Age and Ageing 2022; **51:** 1–12
https://doi.org/10.1093/ageing/afab194
Published electronically 13 October 2021

SYSTEMATIC REVIEW

Traumatic brain injuries among veterans and the risk of incident dementia: A systematic review & meta-analysis

Karen K. Leung[1], Frances M. Carr[2], Matthew J. Russell[3], Suzette Bremault-Phillips[4], Jean A.C. Triscott[1]

[1]Division of Care of the Elderly, Department of Family Medicine, University of Alberta, T6G 2T4
[2]Division of Geriatric Medicine, Department of Medicine, University of Alberta, T6G 2P4
[3]School of Public Policy, University of Calgary, T2P 1H9
[4]Department of Occupational Therapy, Faculty of Rehabilitation Medicine, University of Alberta, T6G 2G4

Address correspondence to: Karen K. Leung, Room 1259 Glenrose Rehabilitation Hospital, 10230 111 Avenue N.W., Edmonton, AB, T5G 0B7. Tel: 1-780-735-8882; Fax: 1-780-735-8846. Email: kkleung@ualberta.ca

Abstract

Background: Traumatic brain injuries (TBI) among military veterans are increasingly recognized as important causes of both short and long-term neuropsychological dysfunction. However, the association between TBI and the development of dementia is controversial. This systematic review and meta-analysis sought to quantify the risks of all-cause dementia including Alzheimer's diseases and related dementias (ADRD), and to explore whether the relationships are influenced by the severity and recurrence of head injuries.
Methods: Database searches of Medline, Embase, Ovid Healthstar, PubMed and PROSPERO were undertaken from inception to December 2020 and supplemented with grey literature searches without language restrictions. Observational cohort studies examining TBI and incident dementia among veterans were analysed using Dersimonian-Laird random-effects models.
Results: Thirteen cohort studies totalling over 7.1 million observations with veterans were included. TBI was associated with an increased risk of all-cause dementia (hazard ratio [HR] = 1.95, 95% confidence interval [CI]: 1.55–2.45), vascular dementia (HR = 2.02, 95% CI: 1.46–2.80), but not Alzheimer's disease (HR = 1.30, 95% CI: 0.88–1.91). Severe and penetrating injuries were associated with a higher risk of all-cause dementia (HR = 3.35, 95% CI: 2.47–4.55) than moderate injuries (HR = 2.82, 95% CI: 1.44–5.52) and mild injuries (HR = 1.91, 95% CI: 1.30–2.80). However, the dose–response relationship was attenuated when additional studies with sufficient data to classify trauma severity were included.
Conclusion: TBI is a significant risk factor for incident all-cause dementia and vascular dementia. These results need to be interpreted cautiously in the presence of significant heterogeneity.

Keywords: older people, veterans, traumatic brain injuries, dementia, meta-analysis, systematic review

Introduction

Compared to the general population, military veterans and active-duty members are at higher risk for adverse outcomes including cardiovascular disease, hospitalizations [1, 2], and mental health conditions such as post-traumatic stress disorder (PTSD) and depression [3, 4]. Traumatic brain injuries (TBI) are increasingly recognized as major health concerns among athletes, older adults, and veterans [5]. While veterans often experience similar injury mechanisms as civilians including motor vehicle accidents (MVAs), sport concussions, and falls [6], they also have more severe TBIs, ranging from penetrating artillery and shrapnel injuries sustained by

World War II [7] and Vietnam War veterans [8] to blast trauma from improvised explosive devices in recent conflicts [9]. These unique circumstances place veterans markedly at risk, and the spectrum of injury severities may aid in understanding the neurological consequences associated with TBI.

Accumulating evidence suggests that TBI cause short and long-term cognitive changes in executive functioning, memory, and processing speed [10]. Whether these neurocognitive symptoms are sufficiently severe enough to cause irreversible impairments in daily functioning to constitute a dementia is controversial [11–13]. Older meta-analyses with predominantly civilians [14, 15] and more recent epidemiological studies [16, 17], including a propensity-matched cohort of over 350,000 veterans [9], have found that TBI increased the risk of dementia. However, other studies have not detected significant associations [18]. These conflicting findings may reflect factors such as recall bias associated with self-reported TBI [18], concurrent psychiatric conditions that cause similar functional impairments [19], and conflation of dementia as synonymous with Alzheimer's disease [20]. In particular, whether TBI predisposes the development of specific dementia subtypes such as Alzheimer's disease, vascular or Lewy body dementia requires exploration [21].

To our knowledge, there has been one rapid review exploring the dementia prevalence among veterans [22]. While the review highlights this issue's magnitude and importance, it is challenging to determine the precise disease-exposure relationship between TBI and dementia in prevalence studies especially in the context of confounding variables such as PTSD and cardiovascular disease, which are also independent predictors of dementia [23]. The primary objective of this systematic review and meta-analysis is to examine the epidemiological risk of incident all-cause dementia among veterans with TBI. The secondary objectives are to explore whether this association is modified by the severity and recurrence of TBI, and whether there are stronger associations between TBI and subtypes of Alzheimer's disease and related dementias (ADRD).

Methods

We conducted a systematic review and meta-analysis using a predetermined protocol (Supplement 1), and in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [24] (Supplement 2). Database searches of MEDLINE, EMBASE, Ovid HealthStar, PubMed and PROSPERO were performed without language restrictions from inception to December 31, 2020 using four search themes developed by the investigators (Supplement 3). Grey literature searches included electronic conference proceedings (Supplement 3) and key websites such as the Long-term Impact of Military-Relevant Brain Injury Consortium—Chronic Effects of Neurotrauma Consortium. Researchers were contacted regarding unpublished cohort studies.

Study selection

Two authors independently performed the initial titles and abstracts screening, and fluent reviewers assessed Chinese and Japanese language abstracts. We retained original studies examining TBI and cognitive changes among *veterans*, broadly defined as personnel who had completed basic training and were discharged from active service. The observed agreement between reviewers was 98.1% ($\kappa = 0.78$), and studies rated discordantly were retained.

The same authors independently completed the full-text review. Studies eligible for inclusion were cohort studies that prospectively examined the exposure of TBI among veterans, had a comparator group of veterans without such injuries, and reported at least one outcome of interest such as the risks of all-cause dementia or ADRD. We excluded case–control studies, cross-sectional studies, qualitative studies, case series, and literature reviews. Where more than one publication described the same cohort (e.g. conference abstract and article), the more comprehensive article was selected. The observed agreement was 95.8% ($\kappa = 0.92$), and one study rated discordantly was resolved through discussion with a third author.

Data extraction and quality assessment

Using a standardized template, we extracted data on the study location, demographics, follow-up duration, and where possible, the period of active military service. The definition of TBI in each study was documented. Where available, we collected information suggestive of a potential dose–response including the injury severity and number of recurrent head injuries. Specifically, among studies that provided the International Classification of Diseases (ICD) codes, we classified the proportion of participants with mild, moderate, or severe injuries using the 2016 surveillance case definitions developed by the US Defense and Veterans Brain Injury Center [25]. Penetrating cranial injuries were classified as severe.

The primary outcomes were the clinical diagnosis of all-cause dementia or ADRD. We reviewed the ICD codes used to formulate the dementia case definitions and noted the presence of other forms of dementia such as prion disease or alcohol-related dementias, which might be attributable to other causes such as environmental exposures [26] or substance use [27]. Secondary outcomes were neuroimaging and neuropsychological batteries that used established cut-off values or scores two standard deviations below normative means [28] as suggestive of dementia. Confounding variables were extracted including cerebrovascular accidents, hypertension, diabetes mellitus as well as psychiatric conditions including PTSD, depression, and substance use.

Indicators of study quality were adapted from the Newcastle-Ottawa Scale for cohort studies [29]. Specifically, risks of selection bias were qualitatively assessed regarding the cohort representativeness, exposure ascertainment, and absence of the outcome at baseline; adjustment for relevant confounding factors were reviewed [29]. Finally,

risks of outcome bias were assessed regarding outcome ascertainment, follow-up duration, and attrition [29]. The most adjusted effect estimates were extracted, although relative risks were hand-calculated where necessary. Authors were contacted for supplemental data when there was insufficient information to determine an appropriate point estimate. If the information was unavailable, the study was excluded from the meta-analysis.

Data synthesis and analysis

Meta-analysis was conducted using Stata IC 16.1 meta-package [30]. Dersimonian-Laird random-effects models were used, which tend to produce more conservative effect estimates in the presence of heterogeneity [31]. Studies mainly reported hazard ratios; relative risks were treated as equivalent to hazard ratios.

In two studies where the hazard ratios were only available by each stratum of injury severity [32] or by ADRD subtypes [16], we selected the largest strata for inclusion in the meta-analysis. Recognizing that this approach would result in lost information [33], we further computed a composite effect estimate using the weighted average of the natural log of each stratum and the study variance after taking into account the between-strata correlation [34]. In addition, one report provided hazard ratios comparing veterans with or without TBI to a reference group of civilians without injuries [35]. To create a single pair-wise comparison of veterans with TBI relative to veterans without, we performed an adjusted indirect meta-analysis [36]. Sensitivity analyses were then conducted to assess the influence of these imputations.

We examined heterogeneity using the τ^2 and I^2 statistics (significance level of $p \leq 0.05$). Stratified analyses and univariate meta-regression were used to explore the potential effects of confounding variables and study quality factors on the heterogeneity metrics. A sensitivity analysis restricted to peer-reviewed publications was performed. To assess for publication bias, we used the Begg's test and visually inspected the funnel plots. Where asymmetry in the funnel plots was observed, we used the 'trim and fill' procedure, which postulates adjusted effect estimates to account for the hypothetical presence of unpublished studies [37].

Results

The search strategy retrieved 487 citations from databases and 745 citations from other sources (Figure 1). After removing duplicates, reviewers excluded 841 citations. Hand searching of bibliographies identified five additional cohort studies, yielding 25 articles for full-text review. Twelve articles were subsequently excluded. In total, 13 articles were included in the systematic review, of which 12 contributed to the meta-analysis of all-cause dementia and five to the meta-analysis of ADRD.

Study characteristics

The study characteristics are presented in Table 1. The cohort sizes ranged from 85 to 4,045,269 totaling over 7.1 million observations, of which approximately 359,000 had sustained at least one TBI. Six cohorts were primary studies with veterans [7, 8, 28, 42] and population studies containing subgroups of veterans [35, 40]. Seven were secondary administrative data analyses of the US Veterans Health Administration records [9, 17, 38, 39, 41] and European conscription databases [16, 32]. Participant wartime experiences ranged from World War II [7] to the Iraq and Afghanistan-era [9, 28]. The follow-up durations were between 30 to 53 years among four studies that examined the dementia incidence from the time of TBI onwards [7, 8, 16, 32]. The remaining studies had shorter follow-up durations of one to 14 years calculated from the study inception date as opposed to the injury date.

Quality indicators are summarized in Table 2. Overall, study quality was rated as moderate to high. One report was an interim federal agency update, and fewer details were available to adjudicate quality [35]. Risks of selection bias were relatively low. Veterans with and without TBI had similar baseline characteristics, which was achieved through propensity score matching, random sampling from large veteran repositories, and selecting controls who were likewise wounded but without TBI to account for combat experiences and hospitalizations. All studies reported the absence of a dementia diagnosis at baseline.

Higher risks of bias were noted regarding unmeasured confounding. While most studies adjusted for demographic variables, less than three-quarters adjusted for cardiovascular disease, depression, and substance use. Only one-quarter examined PTSD and APOEε4 status.

Regarding outcome ascertainment in primary studies, dementia was diagnosed through comprehensive interviews with collateral historians, cognitive testing, and medical examinations in two studies [7, 40], while neuropsychological batteries were used in other studies. Among secondary administrative analyses, clinician diagnoses of dementia made during routine medical care were captured in the health records using ICD codes. Studies employed validated and institution-derived algorithms for ascertaining dementia using ICD codes. To minimize bias, four studies analysed death as a competing risk [9, 17, 38, 41] and imposed time-lag analyses to reduce reverse causation [16, 17, 40, 41].

Risk of all-cause dementia

Among the 12 cohorts that examined all-cause dementia, significant associations were reported except in four smaller cohorts [31, 36, 37, 39]. The pooled hazard ratio (HR) was 1.95 (95% CI: 1.55–2.45), suggesting that TBI were associated with an increased risk of dementia (Figure 2). This result warrants cautious interpretation due to the marked observed heterogeneity ($I^2 = 96.2\%$, $p < 0.01$). Sensitivity analyses restricted to peer reviewed publications and studies that used

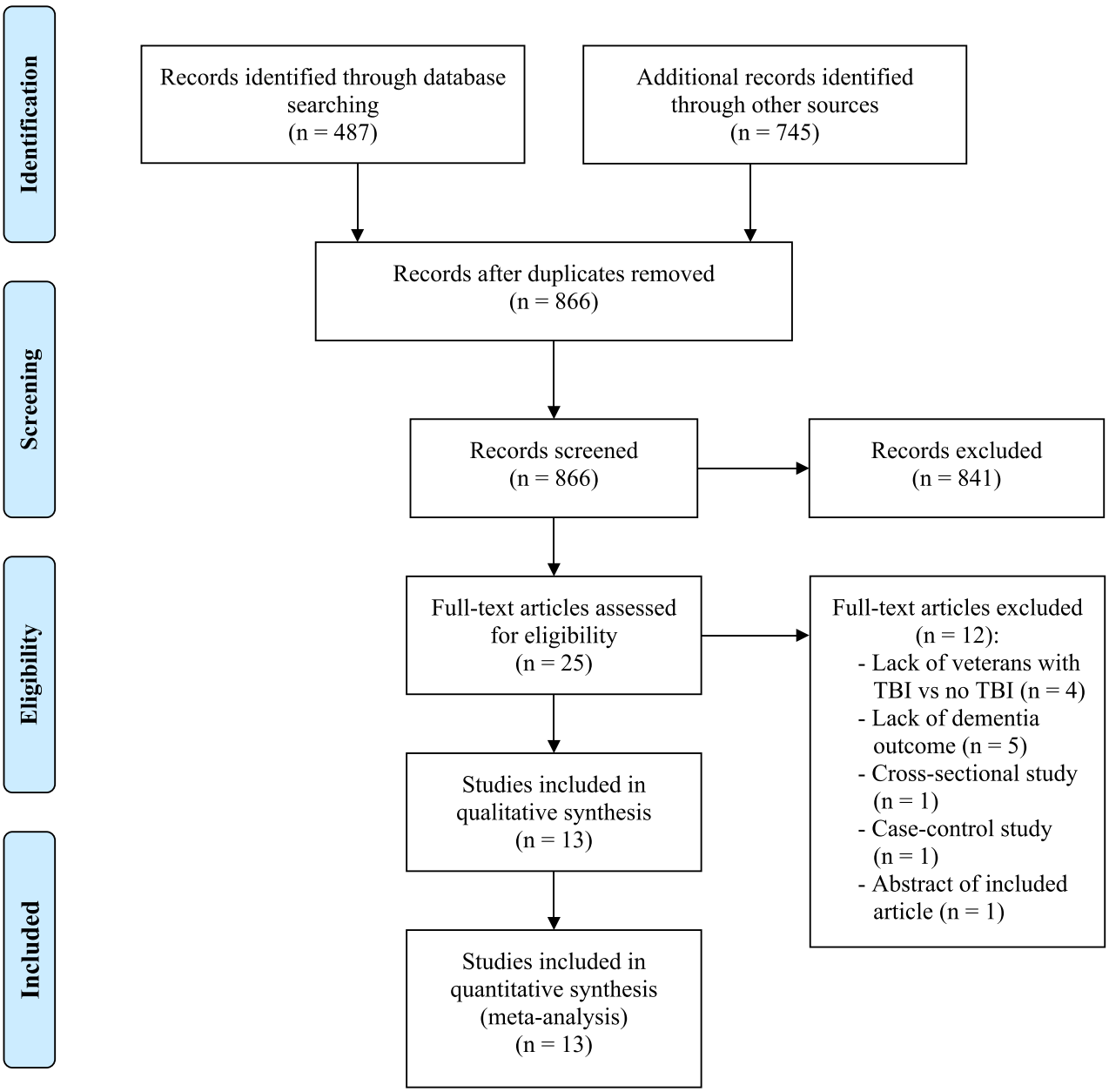

Figure 1. PRISMA flow diagram.

clinician diagnosis (i.e. as opposed to neuropsychological testing) showed minimal influence on the effect estimate (HR = 2.10, 95% CI: 1.69–2.62, $I^2 = 95.9\%$, $p < 0.01$). Likewise, using the imputed effect estimates to correct for stratum selection did not meaningfully alter the effect estimate (HR = 2.00, 95% CI: 1.53–2.62, $I^2 = 96.3\%$, $p < 0.01$).

A possible dose–response relationship was explicitly investigated in four studies [7, 9, 28, 32]. Severe TBI, such as intracranial hemorrhages and penetrating injuries, had the highest risk of all-cause dementia (HR = 3.35, 95% CI: 2.47–4.55). Moderate TBI, such as non-displaced skull fractures with loss of consciousness, also conferred an increased risk (HR = 2.82, 95%CI: 1.44–5.52). Mild TBI, such as concussions with loss of consciousness, had a lower but still significant risk (HR = 1.91, 95% CI: 1.30–2.80). There was less heterogeneity in the pooled effects (severe: $I^2 = 40.3\%$, $p = 0.17$; moderate: $I^2 = 0\%$, $p = 0.84$; and mild: $I^2 = 74.6\%$, $p < 0$ 0.05). Recurrent mild TBI further produced an incremental increase in the risk (HR = 2.25, 95% CI: 1.25–4.02; $I^2 = 79.6\%$, $p < 0.01$). However, this dose–response was attenuated when we included three additional studies with sufficient ICD code-reporting for the reviewers to classify the severity [8, 16, 38]. This yielded hazard ratios of 2.80 for severe and penetrating injuries (95% CI: 2.20–3.57, $I^2 = 89.9\%$, $p < 0.01$) and 1.88 for mild injuries (95% CI: 1.38–2.55, $I^2 = 66.3\%$, $p < 0.05$).

Table 1. Description of studies included in the systematic review and meta-analysis

Author, Year	Source (Cohort Period)	Sample Size (N)		Baseline Age (SD)		Female (%)		Average Follow-up (Yrs)	Risk	Reported Outcomes
		TBI	No-TBI	TBI	No-TBI	TBI	No-TBI			
Barnes, 2014 [38]	US VHA—Age 55+ Cohort (2000–2012)	1,229	187,535	66.8 (8.3)	68.3 (8.0)	3.9	3.5	7.4	HR	Dementia; ADRD Subtype
Barnes, 2018 [9]	US VHA – CTBIE/NPCD Cohort (2001–2014)	178,779	178,779	49.0 (18.4)	50.0 (18.0)	9.2	9.4	4.2	HR	Dementia; Severity
Cheng, 2020 [39]	US VHA – AA & White Cohort (1999–2016)	6,641	4,038,628	65.4 (2.2)[a]	70.4 (6.6)[a]	2.2[b]	–	7.0	HR	Dementia; ADRD Subtype
Dams-O'Connor, 2018 [35]	US Adult Changes in Thought Study (1994)	295[a]	–	74.6 (5.5)[b,c]	–	24.2[b]	–	–	HR	Dementia; ADRD Subtype
Grasset, 2020 [40]	US Health & Retirement Study (1992–2016)	131	676	–	–	–	–	13	HR	Dementia
Kornblith, 2020 [41]	US VHA – Sex & Racial Cohort (2001–2015)	96,178	903,462	68.6 (10.5)	69.8 (9.6)	6.0	4.1	4.3	HR	Dementia
Lippa, 2020 [28]	US DVBIC 15-Year Longitudinal Study (2011)	61	24	38.8 (8.1)	37.0 (7.6)	3.3	4.2	>5	RR	Dementia; Severity
Nordstrom, 2013 [32]	Sweden Conscription Registry (1969)	45,249	766,373	18.4 (0.8)	18.4 (0.8)	0	0	33	HR	Dementia; Severity;
Osler, 2020 [16]	Denmark Conscription Registry (1957–2016)	29,718	628,729	~19 (–)	~19 (–)	0	0	39.3	HR	Dementia
Plassman, 2000 [7]	US World War II Navy & Marines (1944–1997)	548	1,228	73.5[b] (71-75)[d]	72.7[b] (70-74)[d]	0	0	53	HR	Dementia; Severity; ADRD Subtype
Raymont, 2008 [8]	US Vietnam Head Injury Study (1967)	199	55	58.1[c] (2.9)	59.2[c] (3.9)	0	0	~30	RR	Dementia
Weiner, 2017 [42]	US Alzheimer's Disease Neuroimaging Initiative—Vietnam veterans (2012)	22	63	67.9 (4.5)	71.1 (5.9)	0	0	1	RR	ADRD Subtype
Yaffe, 2019 [17]	US VHA – Female Cohort (2004–2015)	488	81,835	69.4 (10.1)	69.2 (9.8)	100	100	4.0	sHR	Dementia

[a]Cheng et al. (2020). Personal communication; [b]Reported pooled values across TBI and no-TBI veterans; [c]Mean age at end of cohort; [d]Interquartile range; = Not reported; AA = African American; ADRD = Alzheimer's Disease and Related Dementias; CTBIE = Comprehensive Traumatic Brain Injury Evaluation; DVBIC = Defense & Veterans Brain Injury Center; HR = Hazard ratio; NPCD = National Patient Care Databases; RR = Hand calculated relative risk; SD = Standard deviation; sHR = subdistribution hazard ratio; US VHA = United States Veterans Health Administration; Yrs = Years.

Risk of Alzheimer's Disease & Related Dementias

The association between TBI and Alzheimer's disease was specifically examined in five cohorts. Most studies used clinician diagnoses. However, the Alzheimer's Disease Neuroimaging Initiative (ADNI) with Vietnam veterans uniquely used ß-amyloid florbetapir positron emission tomography to identify early Alzheimer's disease based on a previously validated cut-point [42]. Overall, the relationship was not significant (HR = 1.30, 95% CI: 0.88–1.91, $I^2 = 54.1\%$, $p = 0.07$). This effect estimate was unchanged when the ADNI cohort was excluded in a sensitivity analysis (HR = 1.39, 95% CI: 0.90–2.13, $I^2 = 62.7\%$, $p = 0.05$).

In contrast, significant associations were observed between TBI and other forms of dementia, which consisted primarily of vascular dementia in two cohorts [7, 9] and a composite of vascular, alcohol, and unspecified dementia in another cohort [32]. The pooled hazard ratio for a vascular-predominant dementia was 2.02 (95% CI: 1.46–2.80, $I^2 = 18.1\%$, $p = 0.3$). Only one study [38] reported the relationship between TBI and the development of Lewy body dementia (HR = 4.14, 95% CI: 1.32–13.01). No studies had sufficient cases to examine frontotemporal dementia.

Stratified analyses

To examine the potential drivers of heterogeneity in the association between TBI and all-cause dementia, we performed exploratory stratified analyses (Table 3). Univariate meta-regression suggests that the sample size may have contributed to heterogeneity, with smaller studies tending to show no significant effect compared to larger studies (HR = 2.53, 95% CI: 2.00–3.20, $p < 0.01$). There were trends toward stronger associations observed in the secondary analyses of administrative data (HR = 2.15, 95% CI: 1.68–2.77, $p = 0.05$) and among cohorts with younger veterans (HR = 2.65, 95% CI: 2.08–3.38, $p = 0.02$). Furthermore, studies with higher prevalence of TBI, and those where the TBI occurred during the course of active military duty, reported the strongest effects (HR = 3.44, 95% CI: 3.33–3.57, $p < 0.01$). Self-reported TBI were not associated with dementia (HR = 1.15, 95%CI: 0.79–1.68).

Publication bias

Although the Begg's tests for publication bias were not statistically significant for all-cause dementia ($p = 0.49$), Alzheimer's disease ($p = 0.17$), or vascular-predominant

Table 2. Qualitative description of the Newcastle-Ottawa quality indicators for observational cohort studies

Author (Year)	Baseline Selection Bias				Group Comparability	Outcome Bias		
	Representative Cohort	Selection of Controls	TBI Ascertainment	Outcome Absent	Adjustment for Confounding	Dementia Ascertainment	Adequate Follow-up	Accounted for Attrition
Barnes (2014) [38]	Yes. • US veterans	Yes. • Random sampling of VHA database	Yes. • VHA databases • ICD codes reported • Validated civilian algorithm	Yes. • Excluded those with ICD codes for dementia at baseline	Higher Adjustment. • Education; income; DM; HTN; MI; CVD; PVD; lung disease; CKD; obesity; depression; PTSD; smoking; EtOH & drug	Yes. • VHA databases • ICD codes reported • Validated to maximize specificity	Yes.	Yes. • Censored at study end, dx • Death as competing risk
Barnes (2018) [9]	Yes. • US veterans	Yes. • 2% random sampling of VHA database • Propensity score matching	Yes. • CTBIE & NPCD (VHA) databases • ICD codes reported • Validated institu-tional algorithm	Yes. • Excluded those with ICD codes for dementia at baseline	Higher Adjustment. • Sex; race; education; income; DM; HTN; MI; CVD; PVD; mood; anxiety; PTSD; stress disorder; substance use; smoking; sleep disorder	Yes. • VHA databases. • ICD codes reported • Validated institutional algorithm	Yes.	Yes. • Censored at study end, dx • Death as competing risk
Cheng (2020) [39]	Yes. • US AA and White veterans	Unclear. • Drawn from large veteran repository	Unclear. • VHA databases • ICD codes not reported	Yes. • Excluded those with ICD codes for dementia at baseline	Higher Adjustment. • Age; sex; race; income; marital status; location; AF; anemia; arthritis; lung disease; cancer; CKD; mood; DM; CHF; HTN; lipid; MI; CVD	Yes. • VHA databases • ICD codes reported • ICD code $\geq$ twice for Dx of dementia	Yes.	Yes. • Censored at death, last medical visit
Dams-O'Connor (2018) [35]	Yes. • National representa-tive study	Unclear.	Unclear. • Self-reported TBI with loss of consciousness	Yes. • Excluded base-line dementia with cognitive screening	Less Adjustment. • Age; gender; race; height; education; APOEε4	Unclear. • Cognitive screening test and medical exams • Consensus conference	Unclear.	Unclear.
Grasset (2020) [40]	Yes. • National representa-tive study	Yes. • Probability sampling of US households	Yes. • Self-reported TBI with loss of consciousness	Yes. • Excluded base-line dementia with algorithm, cognitive test, informant Hx	Higher Adjustment. • Age; gender; race; education; marital status; depression; DM; HTN; MI; CVD; lung disease; arthritis, cancer; smoking	Yes. • Validated model of demographics, cogni-tive test, informant Hx • Maximized accuracy	Yes. • Analyzed with 8-year lag	Yes. • Censored at study end, death • Accounted for follow-up loss
Kornblith (2020) [41]	Yes. • US female, AA, White and Hispanic veterans	Yes. • 2% random sampling of VHA database	Yes. • VHA databases • ICD codes reported • Validated institu-tional algorithm	Yes. • Excluded those with ICD codes for dementia at baseline	Higher Adjustment. • Sex; race; education; income; medical visits, DM; HTN; MI; CVD; mood; chronic pain; PTSD; substance use; smoking	Yes. • VHA databases • ICD codes reported • Validated institutional algorithm	Yes. • Analyzed with 1-year lag	Yes. • Censored at study end, dx • Death as competing risk
Lippa (2020) [28]	Yes. • US Veterans	Yes • Veterans hospitalized for non-TBI injuries	Yes. • Medical records, imaging, interview, • Independent adjudication	Yes. • Used baseline neuropsycho-logical testing	Unadjusted Hand Calculation.[a] • Examined differences in sex; race; education; time since injury; recurrent TBI	Yes. • Neuropsychological testing • 2 SD below adjusted norms	Yes.	Unclear.

(*Continued*)

Table 2. Continued

Author (Year)	Baseline Selection Bias				Group Comparability	Outcome Bias		
	Representative Cohort	Selection of Controls	TBI Ascertainment	Outcome Absent	Adjustment for Confounding	Dementia Ascertainment	Adequate Follow-up	Accounted for Attrition
Lippa (2020) [28]	Yes. • US Veterans	Yes • Veterans hospitalized for non-TBI injuries	Yes. • Medical records, imaging, interview, • Independent adjudication	Yes. • Used baseline neuropsycho-logical testing	Unadjusted Hand Calculation.[a] • Examined differences in sex; race; education; time since injury; recurrent TBI	Yes. • Neuropsychological testing • 2 SD below adjusted norms	Yes.	Unclear.
Nordstrom (2013) [32]	Yes. • Sweden population conscription cohort	Yes. • Drawn from large patient repository • Propensity score matching	Yes. • National patient registry • ICD codes reported • Validation strategy not reported	Yes. • Excluded those with ICD codes for dementia at baseline	Higher Adjustment. • Age; height; weight; strength; education; cognition; income; CVD; blood pressure; depression; drug use; family history of dementia & TBI	Yes. • National patient registry • ICD codes reported • Used validated al-gorithm for dementia	Yes.	Yes. • Censored at emigration, death, study end
Osler (2020) [16]	Yes. • Denmark population conscription cohort	Yes. • Drawn from large patient repository	Yes. • National patient registry • ICD codes reported • Validation strategy not reported	Yes. • Excluded those with ICD codes for dementia at baseline	Lower Adjustment. • Education; cognition; EtOH use; depression; fractures	Yes. • National patient & prescription registry • ICD codes reported • Used validated al-gorithm for dementia	Yes. • Analyzed with 2-year lag	Yes. • Censored at emigration, death
Plassman (2000) [7]	Yes. • US injured WWII veterans	Yes. • Veterans injured or hospitalized for non-TBI	Yes. • WWII-era military records • Used validated scale for rating severity	Yes. • Used baseline telephone interviews, informant Hx neuropsycho-logical testing	Lower Adjustment. • Age; education; APOEε4; Secondary analyses with EtOH use; Smoking; Family Hx of dementia.	Yes. • Telephone interviews, informant Hx, neuro-psychological testing • Sensitivity/specificity • Blinded, independent consensus conference	Yes.	Yes. • Participants similar to refusers
Raymont (2008) [8]	Yes. • US Vietnam War veterans	Yes. • Uninjured Vietnam veterans	Yes. • Vietnam-era military registry of veterans with TBI	Yes. • Used baseline neuropsycho-logical testing	Unadjusted Hand Calculation.[a] • Regression of age; education; pre-injury intelligence; brain volume; laterality; family Hx; EtOH; genetics (APOEε4)	Yes. • Neuropsychological testing & MMSE, genetics, imaging	Yes.	Unclear. • Unclear if those lost to follow-up differed
Weiner (2017) [42]	Yes. • US Vietnam War veterans	Yes. • Vietnam vet-erans connect-ed to non-TBI services	Yes. • VHA databases • Interview and self-reported TBI	Yes. • Used baseline neuropsycho-logical testing and interviews	Unadjusted Hand Calculation.[a] • Regression of age; education; APOEε4	Yes. • Neuropsychological testing & MMSE, genetics, imaging • PET scan for amyloid	No. • Initial follow-up study	Yes. • Accounted for refusers
Yaffe (2018) [17]	Yes. • US female veterans	Yes. • Drawn from large veteran repository	Yes. • VHA databases • ICD codes reported ($\geq$ Twice for dx) • Validated institu-tional algorithm	Yes. • Excluded those with ICD codes for dementia at baseline	Higher Adjustment. • Age; race; education; income; DM; HTN; MI; CVA; EtOH use; depression; PTSD; smoking; follow-up visits.	Yes. • VHA databases • ICD codes reported • Validated institutional algorithm	Yes. • Analyzed with 2-year lag	Yes. • Censored at last medical visit • Death as competing risk

AA = African American; AF = Atrial fibrillation; CHF = Congestive heart failure; CKD = Chronic kidney disease; CTBIE = Comprehensive Traumatic Brain Injury Evaluation; CVD = Cerebrovascular disease; DM = Diabetes mellitus; Dx = diagnosis; EtOH = Alcohol use; Hx = History; HTN = Hypertension; MI = Myocardial infarction; NPCD = National Patient Care Databases; PTSD = Posttraumatic stress disorder; PVD = Peripheral vascular disease; PET = Positron emission tomography; VHA = Veterans Health Administration. [a]Unadjusted hand calculations used in meta-analysis but original studies did examine confounding.

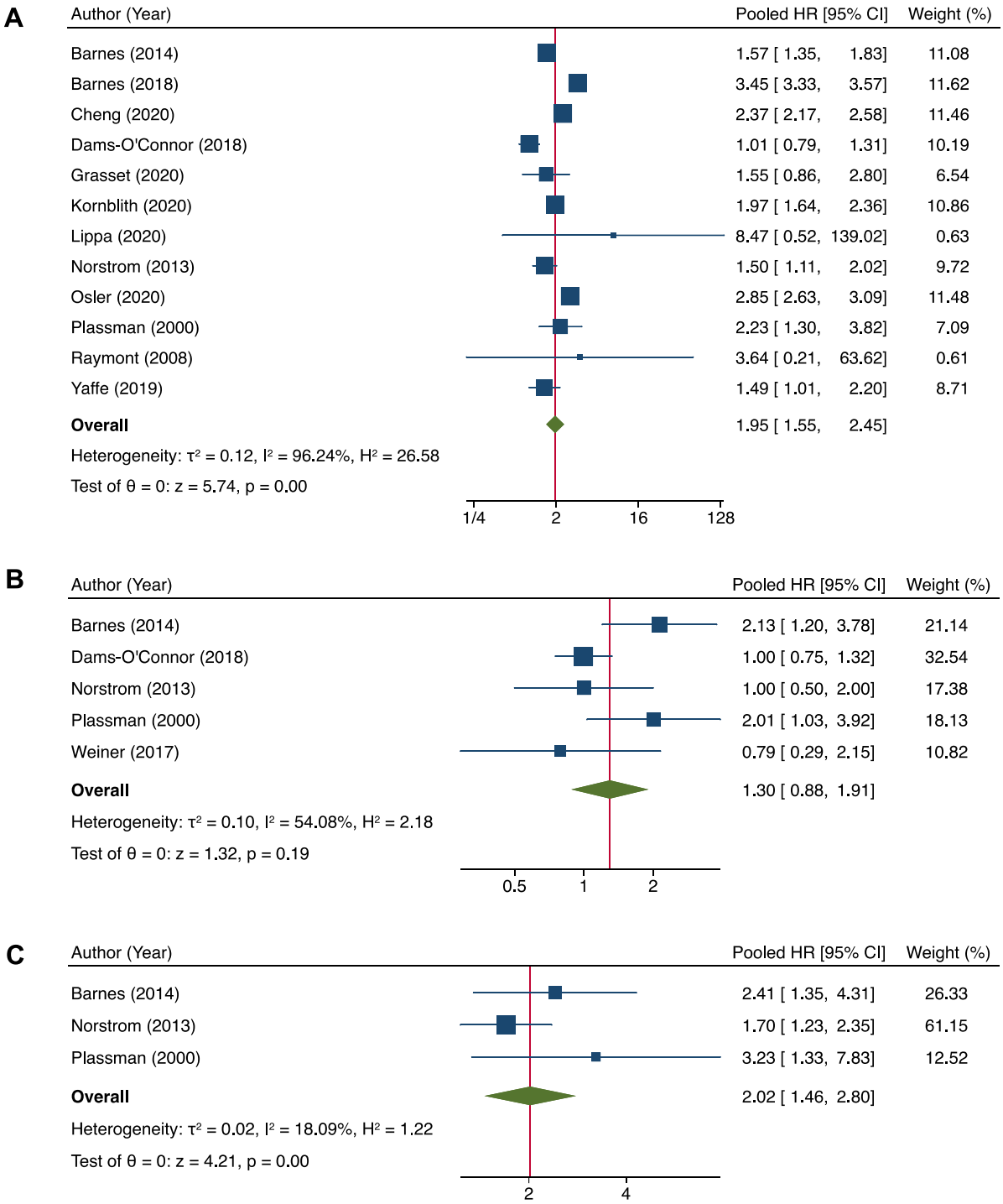

Figure 2. Forest plots of the association between TBI and dementia outcomes.

dementia ($p = 0.12$), there was some asymmetry on visual inspection of the funnel plots for the association with all-cause and vascular dementia (Supplement 4). The trim-and-fill procedure yielded more conservative pooled effect estimates for all-cause dementia (HR = 1.93, 95% CI: 1.54–2.43, $p < 0.01$) and vascular dementia (HR = 1.70, 95% CI: 2.40–3.00, $p < 0.01$). No change was observed in the estimate for Alzheimer's disease.

Discussion

The timely assessment and rehabilitation of major head traumas, including the physical and psychiatric sequelae, are increasingly recognized as the standard of care for active-duty personnel and veterans [43, 44]. Previously considered catastrophic injuries, TBI survivorship has improved significantly over the last four decades, highlighting the need to better understand the long-term consequences of these

Table 3. Stratified analysis of the pooled point estimates for all-cause dementia

Indicator	Studies	Pooled HR (95% CI)	Heterogeneity	
			I^2 (%)	Meta-Regression (*p*)
Sample Size				
< 1,000	4	1.27 (0.81–2.00)	31.9	< 0.01
< 200,000	3	1.60 (1.39–1.83)	0	
≥ 200,000	5	2.40 (1.92–3.01)	96.7	
Data Sources				
Primary Veterans Cohorts	3	2.37 (1.41–3.99)	0	0.05
Veteran Subgroups Nested in Cohorts	2	1.15 (0.79–1.68)	40.3	
Secondary Administrative Data	7	2.12 (1.68–2.69)	97.4	
Administrative Data Sources				
Veterans Affairs (US)	5	2.11 (1.51–2.93)	98.2	0.99
Conscription Databases (Europe)	2	2.10 (1.12–3.94)	93.9	
Mean Age				
< 65 Years	5	2.65 (2.08–3.38)	91.2	0.02
≥ 65 Years	7	1.69 (1.32–2.17)	89.1	
Sample Prevalence of TBI				
< 1%	3	1.81 (1.29–2.55)	91.8	< 0.01
< 20%	4	1.98 (1.42–2.77)	89.9	
≥ 20%	4	3.44 (3.33–3.57)	0	
Not Reported	1	1.01 (0.79–1.31)	–	
TBI Ascertainment				
Self-Report	2	1.15 (0.79–1.68)	40.3	< 0.01
Medical Records (TBI during Active Duty)	4	3.44 (3.33–3.57)	0	
Medical Records (TBI at Any Time)	6	1.96 (1.58–2.43)	92.4	
Adjustment for Confounding				
Moderate (< 7 Factors)	5	2.09 (1.03–4.24)	93.2	0.96
High (≥ 7 Factors)	7	1.95 (1.45–2.62)	97.2	
Dementia Incidence among Veterans without TBI				
< 1%	3	2.85 (2.63–3.10)	0	0.68
< 5%	2	3.02 (2.04–4.48)	60.3	
≥ 5%	3	1.70 (1.43–2.03)	50.5	
Not Reported	4	1.55 (0.96–2.51)	93.4	
Specific Adjusted Covariates				
Cardio-cerebrovascular	7	2.07 (1.52–2.82)	94.3	–
Depression/Anxiety	8	2.19 (1.74–2.77)	96.5	
PTSD	4	2.02 (1.23–3.32)	97.9	
Alcohol/Substance Use	8	2.10 (1.61–2.73)	96.1	
APOEε4	3	1.52 (0.74–3.10)	72.9	
Atypical Conditions Included in Dementia Definition				
Alcohol/Drug-Related	2	1.93 (1.24–3.01)	88.0	–
CJD/Huntington's/HIV	1	2.85 (2.63–3.10)	–	
Excluding Atypical Dementias	9	1.87 (1.23–2.84)	96.5	

injuries including neurocognitive dysfunction and decline [5]. In this systematic review of 13 longitudinal cohort studies with over 7.1 million observations, we found that TBI almost doubled the risk of developing all-cause dementia among veterans. Our analysis further suggested a dose-dependent relationship, where severe and penetrating TBIs were associated with triple the dementia risk. Recurrent, mild TBIs also conferred an elevated—albeit smaller—risk. While only a subset of the studies examined the relationship with ADRD, we nonetheless observed an increased risk for vascular dementia but not Alzheimer's disease.

Although non-randomized studies preclude causal inferences, TBI appears to be a significant risk factor for dementia using Hill's criteria, specifically on the basis of the strength, consistency, dose-dependency, and temporal relationship between the exposure and outcome in longitudinal studies [45]. Regarding biological plausibility [45], the development of persistent cognitive deficits as the direct result of moderate to severe TBI is generally accepted [46]. For instance, penetrating trauma results in the immediate necrosis of astrocytes, neurons, and oligodendrocytes [47], and is frequently accompanied by a hemorrhagic penumbra with loss of functional cerebrovascular perfusion, which induces ischemia and further apoptosis of nearby tissues [48]. Even moderate TBI due to blast injuries can cause vasospasm and cerebral edema, which contributes to intracranial hypertension and disruption of blood brain barrier, leading to secondary cytotoxic and anoxic injuries [48]. Thus, cerebrovascular damage may potentially mediate the increased risk of neurological disability and vascular dementia that we observed [49, 50].

Consistent with more recent research, we did not detect a significant association with Alzheimer's disease [18]. Early seminal work had postulated a link to Alzheimer's [51, 52], as post-mortem studies of patients who had died within weeks of severe TBI due to falls and MVAs had markedly increased deposition of β-amyloid and its precursor proteins around damaged axons and dystrophic dendrites, particularly among those over age sixty [51]. Although no relationship was observed in the current analysis, cautious interpretation is warranted. First, the diagnosis of Alzheimer's disease was primarily clinical rather than histopathological. Only five studies examined Alzheimer's disease as an outcome, and incident cases were rare in the studies, which raises the possibility that this meta-analysis was underpowered [53]. Finally, the median age of veterans with TBI was 66.8 years, which is just when the incidence of Alzheimer's disease starts to rise [54]. Longer follow-up periods may be needed in order to detect sufficient cases.

Overall, our findings are comparable to earlier meta-analyses with mainly civilians [14, 15], which reported relative risks of approximately 1.63 [15]. Slightly larger effect estimates were observed in our analysis, which might reflect differences in populations. Veterans face distinct hazards in the combat theatre, such as blast injuries from improvised explosive devices in modern conflicts [19]. Indeed, our stratified analyses found that veterans who sustained TBIs during military service had higher risks of all-cause dementia, and these injuries tended to be more severe than those self-reported or incurred outside of active duty. Veterans also have higher rates of comorbidities including cardiovascular disease, strokes, depression, and PTSD [23], which are independent risk factors for dementia. Thus, there are likely synergistic interactions between TBI and these major risk factors that increase the vulnerability of veterans to cognitive impairment.

Strengths and limitations

Strengths of this systematic review include using a predetermined protocol, contacting researchers regarding unpublished studies, and conducting comprehensive searches without language restrictions. We adopted relatively narrow inclusion criteria and included only longitudinal studies to reduce the risk of reverse causality, which may have affected previous reviews [18, 54, 55]. Sensitivity analyses were completed to explore the effects of our analytic decisions.

This review also has limitations. First, the majority of studies were conducted in the US, which may limit generalizability to other countries [44]. Second, the largest datasets were the US Veterans Health Administration records. Although several studies used random sampling, we acknowledge that certain cohorts were drawn from overlapping years, which could have resulted in duplicate observations leading to bias and over-precision in the point estimates. We completed post-hoc analyses using the least-overlapping cohorts based on the observation periods, age, and proportion of female and racial groups; no substantive difference was observed (results not shown).

Third, administrative data provide rich, real-world clinical information on comorbidities and health outcomes [55]. Nonetheless, administrative data cannot elucidate more nuanced information such as the pre-injury neuropsychological profiles of military personnel compared to the decremental changes in the cognitive and functional assessments observed during clinical encounters, which are essential to establishing the diagnosis of dementia, and whether delirium and psychiatric disorders that mimic dementia were appropriately ruled out, which could have contributed to diagnostic error and misclassification bias [56]. Fourth, chronic traumatic encephalopathy and TBI-associated major neurocognitive disorder (NCD), the latter described in the Diagnostic and Statistical Manual for Mental Disorders 5th Edition (DSM-5), were not explicitly examined [57]. Evidence suggests that even after the initial neurological recovery period, TBI can cause substantial, persistent cognitive and functional impairments [57]. Potentially, TBI-associated NCD rather than neurodegenerative diseases such as Alzheimer's may be driving the increased risk of all-cause dementia that we observed among younger veterans in our exploratory stratified analyses. Improved harmonization of ICD codes with DSM-5 diagnoses will enhance the epidemiological investigations of these relationships.

Fifth, significant heterogeneity remained despite stratified analyses, suggesting the presence of residual confounding. We further observed a slight attenuation of the dementia risk when the studies that had sufficient ICD codes for classifying severity were included, which underscores the importance of transparent reporting of ICD codes and case definitions in administrative data [58].

Future directions

This systematic review identified an increased risk for dementia particularly among veterans with moderate to severe TBI. Randomized trials have demonstrated that early cognitive rehabilitation and promoting adaptive activities of daily living can improve independence at one-year post-injury [59]. To develop effective interventions, a better understanding of the transition from TBI to dementia is needed. Future studies may include triangulating longitudinal neuropsychiatric testing with periodic functional assessments to delineate when a dementia becomes diagnostically evident, particularly among older veterans who face additional challenges associated with aging. Finally, increasing research suggests that untreated depression and PTSD are associated with persistent neuropsychological deficits and functional impairment, even after adjusting for the presence of TBI [60]. A multidisciplinary approach is necessary to address the physical and psychosocial needs of veterans with TBI.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Acknowledgements: The authors thank all of the researchers who provided additional information and data.

Declaration of Conflicts of Interest: None.

Declaration of Sources of Funding: None.

References

1. Agha Z, Lofgren RP, Van Ruiswyk JV, Layde PM. Are patients at Veterans Affairs medical centers sicker?: A comparative analysis of health status and medical resource use. Arch Intern Med 2000; 160: 3252–7.
2. Hoerster KD, Lehavot K, Simpson T, McFall M, Reiber G, Nelson KM. Health and health behavior differences: US Military, veteran, and civilian men. Am J Prev Med 2012; 43: 483–9.
3. Dursa EK, Reinhard MJ, Barth SK, Schneiderman AI. Prevalence of a positive screen for PTSD among OEF/OIF and OEF/OIF-era veterans in a large population-based cohort. J Trauma Stress 2014; 27: 542–9.
4. Hassija CM, Jakupcak M, Maguen S, Shipherd JC. The influence of combat and interpersonal trauma on PTSD, depression, and alcohol misuse in US Gulf War and OEF/OIF women veterans. J Trauma Stress 2012; 25: 216–9.
5. Wilson L, Stewart W, Dams-O'Connor K *et al.* The chronic and evolving neurological consequences of traumatic brain injury. The Lancet Neurology 2017; 16: 813–25.
6. Elder GA, Ehrlich ME, Gandy S. Relationship of traumatic brain injury to chronic mental health problems and dementia in military veterans. Neurosci Lett 2019; 707: 134294.
7. Plassman BL, Havlik RJ, Steffens DC *et al.* Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology 2000; 55: 1158–66.
8. Raymont V, Greathouse A, Reding K, Lipsky R, Salazar A, Grafman J. Demographic, structural and genetic predictors of late cognitive decline after penetrating head injury. Brain 2008; 131: 543–58.
9. Barnes DE, Byers AL, Gardner RC, Seal KH, Boscardin WJ, Yaffe K. Association of mild traumatic brain injury with and without loss of consciousness with dementia in US military veterans. JAMA Neurol 2018; 75: 1055–61.
10. Millis SR, Rosenthal M, Novack TA *et al.* Long-term neuropsychological outcome after traumatic brain injury. J Head Trauma Rehabil 2001; 16: 343–55.
11. Barr WB. Point/Counterpoint—Links between traumatic brain injury and dementia remain poorly defined. Arch Clin Neuropsychol 2020; 35: 128–32.
12. Elder GA. Update on TBI and cognitive impairment in military veterans. Curr Neurol Neurosci Rep 2015; 15: 68.
13. Rosenfeld JV, McFarlane AC, Bragge P, Armonda RA, Grimes JB, Ling GS. Blast-related traumatic brain injury. The Lancet Neurology 2013; 12: 882–93.
14. Huang C, Lin C, Lee Y *et al.* Is traumatic brain injury a risk factor for neurodegeneration? A meta-analysis of population-based studies. BMC Neurol 2018; 18: 184.
15. Li Y, Li Y, Li X *et al.* Head injury as a risk factor for dementia and Alzheimer's disease: a systematic review and meta-analysis of 32 observational studies. PLoS One 2017; 12: e0169650.
16. Osler M, Rozing MP, Eliasen MH, Christensen K, Mortensen EL. Traumatic brain injury and risk of dementia at different levels of cognitive ability and education. Eur J Neurol 2020; 27: 399–405.
17. Yaffe K, Lwi SJ, Hoang TD *et al.* Military-related risk factors in female veterans and risk of dementia. Neurology 2019; 92: e205–11.
18. Sugarman MA, McKee AC, Stein TD *et al.* Failure to detect an association between self-reported traumatic brain injury and Alzheimer's disease neuropathology and dementia. Alzheimers Dement 2019; 15: 686–98.
19. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in US soldiers returning from Iraq. N Engl J Med 2008; 358: 453–63.
20. Schneider ALC, Dams-O'Connor K. Demographic differences in the association of traumatic brain injury with dementia: Race matters. Neurology 2020; 95: 561–2.
21. Gardner RC, Yaffe K. Epidemiology of mild traumatic brain injury and neurodegenerative disease. Mol Cell Neurosci 2015; 66: 75–80.
22. Peterson K, Veazie S, Bourne D, Anderson J. Association between traumatic brain injury and dementia in veterans: a rapid systematic review. J Head Trauma Rehabil 2020; 35: 198–208.
23. Qureshi SU, Kimbrell T, Pyne JM *et al.* Greater Prevalence and Incidence of Dementia in Older Veterans with Posttraumatic Stress Disorder. J Am Geriatr Soc 2010; 58: 1627–33.
24. Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097.
25. DVBIC. Surveillance Case Definitions. https://www.health.mil/Military-Health-Topics/Combat-Support/Armed-Forces-Health-Surveillance-Branch/Epidemiology-and-Analysis/Surveillance-Case-Definitions. 2016.
26. Glatzel M, Stoeck K, Seeger H, Lührs T, Aguzzi A. Human prion diseases: molecular and clinical aspects. Arch Neurol 2005; 62: 545–52.
27. Ridley NJ, Draper B, Withall A. Alcohol-related dementia: an update of the evidence. Alzheimers Res Ther 2013; 5: 3.
28. Lippa SM, French LM, Bell RS, Brickell TA, Lange RT. United States Military Service Members Demonstrate Substantial and Heterogeneous Long-Term Neuropsychological Dysfunction after Moderate, Severe, and Penetrating Traumatic Brain Injury. J Neurotrauma 2020; 37: 608–17.
29. Wells G. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta analysis. http://ohri.ca/programs/clinical_epidemiology.oxford.htm. 2004.
30. Stata Corp L. Stata statistical software: release 16. College Station, Texas: StataCorp LLC, 2019.
31. Laird NM, Mosteller F. Some statistical methods for combining experimental results. Int J Technol Assess Health Care 1990; 6: 5–30.
32. Nordström P, Michaëlsson K, Gustafson Y, Nordström A. Traumatic brain injury and young onset dementia: a nationwide cohort study. Ann Neurol 2014; 75: 374–81.
33. Higgins JPT, Deeks JJ, Altman DG. Chapter 16.5. 4: How to include multiple groups from one study. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.
34. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Introduction to meta-analysis. Chichester, West Sussex, UK: John Wiley & Sons, 2011.

35. Dams-O'Connor K, Crary J, Crane P, Keene K, Larson E, Power M. Late-Life Consequences of TBI and Military Service: A Population-Based Study, 2019. https://apps.dtic.mil/sti/pdfs/AD1095240.pdf.

36. Song F, Altman DG, Glenny AM, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. BMJ 2003; 326: 472.

37. Duval S, Tweedie R. Trim and fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000; 56: 455–63.

38. Barnes DE, Kaup A, Kirby KA, Byers AL, Diaz-Arrastia R, Yaffe K. Traumatic brain injury and risk of dementia in older veterans. Neurology 2014; 83: 312–9.

39. Cheng Y, Ahmed A, Zamrini E, Tsuang DW, Sheriff HM, Zeng-Treitler Q. Alzheimer's Disease and Alzheimer's Disease-Related Dementias in Older African American and White Veterans. J Alzheimers Dis 2020; 75: 311–20.

40. Grasset L, Glymour MM, Yaffe K *et al.* Association of traumatic brain injury with dementia and memory decline in older adults in the United States. Alzheimers Dement 2020.

41. Kornblith E, Peltz CB, Xia F, Plassman B, Novakovic-Apopain T, Yaffe K. Sex, race, and risk of dementia diagnosis after traumatic brain injury among older veterans. Neurology 2020; 95: e1768–75.

42. Weiner MW, Crane PK, Montine TJ, Bennett DA, Veitch DP. Traumatic brain injury may not increase the risk of Alzheimer disease. Neurology 2017; 89: 1923–5.

43. Eapen BC, Allred DB, O'Rourke J, Cifu DX. Rehabilitation of moderate-to-severe traumatic brain injury. In: Seminars in neurology. Semin Neurol 2015; 35: e1–13.

44. Jones C, Harasym J, Miguel-Cruz A, Chisholm S, Smith-Mac Donald L, Brémault-Phillips S. Neurocognitive assessment tools for military personnel with mild traumatic brain injury: Scoping literature review. JMIR Mental Health 2021; 8: e26360.

45. Schunemann H, Hill S, Guyatt G, Akl EA, Ahmed F. The GRADE approach and Bradford Hill's criteria for causation. J Epidemiol Community Health 2011; 65: 392–5.

46. Selassie AW, Zaloshnja E, Langlois JA, Miller T, Jones P, Steiner C. Incidence of long-term disability following traumatic brain injury hospitalization, United States, 2003. J Head Trauma Rehabil 2008; 23: 123–31.

47. Kurland D, Hong C, Aarabi B, Gerzanich V, Simard JM. Hemorrhagic progression of a contusion after traumatic brain injury: a review. J Neurotrauma 2012; 29: 19–31.

48. Jullienne A, Obenaus A, Ichkova A, Savona-Baron C, Pearce WJ, Badaut J. Chronic cerebrovascular dysfunction after traumatic brain injury. J Neurosci Res 2016; 94: 609–22.

49. Griffin AD, Turtzo LC, Parikh GY *et al.* Traumatic microbleeds suggest vascular injury and predict disability in traumatic brain injury. Brain 2019; 142: 3550–64.

50. Román GC, Erkinjuntti T, Wallin A, Pantoni L, Chui HC. Subcortical ischaemic vascular dementia. The Lancet Neurology 2002; 1: 426–36.

51. Roberts GW, Gentleman SM, Lynch A, Murray L, Landon M, Graham DI. Beta amyloid protein deposition in the brain after severe head injury: implications for the pathogenesis of Alzheimer's disease. J Neurol Neurosurg Psychiatry 1994; 57: 419–25.

52. Smith DH, Chen X, Iwata A, Graham DI. Amyloid β accumulation in axons after traumatic brain injury in humans. J Neurosurg 2003; 98: 1072–7.

53. Jia P, Lin L, Kwong JS, Xu C. Many meta-analyses of rare events in the Cochrane Database of Systematic Reviews were underpowered. J Clin Epidemiol 1920; 131: 113–22.

54. Jorm AF, Jolley D. The incidence of dementia: a meta-analysis. Neurology 1998; 51: 728–33.

55. St Germaine-Smith C, Metcalfe A, Pringsheim T *et al.* Recommendations for optimal ICD codes to study neurologic conditions: a systematic review. Neurology 2012; 79: 1049–55.

56. Sachdev PS, Blacker D, Blazer DG *et al.* Classifying neurocognitive disorders: the DSM-5 approach. Nat Rev Neurol 2014; 10: 634.

57. Wortzel HS, Arciniegas DB. The DSM-5 approach to the evaluation of traumatic brain injury and its neuropsychiatric sequelae. Neuro Rehabilitation 2014; 34: 613–23.

58. Carlson KF, Barnes JE, Hagel EM, Taylor BC, Cifu DX, Sayer NA. Sensitivity and specificity of traumatic brain injury diagnosis codes in United States Department of Veterans Affairs administrative data. Brain Inj 2013; 27: 640–50.

59. Vanderploeg RD, Schwab K, Walker WC *et al.* Rehabilitation of traumatic brain injury in active duty military personnel and veterans: Defense and Veterans Brain Injury Center randomized controlled trial of two rehabilitation approaches. Arch Phys Med Rehabil 2008; 89: 2227–38.

60. Vasterling JJ, Brailey K, Proctor SP, Kane R, Heeren T, Franz M. Neuropsychological outcomes of mild traumatic brain injury, post-traumatic stress disorder and depression in Iraq-deployed US Army soldiers. Br J Psychiatry 2012; 201: 186–92.

Received 27 February 2021; editorial decision 3 August 2021