focused papers reported that comorbid substance use disorder (SUD) was a significant risk factor for suicide, or a moderator of the severity of risk in combination with depression and, for military or veterans, with post-traumatic stress disorder (PTSD) (9,14–16,26,29,33,37,43,47,50,51).

Post-traumatic stress disorder (PTSD)

Forty percent of military authors found that PTSD was a significant suicide risk factor, in combination with comorbid depression, in veterans and active duty military study participants with, or even without TBI (12,14,26,29,37,43,45–47). While no civilian authors reported PTSD as a risk factor, 28% reported anxiety disorder, which is within the same diagnostic family of PTSD, as a risk factor for suicide after TBI (11,15,17,48,49).

Previous suicide attempts

History of previous suicide attempts was reported by 27% of both civilian and military authors to be a prominent risk factor for comorbid post-TBI suicidal behaviour (2,5,10,12,18,37,42,47,52).

Suicidal ideation

Twenty-four percent of civilian and military authors observed that self-reported, frequent suicidal ideation increased likelihood of suicidal behaviour, especially after severe TBI or in combination with PTSD, for active duty military personnel or veterans (10,12–15,31,37,40,42,44,45,51).

Moderators and mediators of results

Despite the above broad results, review findings are complex. Many variables exerted influence on the risk of SI and SB. Factors beyond PTSD and major depression moderated or mediated the prominent effects of those two disorders. For example, as stated above, while TBI increased risk factor for SI and SB in male veterans, PTSD increased risk to a greater degree with this population (12,26,38,46). In another example, while multiple TBIs over time increased risk, two authors found that severity of insomnia mediated the relationship between TBI and SI (45,51). Civilian researchers found that psychological variables mediated risk of SI and SB, including alexithymia (53), worthlessness (31), anger (51), and hopelessness (31,33). Investigators who enrolled the largest numbers of women reported sex and gender as moderators of risk (11,18,34). These moderators and mediators of risk are further detailed below.

Civilian/military study sample differences in injury severity as risk factor for suicide

Participant samples in studies enrolling civilians included persons with mild to severe TBI while participants enrolled in studies of veterans and active duty military personnel had primarily mild TBI. Few authors commented on the effect of injury severity per se on the risk of suicide. Among civilian investigators of suicidal risk after TBI, Teasdale (18) found a greater risk of attempts in persons who sustained contusions or haemorrhages compared to those who had a concussion or cranial fractures. Kesinger et al. (9) found an association between severity of *the extra-cranial* injury and increased suicidal ideation in civilian participants with TBI. In contrast, Breshears et al., in a study analyzing veterans' electronic medical records, observed the greatest risk of SB in those with mild TBI (52). However, other military TBI investigators linked brain-related imaging indicators of at least moderately severe TBI to increased suicidal ideation or behaviour. In a retrospective study, Brenner et al. (42) found that

veterans with cranial fractures, cerebral contusions, or intracranial haemorrhages were more likely to die by suicide. Yurgelin-Todd et al. (35), using diffusion tensor imaging (DTI), observed significant associations between reduced fractional anisotropy (FA) of the left cingulum and left and total genu of veterans with TBI and increased SB. In comparison, Lopez-Larson (39) found enlarged thalamic volumes and increased FA were associated with increased suicide risk for veterans with or without a history of SB. In summary, military TBI investigators found imaging evidence of neurobiologic and frontal-thalamic-limbic dysfunction leading to vulnerability to suicide after TBI. In a sample of civilians with severe TBI, Juengst et al. (54) found tumour necrosis factor-α to be a molecular marker of vulnerability to suicidal behaviour.

Civilian/military differences in sex of participants. Effects of sex and gender on findings

Military studies of TBI and suicide risk were more likely to enroll men only, or very few women. Active duty military or veteran study participant results were often described in terms of percentage of men rather than separate data reports for men and women. This is discouraging given the reported higher risk of suicide for women veterans than female civilians (55,56). Importantly, military studies that did enroll women in sufficient numbers to allow powered comparisons with men found that risk of suicide after TBI for women was significantly more often linked to comorbid depression and not predicted by presence or absence of TBI (45,57). In contrast, compared to women active duty service members or veterans, the risk for male service members or veterans with TBI was more often associated with both comorbid depression and PTSD (58). In terms of likelihood of death by suicide, in comparison with women in the general and civilian US populations, women active duty personnel or veterans have an alarmingly high rate of death by suicide (58,59). It appears that their rate may be higher than both civilian women and men but also higher than men in the military. Civilian as well as military researchers are raising concerns for the adequacy of screening for risk and prevention of suicide in women. One is the finding (26) that women in the military are less likely to report suicidal ideation but more likely to attempt suicide than men. Similarly, civilian researchers such as Oquendo et al. (51), found that TBI was most predictive of suicidal ideation and behaviour in men. Women had a higher rate of fatal suicide attempts, with or without TBI. Further study of these differences is imperative, especially given the ongoing inconsistency of equal enrollment of women in many military and civilian TBI and suicide risk studies.

Civilian/military sex differences in substance use disorder (SUD) as post-TBI risk factor for suicidal ideation and behaviour

Comorbid substance use (SUD) was a significant added risk for depressed men and women after TBI. However, women military personnel or veterans, compared to active duty or veteran men, and older veteran men are more likely to misuse central nervous system (CNS) polypharmacy and opioids (50). Suicide attempts by women in the military were more often associated with overdoses of CNS polypharmacy (51). Active military or veteran men primarily misuse alcohol and other drugs (50)

Additional moderators and mediators of post-TBI risk of suicide

Deployment

Within military participant studies, risk of suicide is linked to being deployed, especially being deployed multiple times (45). However, in one case, not being deployed with an "undesignated" employment assignment and lower rank increased risk of suicide (37). Phillips et al. suggested that some active duty personal in the military may feel depressed about staying behind and may see less value attached to their rank and performance of military duties not occurring in war theaters (37). Brickell et al. (58) found that both non-combat and combat-related TBI increased suicidal risk for US veterans of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF). Women in the military have less chance of being deployed and thus less chance of combat exposure but are at risk for exposure to other service-related stressors in war time such as military sexual trauma (55,57).

Number of TBIs

Fifteen percent of papers (5,14,29,30,40,41,47) found a significant association between the risk of suicide and repeated TBIs, especially three or more (30).

Sociocultural, behavioural, psychological and demographic moderators and mediators of suicide risk

Included papers reported associations between post-injury risk of suicide and being: married (45), divorced or widowed (13), exposed to early childhood or psychological trauma (15,29), of a younger age at the time of injury (11,16), unable to get restorative sleep (10,47,60), socially isolated (13), in pain with headache or other body aches (53), or if self-reporting poor quality of life (17,54). Investigators reported associations between scores on measures of specific psychological constructs or personality type and suicide risk, including hopelessness, anger/aggression, alexithymia and personality disorders (15,29,33,38,45,52, 53).

Discussion

The evidence from our review identifies comorbid depression as a notable risk factor for SI and SB after TBI, especially in combination with comorbid SUD and, for male military or veteran participants, with comorbid PTSD. In fact, several military researchers found that TBI did not appreciably add the risk of suicide beyond the presence of PTSD (12,26,38,46). These findings from very large sample studies underscore the unique risk factor of comorbid PTSD for suicide among military service members/veterans. Differences between military and civilian study findings in our results suggest a need for

investigator as well as clinician cross-talk in those two population study domains for advancing both fields and meeting care needs. However, it is important to see these differences in perspective. While many clinicians have noted similarities in neurological, psychological, behavioural consequences in both blast mTBI and concussion in civilians (61); there are important differences in the mechanisms of injury as well as the military sociocultural influences on coping and the multiple comorbidities so often associated with blast mTBI (60,61). Many veterans are returning to civilian life and facing significant adjustments while dealing with residual effects of their service-connected mTBI and comorbidities (62,63). It is thus critical for civilian mental health and rehabilitation clinicians to be aware of differing mental health needs and risk factors for self-harm of military service personnel and veterans compared to civilians with TBI.

We identified a range of variables, such as demographics and injury-related factors, that moderate or mediate the association between TBI and suicide, such as depression and PTSD. However, we also note additional moderators and mediators of risk including insomnia (28,44), sex (11,18,34,64), underlying physical health and neurologic status (9,10,35,36,39,54), SUD (49,50), and others we report above. Further study of these variables is imperative if we are to reduce the number of suicides in the US, address our national crisis in the rise of suicide, and address the unique mental health needs of veterans returning to civilian communities. Further research will also lead us toward improving prevention of suicide and long-term outcomes for both civilians and veterans or active duty military personnel with TBI.

Our findings highlight disparities for women, especially active duty, or veteran women, in the identification of risk of suicide, prevention of suicide, and in treatment of depression after TBI. Variables underlying post-TBI suicide risk appear to be different for women and men, especially military or veteran women and men. The direction of the differences is unique as it contrasts with most reports of suicide attempts mostly being made by men (31) in studies of post-TBI depression in the civilian population. It is important to further study these differences and address the disparities for women through research with sufficiently powered studies that sex-stratify data. Recent research has contributed to the understanding of factors that may underlie the sex- and gender-based differences in suicidal risk, ideation and behaviour (29,58,59,64–68). In addition to exposure to blast injury and mTBI in war theatres when they are deployed, women experience intimate partner violence and military sexual trauma resulting in TBI more frequently than male service members (64–68). The two kinds of trauma seem to have differing psychological effects. They are also now thought to contribute to in sex and gender differences in rates and symptoms of PTSD as well as in likelihood that PTSD or depression will have a role in increased suicidal ideation or behaviour (56,67,68). Further, a recent study has also identified disparities in depression care for those women in the military who identify as lesbian, bisexual, gay, and transgender, perhaps increasing suicidal risk post-TBI for service women (67). Unfortunately, despite federal guidelines to treat sex as a biological variable in all aspects of research (21), our review uncovers continued investigator inconsistency of enrollment of women or sex-stratification of data. We conclude that *gender* and sex differences in post-TBI suicide risk call for different, tailored prevention and treatment programs initiated much earlier after injury and continued for longer periods of monitoring.

There are several limitations of the literature reviewed as well as review methods. First, there were a number of inconsistencies in the literature that may have resulted in increased bias. For example, data were analyzed with a range of statistical techniques and models. In addition, results of studies were reported using a wide range of statistical terms. Some reported odds ratios, some hazard and some risk ratios, all of which relate to differing aspects of risk. Other authors used correlations, nonparametric analyses, or path analyses. As a result, it is challenging to directly compare findings across studies. In addition, the range of measures used in studies makes it difficult to draw conclusions about some of the psychological constructs reported as significantly associated with increased SI or SB. Sample sizes of reviewed studies also varied widely, with smaller participant numbers reducing confidence in conclusions based on reported findings. The young age range of some of the study participants limits the ability to generalize findings to older individuals with chronic TBI who are depressed and manifest both suicidal ideation and behaviour. Few studies enrolled women in equal numbers to men, or at all, reducing the ability to look at sex differences in risk as well as disparities in identification and access to treatment. With regard to our methods, we only searched four databases and may have missed some papers that contain relevant information as a result. However, we did screen and review over 20 years of articles on the topics of suicide after TBI. The long span of years enhanced our ability to elucidate a number of moderators and mediators of risk of suicide after TBI.

Recent years have seen increases in military service members and veterans returning to civilian life. Many have residual and severe PTSD, TBI, pain and sleep problems, and they seek the care of civilian mental health providers. The information from this review may be helpful in calling provider and clinician attention to the unique aspects of military blast mTBI, encouraging them to seek provider training, and potentially making nonmilitary provider, community-based mental health services more helpful and preventive of self-harm for this population (62,63). A recent comprehensive review of treatment efficacy for military service members and veterans with the depression, PTSD, and suicidal ideation or behaviour reported limited quality of evidence for treatments and need for further well-conducted trials (69)

Summary and recommendations

The results of this review provide evidence that helps us understand the rising tide of suicide that is taking a toll on our civilian and military men and women with TBI. The variables involved and their overall effects on thoughts of or behaviours leading to self-harm or death are complex and not yet well studied. Our findings highlight a critical need for attention to the heightened suicide risk of women

after TBI. Women veterans or active duty military personnel have a higher risk of suicide than civilian women. There is increasing evidence that their depression symptoms and suicide risk factors may be different than those of men with TBI due to their gender-related experiences, particularly of intimate partner violence or military sexual assault. However, despite federal agency research guidelines mandating researchers treat sex as a biological variable in all phases of studies (21), we are still noting inconsistency in enrollment of women or sex-stratification of data in reviewed papers. We are, as a result, failing to address gender-unique, highly important differences with TBI, post-injury depression and post-injury suicide risk for civilian and military women and men.

While previous reviews have focussed on TBI and suicide risk, the current article adds uniquely to the scientific literature. First, the review comprehensively culled information about a range of risk factors for post-TBI SI and SB rather solely on efficacy trials for reducing SI and SB. Having a greater understanding of what factors can increase as well as moderate or mediate risk can inform future interventions. Second, this article reviewed research from both the civilian as well as the military service member/veteran TBI literature. While the mechanisms of injury, as well as the psychosocial and cultural issues related to TBI are different for these two populations, information gained from this review about risk factors for suicidal ideation and suicidal behaviour is unique and important for civilian clinician journal readers to know. It is precisely because of these differences in populations, and the return to the community of so many service members and veterans who seek civilian providers for help with residual mental health and cognitive issues, that the current findings are needed. Third, this review showed that, despite recent guidance for sex stratification of data, many investigators enroll insufficient numbers of women in their studies for exploring differential evidence for risk of SI and SB based on gender and sex.

Prevention and development of targeted treatment for depression and PTSD should be considered at even the earliest phases of recovery from TBI. In particular, screening for variables that potentially exacerbate risk such as suicidal ideation, comorbid PTSD and substance use disorder should be prioritized with early initiation of adequate safety planning. Assessing for risk factors early on could be helpful for the prevention of suicide and lead to interventions for high-risk groups through empirical prescribing of medications or non-pharmacological cognitive behavioural treatments. Continued study of sex-based differences in response to and recovery from TBI will also help tailor interventions toward more adequately meeting the different and specific needs of men and women with post-injury depression and suicidal behaviour.

Disclosure of Interest

The authors report no conflict of interest.

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