Title

Systematic Review, Meta-Analysis, and Population Attributable Risk of Dementia Associated with Traumatic Brain Injury in Civilians and Veterans.

Journal

Journal of Neurotrauma, 40(7-8)

Authors

Gardner, Raquel
Bahorik, Amber
Kornblith, Erica
et al.

Publication Date

2023-04-01

DOI

10.1089/neu.2022.0041

Peer reviewed

Journal of Neurotrauma
40:620–634 (April 2023)

DOI: 10.1089/neu.2022.0041

Journal of Neurotrauma

REVIEW

Systematic Review, Meta-Analysis, and Population Attributable Risk of Dementia Associated with Traumatic Brain Injury in Civilians and Veterans

Raquel C. Gardner,[1-3,*] Amber Bahorik,[1,4] Erica S. Kornblith,[1,4] Isabel Elaine Allen,[5] Brenda L. Plassman,[6] and Kristine Yaffe[1,2,4,5]

Abstract

Traumatic brain injury (TBI) is an established risk factor for dementia. However, the magnitude of risk is highly variable across studies. Identification of sub-populations at highest risk, with careful consideration of potential sources of bias, is urgently needed to guide public health policy and research into mechanisms and treatments. We conducted a systematic review and meta-analysis of risk of all-cause dementia after all-severity TBI. We assessed for effect of participant age and sex, veteran status, research methods, and region. The search window covered January 1990 to January 2019. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines. Thirty-two studies met inclusion criteria. Data were pooled using random effects models. Population attributable risk (PAR) of dementia due to TBI in the U.S. was calculated by sex and veteran status. Pooled risk ratio (RR) for dementia after TBI was 1.66 (95% confidence interval 1.42-1.93). Younger age, male sex, and studies from Asia were associated with significantly higher risk; veteran status was not. Risk of dementia associated with "head injury/trauma" was not significantly different from that associated with "TBI" diagnosis specifically. PAR of dementia due to TBI among U.S. veterans was twice that of the general U.S. population, largely due to the high prevalence of TBI exposure in the majority male veteran population. This meta-analysis found that TBI is associated with nearly 70% increased risk of dementia. Risk may be highest among younger adults, men, and cohorts in Asia. Efforts to prevent TBI and also to prevent post-TBI dementia are of high importance. Additionally, improved methods for diagnosing and tracking TBI on a public health level, such as national registries, may improve the quality and generalizability of future epidemiological studies investigating the association between TBI and dementia.

Keywords: dementia; systematic review; traumatic brain injury; veterans

Introduction

Traumatic brain injury (TBI) is very common across the life-course and is increasingly recognized as an important risk factor for dementia. Several meta-analyses have investigated this association and nearly all have reported a pooled risk ratio in the range of 1.6-1.9.[1–6] However, there is substantial heterogeneity in the magnitude of reported risk across individual studies with some reporting risk ratios as high as 3 or 4.[7,8] This heterogeneity suggests that there are either sub-groups at especially high

[1]San Francisco Veterans Affairs Medical Center, San Francisco, California, USA.
[2]Department of Neurology, [4]Department of Psychiatry, [5]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California, USA.
[3]Joseph Sagol Neuroscience Center, Sheba Medical Center, Tel Hashomer, Israel.
[6]Department of Neurology, Duke University School of Medicine, Durham, North Carolina, USA.

*Address correspondence to: *Raquel C. Gardner, MD, Sheba Medical Center, Tel Hashomer, Derech Sheba 2, Ramat Gan, Israel 52621 Email:* raquel.gardner@sheba.health.gov.il

risk for post-TBI dementia or methodological sources of bias or both. In order to provide the best evidence to inform public health strategies and guide further research into modifiable or targetable mechanisms underlying the connection between TBI and dementia, a deeper understanding of the major contributors to this heterogeneity—including identification of sub-populations at highest risk—is urgently needed.

Leveraging the large number of recent, high quality, large scale epidemiological studies published across several countries in recent years, we sought to: 1) conduct a meta-analysis of risk of dementia after TBI; 2) investigate the role of several potential contributors to heterogeneous findings across studies including age, sex, geographical location, quality of TBI exposure ascertainment, TBI definition (e.g., TBI vs. head trauma/injury), lag from TBI to dementia diagnosis, quality of dementia ascertainment, dementia definition, military veteran status, study design, and publication year; and 3) estimate population attributable risk of dementia due to TBI in the U.S. with specific attention to comparisons across subgroups of men versus women and civilians versus veterans rather than the absolute PAR value, which can be challenging to generalize due to the many assumptions that must be made.

We hypothesized that several factors would account for much of the heterogeneity across different studies. We specifically hypothesized that risk would be lower for studies using an insensitive TBI exposure ascertainment method due to exposure misclassification, that risk would be lower for studies requiring at least a 1-year lag between TBI and dementia diagnosis due to mitigation of reverse-causation, and that risk would be higher for men and for military veterans due to their propensity towards more severe or more frequent TBIs.[9]

Methods

Literature search

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline. We added articles published before March 2015 based on the previous meta-analysis of risk of all-cause dementia after all-severity TBI by Li and colleagues that covered the period from January 1, 1990 to March 31, 2015.[2] Additional primary articles were identified through a systematic search of manuscripts published in PubMed, Embase, and Web of Science from March 2015 to January 2019. We used a combined text and MeSH heading search strategy including several terms for TBI/brain injury and dementia. The protocol for the meta-analysis was registered on the international prospective register of systematic reviews (Prospero ID CRD42020162106).

Inclusion criteria and study selection

We first applied broad inclusion criteria to select articles for full-text review based on initial title and abstract review by two independent reviewers. Discrepancies were resolved by a third independent reviewer. We selected studies for full-text review if they were original case control or cohort studies published in peer reviewed journals and if they assessed the association between any severity of TBI and any type of clinical diagnosis of dementia. Studies were excluded if they were book chapters, reviews, or conference abstracts.

Articles that met broad inclusion criteria underwent full-text review by two independent reviewers who applied detailed inclusion criteria to determine inclusion in the meta-analysis (RCG, AB). Discrepancies were resolved via discussion with a third reviewer (KY). Detailed inclusion criteria were: 1) study assessed all cause TBI as the exposure (which we defined broadly so as to include the many high quality studies published pre-2010 that universally defined the exposure as ''head injury/trauma'' and not as ''TBI'' specifically); 2) compared participants without TBI to participants with TBI; 3) ascertained TBI using a TBI screen/interview or International Classification of Diseases, Ninth Revision or Tenth Revision, Clinical Modification (ICD-9 or 10-CM) codes; 4) evaluated dementia as the outcome; 5) compared participants without dementia to participants who developed dementia; 6) reported at least age-adjusted relative risk estimates or odds ratios with their corresponding 95% confidence intervals (Cis; or the corresponding author was able to provide an age-adjusted estimate upon request); 7) reported a mean age of at least 40 years during the study; 8) included sufficient TBI-exposed participants (e.g., for small case-control studies, at least five exposed participants in each group); and 9) included a sufficiently generalizable population (e.g., not restricted to a narrow population of participants with a specific, relatively rare, pre-existing condition such as type-1 diabetes or thalassemia).

Data extraction and quality scoring

The following data fields were extracted for each study by a single reviewer and then validated by a second reviewer: publication year, study design (cohort or case-control), region, U.S. military veteran status of cohort, sample size, age, TBI ascertainment method, TBI definition/severity, required lag from TBI to dementia diagnosis, dementia ascertainment method, dementia definition, the maximally-adjusted dementia risk estimate reported, adjustment/matching variables applied to reported risk estimate. When possible, mean age of the entire study cohort was extracted. When this was not available, mean age was calculated based on reported mean or median age of cases, controls, or other reported sub-groups within each study.

Quality scoring was performed by a single reviewer using a modified Newcastle Ottawa Quality Scoring system[10] tailored for case-control or cohort studies

assessing risk of dementia after TBI. While the Prospero protocol originally stated that we would use the QUADAS tool for quality scoring, the QUADAS tool was designed for diagnostic accuracy studies and was deemed less appropriate for the studies in this meta-analysis. For case control studies, the quality scoring system assessed adequacy of the dementia definition, representativeness of the dementia cases, selection of controls, definition of controls, comparability of cases and controls, and quality and comparability of the TBI exposure ascertainment. For cohort studies, the quality scoring system assessed representativeness of the TBI-exposed cohort, selection of the no TBI cohort, ascertainment of the TBI exposure, demonstration that the dementia outcome was not present at the start of the study, comparability of the TBI and no TBI cohorts, and quality of assessment of dementia outcome. Itemized scores for each study are reported in the Supplementary Data.

Statistical analysis

Because prevalence of dementia is low, odds ratios (ORs) were considered an approximation of risk ratios (RRs), per the rare disease assumption.[11,12] Because studies reporting hazard ratios (HRs) used incidence for an overall time period, then HRs were considered equivalent to RRs.[11] Data were pooled using random effects models. Between-study heterogeneity was assessed using the I^2 statistic and Q test. RRs for dementia associated with TBI were calculated with a 95% CI and the individual and pooled RRs were visualized using a forest plot. Publication bias was assessed using a funnel plot with Hedges G[13] and Egger and Begg statistics.[14] All analyses were performed using R version 4.0.2.

Heterogeneity was analyzed using several statistical approaches, sub-group analyses, and meta-regression analyses. See the Supplementary Data for a detailed description of these methods.

We calculated population attributable risk (PAR) of dementia due to TBI in the U.S. among relevant sub-populations, including U.S. veterans versus civilians, using the following formula: $PAF = [P \times (HR - 1)] / [1 + P \times (HR\text{-}1)]$, where P = lifetime prevalence of TBI in the sub-population and HR is the pooled risk estimate in the sub-population. We used the pooled risk estimate, including both cohort and case-control studies, because the pooled risk estimates ultimately were identical for pooled cohort and pooled case-control studies (see the Results section).

For TBI prevalence, we used the U.S. national prevalence of lifetime TBI exposure derived from the Health and Retirement Study (HRS) 2014 TBI module survey, which administered the Ohio State TBI Identification Method (OSU TBI-ID) to a random sub-set of respondents to the 2014 core HRS survey ($n = 1489$ of the 16,642 non-proxy HRS respondents). The OSU TBI-ID is an NINDS TBI Common Data Element[15] and is currently considered a gold standard for self-reported lifetime history of TBI. TBI was defined as any prior history of head injury that resulted in loss of consciousness or peri/post-traumatic amnesia or feeling dazed. Using raking and weight trimming, HRS sampling weights were applied to derive nationally representative prevalence of TBI for the entire community-dwelling older adult population as well as sub-groups identified in the 2000 US Census and 2004 Current Population Survey: males, females, veterans, civilians.[16] Additional background, analysis, and discussion of the unexpectedly lower lifetime prevalence of TBI among U.S. male veterans versus male civilians identified in the Health and Retirement 2014 survey was reported previously.[9] Prevalence of TBI reported in this HRS survey is within the range of estimates reported previously by other large population-based surveys among civilian adults of all ages.[17]

Results

Figure 1 shows the study screening and selection flowchart. The database search generated 1001 original articles. An additional 78 original articles were derived from the reference lists of relevant reviews. After duplicates were removed, 795 articles underwent title and abstract screening, of which, 751 were removed due to not meeting broad inclusion criteria; most either did not assess the relationship between TBI and dementia or were book chapters, reviews, or conference abstracts. A total of 76 studies were retained for full-text review. Three articles met all inclusion criteria except did not report an age-adjusted risk estimate.[18-20] For these studies, authors were contacted via email to request an age-adjusted risk estimate and one author provided an estimate for inclusion in the meta-analysis.[18] A total of 32 studies, reporting a total of 39 risk estimates, ultimately met all inclusion criteria and were included in the meta-analysis (Table 1).[7,8,18,21–49]

Overall, study quality was high (Table 1). Among both case-control and cohort studies, the most common reason for losing points on quality scoring was low quality TBI exposure ascertainment (e.g., TBI ascertainment method different for cases and controls, interviewers not blinded to case/control status, patients with dementia reporting own history of TBI, or very brief TBI screen).

The overall pooled RR for dementia associated with TBI from the 39 risk estimates, representing 7,634,844 individuals was 1.66 (9 5% CI 1.42-1.93; Fig. 2), indicating that TBI was significantly associated with a nearly 70% increased risk of dementia. As expected, there was substantial heterogeneity ($I^2 = 98.7\%$, Q test $p < 0.001$). Several pre-planned statistical approaches were used to investigate sources of heterogeneity and are described in

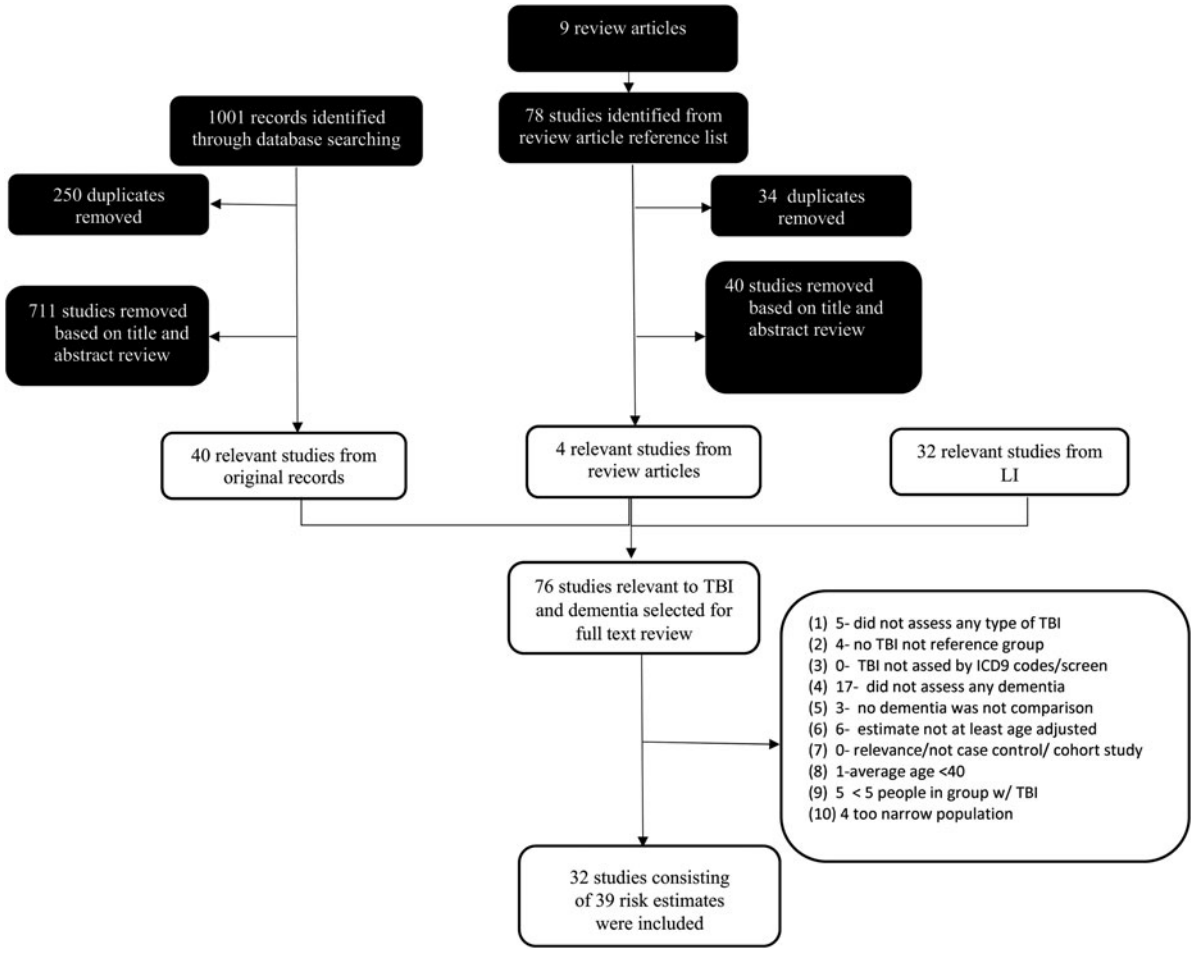

FIG. 1. Study screening and selection flowchart. The search window spanned January 1990 to January 2019 and included searches in PubMed, Embase, and Web of Science databases.

detail in the Supplementary Data. In summary, removal of studies found to be outliers based on statistical approaches did not significantly reduce heterogeneity.

To identify sub-groups at greatest risk for post-TBI dementia, several pre-planned sub-group analyses were conducted using meta-regression as shown in Table 2. Overall, age, sex, region, TBI ascertainment method, lag between TBI and dementia diagnosis, and dementia ascertainment method all contributed to heterogeneity (all $p < 0.07$). Specifically, risk was significantly higher for studies using ICD codes compared with those using a brief screen to identify TBI exposure, risk was higher for studies using ICD codes compared with those using other methods for dementia diagnosis, risk was lower for studies requiring at least a 1-year lag between TBI and dementia diagnosis, risk was lower with higher age, risk was highest in studies from Asia and lowest in studies from North America, and risk was highest in studies with <50% females compared with those with >50% females. While risk for U.S. veterans was slightly higher than others, this difference was not statistically significant. Risk for AD was also not significantly different from unspecified/other dementias.

Visual inspection of the funnel plot (Fig. S2 in the Supplementary Data) showed that the studies were distributed fairly symmetrically around the effect size, suggesting little evidence of publication bias. Egger and Begg's tests for small sample bias were not significant (bias, 0.39; standard error 1.70; $p = 0.81$ and $p = 0.40$, respectively), additionally suggesting little potential for publication bias.

Population attributable risk (PAR) of dementia due to TBI exposure in the U.S. population, including among sub-groups of U.S. veterans, men, and women, is reported in Table 3. Women had the lowest estimated PAR (9% U.S. females; 3.8% U.S. female veterans) while men had the highest estimated PAR (32% U.S. males; 29% U.S. male veterans). Estimated PAR of dementia due to TBI among U.S. veterans was twice that of the general U.S. population. Estimated PAR of dementia due to TBI among U.S. men was four times that of U.S. women.

Table 1. Characteristics of Studies Included in Meta-Analysis

Source	Design	Region	U.S. military veterans?	Total sample size	Mean age	TBI ascertainment method	TBI definition	Dementia ascertainment method	Dementia definition	Quality score (range 0-8)	Risk estimate	Adjustment/ matching variables
Broe and colleagues,[21] 1990	Case control	EU	N	340	78	Brief screen	Head injury with LOC >15 min	NINCDS ADRDA	AD	7	OR: 1.33 (0.46-3.83)	Age, sex
Ferini-Strambi and colleagues,[22] 1990	Case control	EU	N	189	59	Brief screen	Head injury with LOC	clinical diagnosis of probable AD according to published criteria	AD	5	OR: 1.00 (0.32-3.10)	Age, sex, residential area, education, social status
Graves and colleagues,23 1990	Case control	NA	N	260	65	Brief screen	Head injury with LOC or prompting medical care	DSM-III NINCDS ADRDA	AD	5	OR: 3.50 (1.50-8.30)	Age, family history of AD
Van Duijn and colleagues,24 1992	Case control	EU	N	396	57	Brief screen	Head injury	NINCDS ADRDA	AD	7	OR: 1.60 (0.80-3.40)	Age and sex-matched population controls + adjusted for sex, age, family history of dementia, education
Mayeux and colleagues,25 1993	Case control	NA	N	331	78	Brief screen	Head injury with LOC	NINCDS ADRDA	AD	6	OR: 3.70 (1.40-9.70)	Gender, age, years of education, ethnic group, head injury
Canadian Study of Health and Aging,[26] 1994	Case control	NA	N	637	80	Brief screen	Head injury	DSM-III-R NINCDS ADRDA	AD	7	OR: 1.66 (0.97-2.84)	Age, sex, residence in community or institution, and education. controls adjusted for education bias of screening test.
Forster and colleagues,[27] 1995	Case control	EU	N	218	58	Brief screen	Head injury	NINCDS ADRDA	AD	7	OR: 1.20 (0.57-2.56)	Age and sex
O'Meara and colleagues,[28] 1997	Case control	NA	N	691	78	Brief screen	Head injury with LOC	DSM-III-R NINCDS ADRDA	AD	7	OR: 2.10 (1.10-3.80)	Age and sex (matched)
Salib and colleagues,[29] 1997	Case control	EU	N	538	75	Brief screen	Head injury	NINCDS ADRDA; non-AD dementias diagnosed by a single provider (criteria not listed)	dementia	7	OR: 2.46 (1.42-4.10)	Age, sex, time lag between head injury and onset, duration of condition and family history of dementia
Mehta and colleagues,[30] 1999	Cohort	EU	N	6645	69	Brief screen	Head injury with LOC	DSM-III-R NINCDS ADRDA	dementia	7	†RR: 1.00 (0.50-2.00)	Age, education, sex
Guo et a,[7] 2000	Case control	NA	N	521	70	Brief screen	Head injury with LOC prompting medical care	NINCDS ADRDA	AD	7	OR: 4.60 (3.70-5.90)	Age, gender
Plassman and colleagues,[31] 2000	Cohort	NA	Y	1776	73	Medical record	Head injury	TICS-m IQCODE NINCDS ADRDA followed by expert consensus conference	dementia	8	OR: 2.46 (1.43-4.24)	Education, age

(*continued*)

Table 1. (Continued)

Source	Design	Region	U.S. military veterans?	Total sample size	Mean age	TBI ascertainment method	TBI definition	Dementia ascertainment method	Dementia definition	Quality score (range 0-8)	Risk estimate	Adjustment/ matching variables
Lindsay and colleagues,[32] 2002	Case control	NA	N	3745	81	Brief screen	Head injury with and without LOC	NINCDS ADRDA; DSM-III/IV	AD	8	OR: 0.87 (0.56-1.36)	Age, sex, education
Bachman and colleagues,[33] 2003	Case control	NA	N	481	71	Brief screen	Head injury prompting medical care	NINCDS ADRDA	AD	6	OR: 2.40 (1.80-3.10)	Age, sex, race, education, head trauma, alcohol and smoking
Ogunniyi and colleagues,[34] 2006	Cohort	NA	N	470	79	Brief screen	Head injury	NINCDS ADRDA	AD	7	OR: 0.75 (0.24-1.98)	Age, gender
Rippon and colleagues,[35] 2006	Case control	NA	N	1498	68	Brief screen	Head injury with LOC or amnesia	NINCDS ADRDA	AD	6	OR: 1.00 (0.70-1.50)	Apoe4, age, gender, education
Suhanov and colleagues,[36] 2006	Case control	AS	N	520	69	Brief screen	Head injury with LOC	DSM-IV NINCDS ADRDA	AD	7	OR: 1.70 (1.00-2.80)	Age, sex, level of education, and place of birth (matched), + family history of dementia, family history of parkinsonism, and hypertension
Wang and colleagues,[37] 2012	Cohort	AS	N	269550	41	Medical record	ICD-9 codes for any TBI	ICD-9	Dementia	8	HR: 1.68 (1.57-1.80)	Age, sex, index use of healthcare (matched) + stroke, diabetes, hyperlipidemia, hypertension, coronary heart disease, heart disease, heart failure, atrial fibrillation
Lee and colleagues,[38] 2013	Cohort	AS	N	720933	43	Medical record	ICD-9 codes for mild TBI excluding those that were hospitalized	ICD-9	Dementia	8	HR: 3.26 (2.69-3.94)	Age, gender, urbanization level, socioeconomic status, diabetes, hypertension, coronary artery disease, hyperlipidemia, history of alcohol intoxication, history of ischemic stroke, history of intracranial hemorrhage, and Charlson Comorbidity Index score
Abner and colleagues,[18] 2014	Cohort	NA	N	649	73	Brief screen	TBI with LOC	DSM-IV	Dementia	7	OR: 1.69 (0.94-3.02)	Age, APOE, prior cognitive state

(*continued*)

Table 1. (Continued)

Source	Design	Region	U.S. military veterans?	Total sample size	Mean age	TBI ascertainment method	TBI definition	Dementia ascertainment method	Dementia definition	Quality score (range 0-8)	Risk estimate	Adjustment/ matching variables
Gardner and colleagues,[39] 2014	Cohort	NA	N	164661	71	Medical record	ICD-9 codes for any TBI	ICD-9	Dementia	8	HR: 1.26 (1.21-1.32)	Age, sex, race, income quartile, depression, delirium, drug or alcohol use disorders, hypertension, hyperlipidemia, diabetes, coronary artery disease, peripheral vascular disease, cerebrovascular disease, trauma mechanism, health care use, trauma severity
Nordstrom and colleagues,[40] 2014	Cohort	EU	N	801071	52	Medical record	ICD-8, ICD-9, or ICD-10 codes for mild TBI	ICD-8, ICD-9, ICD-10	Dementia	8	HR: 1.5 (1.1-2.0)	Age, place and year of conscription, cognition, alcohol use, weight, height, knee strength, TBI in parents, dementia in parents, income, education, blood pressure, drugs, depression, cardiovascular risk factors
Nordstrom and colleagues,[40] 2014	Cohort	EU	N	772355	52	Medical record	ICD-8, ICD-9, or ICD-1o codes for moderate-severe TBI	ICD-8, ICD-9, ICD-10	D0ementia	8	HR: 2.30 (1.50-3.60)	Age, place and year of conscription, cognition, alcohol use, weight, height, knee strength, TBI in parents, dementia in parents, income, education, blood pressure, drugs, depression, cardiovascular risk factors
Barnes and colleagues,[41] 2014	Cohort	NA	Y	188764	68	Medical record	ICD-9 codes for any TBI	ICD-9	Dementia	8	HR: 1.57 (1.35-1.83)	Demographics, medical, psychiatric

(*continued*)

Table 1. (Continued)

Source	Design	Region	U.S. military veterans?	Total sample size	Mean age	TBI ascertainment method	TBI definition	Dementia ascertainment method	Dementia definition	Quality score (range 0-8)	Risk estimate	Adjustment/ matching variables
Chu and colleagues**0**,[42] 2016	Cohort	AS	N	64655	43	Medical record	ICD-9 codes for any TBI	ICD-9	D0ementia	8	HR: 3.21 (2.65-3.90)	Age and sex (matched), urbanization, monthly income, geographic region, diabetes, chronic renal failure, chronic liver disease, thyroid disease, cardiovascular disease
Crane and colleagues,[43] 2016	Cohort (ACT)	NA	N	4092	80	Brief screen	TBI with LOC ≤1 hour	DSM-IV NINCDS	Dementia	6	HR: 1.03 (0.83-1.27)	Age at study entry, sex, educational level, study cohort
Crane and colleagues,[43] 2016	Cohort (ACT)	NA	N	3716	80	Brief screen	TBI with LOC >1 h	DSM-IV NINCDS	Dementia	6	HR: 1.18 (0.77-1.78)	Age at study entry, sex, educational level, study cohort
Crane and colleagues,[43] 2016	Cohort (ROS+ MAP)	NA	N	2791	80	Brief screen	TBI with LOC ≤1 hour	DSM-IV NINCDS	Dementia	6	HR: 0.87 (0.58-1.29)	Age at study entry, sex, educational level, study cohort
Crane and colleagues,[43] 2016	Cohort (ROS+ MAP)	NA	N	2691	80	Brief screen	TBI with LOC >1 hour	DSM-IV NINCDS	Dementia	6	HR: 0.84 (0.44-1.57)	Age at study entry, sex, educational level, study cohort
Tolppanen and colleagues,[44] 2017	Case control	EU	N	344423	80	Medical record	ICD-9 or ICD-10 codes for any TBI	NINCDS ADRDA DSM-IV	AD	7	OR: 1.23 (1.18-1.29)	Socioeconomic status, substance abuse, stroke, cardiovascular disease, diabetes, hip fracture, pulmonary disease, use of antipsychotics, antidepressants, antiepileptics, and benzos and related drugs
Lin and colleagues,[45] 2017	Cohort	AS	N	49955	40	Medical record	ICD-9 codes for any TBI	ICD-9	Vascular dementia	8	HR: 2.20 (1.49-3.29)	Age-sex-enrollment-date matched + hypertension, diabetes, dyslipidemia, coronary artery disease, congestive heart failure, cerebrovascular disease, malignancy, urbanization level, monthly income

(*continued*)

Table 1. (Continued)

Source	Design	Region	U.S. military veterans?	Total sample size	Mean age	TBI ascertainment method	TBI definition	Dementia ascertainment method	Dementia definition	Quality score (range 0-8)	Risk estimate	Adjustment/ matching variables
Cations and colleagues,[46] 2018	Case control	EU	N	254	64	Brief screen	Mild TBI with LOC	consensus interview	Young-onset dementia	5	OR: 0.65 (0.31-1.38)	Age at interview (matched)
Cations and colleagues,[46] 2018	Case control	EU	N	216	64	Brief screen	Severe TBI with LOC	consensus interview	Young-onset dementia	5	OR: 0.92 (0.35-2.44)	Age at interview (matched)
Fann and colleagues,[47] 2018	Cohort	EU	N	2794852	81	Medical record	ICD-8 or ICD-10 codes for any TBI	ICD-8, ICD-10	Dementia	8	HR: 1.24 (1.21-1.27)	Age, sex, marital status, calendar period, medical and neurological comorbidities, psychiatric comorbidities
Nordstrom and colleagues,[48] 2018	Cohort (primary)	EU	N	491252	59	Medical record	ICD-8, ICD-9, or ICD-10 codes for any TBI	ICD-8, ICD-9 ICD10	Dementia	8	OR: 1.81 (1.75-1.86)	Age, civil status, education, early retirement pension, diagnoses at baseline + (matched by age at birth year and sex)
Nordstrom and colleagues,[48] 2018	Cohort (sibling)	EU	N	93940	48	Medical record	ICD-8, ICD-9, or ICD-10 codes for any TBI	ICD-8, ICD-9, ICD-10	Dementia	8	OR: 1.89 (1.62-2.22)	Age, civil status, education, early retirement pension, and diagnoses at baseline
Nordstrom and colleagues,[48] 2018	Case control	EU	N	404887	80	Medical record	ICD-8, ICD-9, or ICD-10 codes for any TBI	ICD-8, ICD-9, ICD-10	Dementia	8	OR: 1.71 (1.66-1.76)	Age, civil status, early retirement pension, and diagnoses at baseline + (matched by age at birthyear and sex)
Barnes and colleagues,[8] 2018	Cohort	NA	Y	357558	49	Medical record or validated VHA screen	ICD-9 codes for any TBI or validated VHA screen for military TBI	ICD-9	Dementia	8	HR: 3.45 (3.33-3.57)	Sex, race, education, income, diabetes, mi, cerebrovascular disease, mood disorder, anxiety, post-traumatic stress disorder, substance use disorder, tobacco, sleep disorder
Yaffe and colleagues,[49] 2019	Cohort	NA	Y	82323	69	Medical record	ICD-9 codes for any TBI	ICD-9	Dementia	7	HR: 1.49 (1.01-2.20)	Age, race, education, income, diabetes, hypertension, stroke/ transient ischemic attack, alcohol abuse, tobacco use

[†]OR obtained through logistic regression but reported as RR due to low prevalence of the outcome.

TBI, traumatic brain injury; EU, European Union and Australia; N, no; LOC, loss of consciousness; NINCDS ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association expert consensus criteria for dementia ; AD, Alzheimer's dementia; OR, odds ratio; NA, North America; DSM, Diagnostic and Statistical Manual of Mental Disorders; Y, yes; TICS-m, Telephone Interview for Cognitive Status-Modified ; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; AS, Asia; ICD, International Classification of Diseases; HR, hazard ratio; ACT, Adult Changes in Thought study; MAP, Memory and Aging Project; VHA, Veterans Health Administration; RR, relative risk.

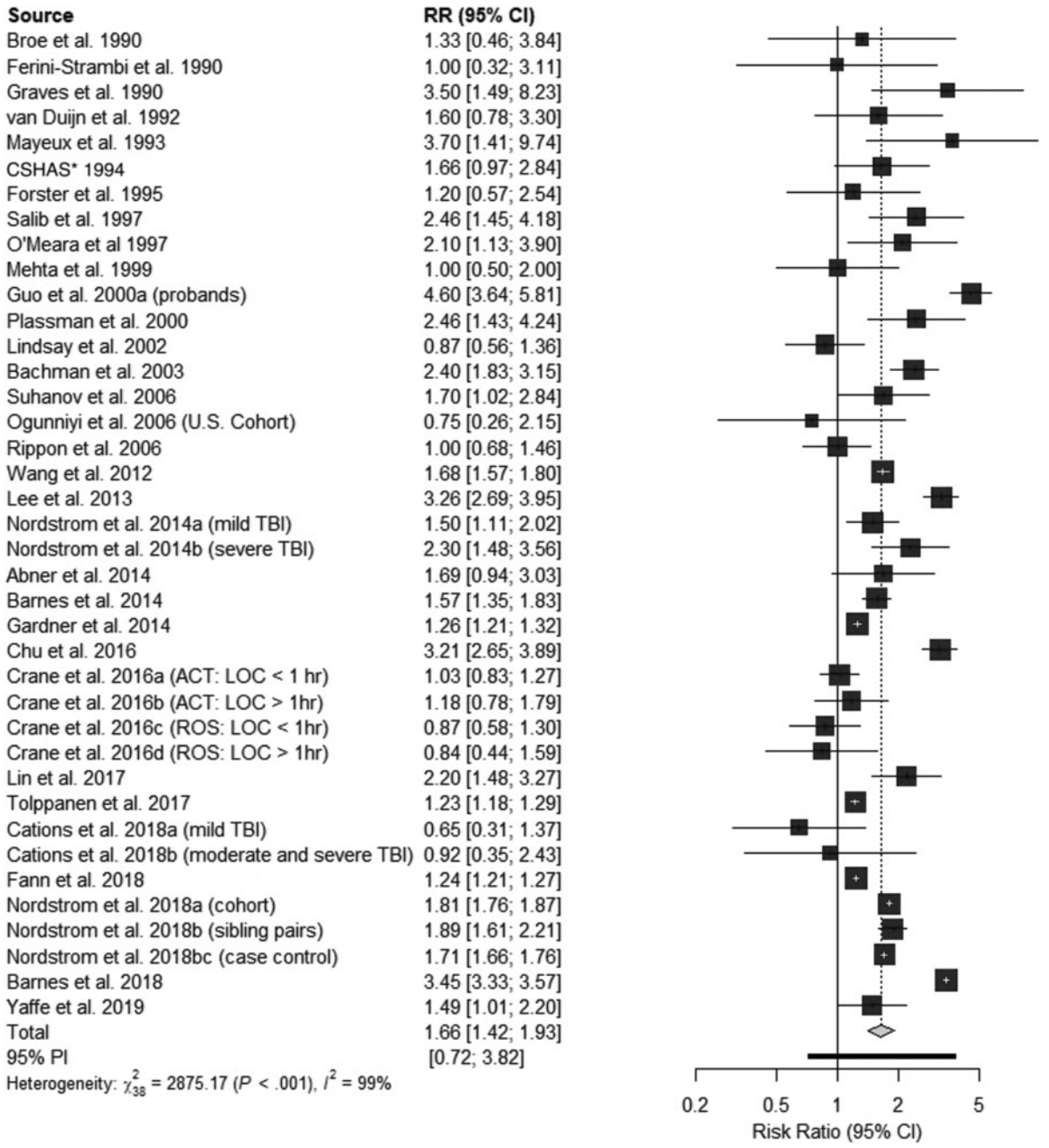

FIG. 2. Pooled risk ratios (RRs) for dementia risk associated with traumatic brain injury (TBI). Studies are listed in chronological order. Individual study RRs are depicted as squares; the pooled RR is depicted as a diamond. CI, confidence interval; *CSHAS, Canadian Study of Health and Aging Study group.

Discussion

This meta-analysis of 39 risk estimates from 32 studies, representing 7,634,844 individuals, identified a 66% increased risk of all-cause dementia associated with all-severity TBI with substantial heterogeneity across studies. Younger age, male sex, studies from Asia, studies that did not require at least a 1-year lag between TBI and dementia diagnosis, and studies that relied on medical records data for TBI or dementia diagnosis were all associated with higher risk. Notably, while the risk estimate of dementia after TBI was slightly higher among U.S. veterans versus non-U.S. veterans, this difference was not statistically significant. Further, the risk estimate for AD after TBI was essentially identical to that for other dementias after TBI. Lastly, PAR of dementia due to TBI was found to be highest for U.S. men (32%) and lowest

Table 2. Sub-Group Risk Estimates

Sub-group	*Categories (n = number of studies)*	*RR (95% CI) or B (95% CI)*	*Contribution to heterogeneity*
Mean age	N/A	-0.02 (-0.01- 0.00)	$p < 0.01$
Age category	Mean age <65 years ($n = 15$)	1.99 (1.58-2.50)	$Q = 3.67$, $p = 0.05$
	Mean age >65 years ($n = 24$)	1.49 (1.25-1.79)	
Sex	< 50% female ($n = 14$)	2.07 (1.61-2.65)	$Q = 5.83$, $p < 0.05$
	> 50% female ($n = 25$)	1.43 (1.22-1.68)	
U.S. veterans	U.S. veterans ($n = 4$)	2.13 (1.42-3.21)	$Q = 1.65$, $p = 0.19$
	All non-veterans ($n = 35$)	1.60 (1.37-1.87)	
U.S. vs. non-U.S.	U.S. ($n = 15$)	1.52 (1.18-1.96)	$Q = 0.76$, $p = 0.38$
	Non-U.S. ($n = 24$)	1.75 (1.46-2.09)	
Region	North America ($n = 19$)	1.63 (1.25-2.13)	$Q = 7.18$, $p < 0.05$
	EU/Australia ($n = 15$)	1.51 (1.29-1.77)	
	Asia ($n = 5$)	2.36 (1.56-3.57)	
TBI type	TBI ($n = 22$)	1.62 (1.35-1.94)	$Q = 0.16$, $p = 0.68$
	Head injury ($n = 17$)	1.73 (1.34-2.23)	
TBI severity	TBI with LOC ($n = 14$)	1.38 (1.02-1.88)	$Q = 2.10$, $p = 0.14$
	All other studies ($n = 25$)	1.79 (1.53-2.08)	
TBI ascertainment	ICD codes ($n = 16$)	1.88 (1.58-2.23)	$Q = 3.34$, $p = 0.06$
	Brief screen ($n = 23$)	1.44 (1.16-1.80)	
Dementia type	AD ($n = 16$)	1.68 (1.30-2.18)	$Q = 0.02$, $p = 0.88$
	Dementia ($n = 23$)	1.64 (1.37-1.97)	
Dementia ascertainment	ICD codes ($n = 14$)	1.92 (1.60-2.30)	$Q = 3.66$, $p = 0.05$
	Other methods ($n = 25$)	1.46 (1.19-1.80)	
Lag between TBI and dementia	At least 1-year lag required ($n = 3$)	1.24 (1.18-1.32)	$Q = 11.90$, $p < 0.001$
	No/unspecified lag ($n = 36$)	1.67 (1.43-1.96)	
Design	Case-control ($n = 18$)	1.66 (1.29-2.12)	$Q = 0.01$, $p = 0.99$
	Cohort ($n = 21$)	1.66 (1.38-1.99)	
Publication year	N/A	-0.01 (-0.02-0.01)	$p = 0.27$

RR, risk ratio; CI, confidence interval; B, beta coefficient; N/A, not applicable; EU, European Union; TBI, traumatic brain injury; LOC, loss of consciousness; ICD, International Classification of Disease; AD, Alzheimer's dementia.

for U.S. veteran women (3.8%). PAR for U.S veterans was higher than that of U.S. civilians overall and slightly lower than that of U.S. men and reflects the majority male sex composition of current U.S. veterans. Overall, these findings confirm that TBI is a significant risk factor for all-cause dementia and that this risk may be greatest for younger adults, men, and possibly for individuals in Asia.

Our findings are consistent with prior meta-analyses on this topic that have reported pooled risk ratios between 1.6-1.9.[1–6] Given the large number of studies published on this topic to date, we were able to thoughtfully refine inclusion and exclusion criteria with the goal of optimizing the quality of studies included in this updated meta-analysis, such as requiring risk estimates to be age adjusted and excluding studies that did not have at least a minimum number of TBI-exposed individuals in each group. This approach is reflected in the fairly high-quality scores assigned to all included studies.

Notably, a recent meta-analysis of 25 studies assessing risk of dementia after TBI reported a similar pooled OR of 1.81.[6] This meta-analysis, however, excluded studies of ''head injury/trauma.'' This resulted in exclusion of most high-quality studies published before 2010, including a landmark study in veterans[31] as well as many studies that defined the exposure as ''head injury/trauma with LOC [loss of consciousness].'' We specifically chose to include studies that defined the exposure as head trauma/injury in our meta-analysis. We hypothesized that the biological difference between ''TBI'' and ''head injury/trauma'' in the epidemiological studies of associated risk of dementia conducted to date – all of which have

Table 3. Population Attributable Risk (PAR) of Dementia due to Traumatic Brain Injury (TBI) in the United States

Population	*Estimated RR*	*TBI Prevalence*	*PAR*	*Estimated total cases of dementia in U.S.*	*Estimated cases of dementia attributable to TBI exposure*
Total U.S. population	1.52	31%	14%	6,200,000	860,696
U.S. males	2.07	43%	32%	2,400,000	756,277
U.S. females	1.43	22%	9%	3,800,000	328,412
U.S. veterans	2.13	35%	28%	767,544	217,530
U.S. male veterans	2.13	36%	29%	738,304	213,493
U.S. female veterans	2.13	3.5%	3.8%	29,240	1112

Estimated risk ratios (RR) are from Table 2; estimates for men and women are based on the pooled estimate of studies including <50% females vs. >50% females, respectively. TBI prevalence is based on weighted estimates from the 2014 Health and Retirement Study TBI module survey and is representative of community-dwelling older adults in the U.S. Estimates of total dementia cases in the U.S. are from the 2021 Alzheimer's Disease Facts and Figures[50] and from an expert consensus projection report published online in 2013 by the Department of Veterans Affairs.[51]

employed either brief self/proxy-reported screens or retrospective medical record analysis—was likely minimal. And indeed, we found that the pooled risk estimate was not significantly different across epidemiological studies that defined the exposure as head injury/trauma (HR 1.73, 95% CI 1.34-2.23) versus TBI specifically (HR 1.62, 95% CI 1.35-1.94; p for contribution to heterogeneity 0.68). Thus, our meta-analysis included 32 studies and was perhaps better powered to study certain sub-groups of interest (e.g., AD, TBI with LOC).

Whether risk of dementia after TBI differs in veterans versus civilians has not been rigorously studied directly. While some have hypothesized that TBI and dementia are more prevalent among veterans,[52] this hypothesis has not been supported by recent evidence. For example, we found that prevalence of lifetime history of TBI is slightly lower among male veterans versus male civilians.[9] Similarly, a study of veterans in England identified a lower prevalence of dementia among veterans compared with matched civilians[53] and the Adult Changes in Thought Study reported that military employment was not associated with cognitive decline or dementia in later life.[54] However, a recent systematic review of TBI and risk of all-cause dementia in veterans (U.S. and non-U.S.) reported a pooled hazard ratio of 1.95,[55] which, is slightly higher than that reported in most prior meta-analyses that included mostly civilians.[1–5] Ultimately, our meta-analysis did identify a similarly elevated risk of dementia after TBI among U.S. veterans (HR 2.13), and while this point estimate was indeed higher than the point estimate for the other studies of civilians, it was not statistically significantly higher. Thus, at this time, there is no clear evidence to support a significantly higher risk of dementia after TBI among veterans compared with civilians.

To investigate how severity of TBI was associated with risk of dementia, we assessed risk of dementia after ''TBI with LOC'' as this is the most common severity-related TBI definition used in epidemiological studies (used by $n = 14$ of the studies in our meta-analysis). It is notable that the risk estimate for TBI with LOC (HR 1.38) is lower than most of the other estimates. This is surprising because ''TBI with LOC'' would be expected to capture not only mild TBI with LOC but also moderate and severe TBIs. One explanation of this finding is that most of these 14 studies defined TBI based on self-report in response to a brief screen. Brief screens are known to be poorly sensitive[56] making exposure misclassification likely. Exposure misclassification would in turn lead to attenuation of the detectable effect size associated with the exposure.

Indeed, most high-quality case-control studies published to date have used a very brief TBI screen to assesses lifetime history of TBI and also ask a proxy-informant to report on this exposure both in cases and controls. While this approach avoids differential ascertainment bias between cases and controls, it does lead to substantial under-reporting of the TBI exposure and subsequent massive exposure mis-classification. To put this in perspective, the overall lifetime prevalence of at least one TBI in community dwelling older adult respondents to the nationally representative HRS 2014 comprehensive Oregon Health & Science University TBI-ID survey was 31%.[57] Among the 18 case-control studies included in this meta-analysis, the lifetime prevalence of TBI among cases and controls ranged from 4 to 24% with only four studies reporting prevalence 20% or higher among either cases,[23,33] or controls[46] or both.[27] Under-reporting will lead to exposure mis-classification and reduction of the magnitude of any identified association between exposure and outcome. This is in fact what we observed when we compared studies that employed a brief screen (HR 1.44) versus those that relied upon ICD codes/medical records (HR 1.88). There is also the challenge that among most case control studies, the exposure of interest is lifetime TBI while most large prospective cohort studies using medical records only capture isolated incident cases of TBI during a specified timeframe, not lifetime exposure.

Only three prior studies included a required one-plus year lag between TBI and dementia diagnosis in their primary analysis and were included in our lag sub-group analysis.[31,39,44] However, several prior well-designed studies have conducted multi-level sensitivity analyses with ever-increasing lags between TBI and dementia diagnosis. All have found that the risk estimates decline as the lag increases and most level off near a RR of 1.2 by 10+ or 30+ years,[23,44,47,48] with only three studies—none of them cohort studies—reporting no significant risk after $10+$[24] or $30+$ years.[23,48] Fann and colleagues[47] specifically showed that dementia risk is exceptionally high immediately after TBI but declines rapidly over 2 years, leveling out and remaining fairly stable out to at least 14 years post-injury. This elegant study suggests that future studies investigating mechanisms of post-TBI dementia should perhaps treat the early post-TBI period within 2 years of injury separately from the chronic phase beginning 2 or more years post-injury.

Consistent with these prior studies that dove deeply into this issue, our lag sub-group analysis also found that studies requiring a 1-year lag reported significantly lower risk estimates (pooled RR 1.24) than studies not requiring a lag (pooled RR 1.67). There are many potential explanations for this finding. It is possible that TBI may (rarely) directly cause an immediate diagnosis of TBI-related dementia, similar to the concept of stroke-related dementia. In these cases, the risk estimate would be falsely low after excluding dementia diagnosed within one year of TBI. However, it is debatable whether these cases should be classified as ''dementia'' or simply

TBI-related cognitive impairment. A more relevant and likely explanation is reverse-causation. That is, dementia may be present before the TBI, might be a risk factor for sustaining the TBI, but may not be diagnosed until after the TBI as a result, perhaps, of increased neurological care received for the TBI.

Indeed, our prior study evaluating risk of dementia after TBI versus non-TBI trauma was designed specifically to address this question of revere-causation by comparing patients who only differed on the location of their trauma and therefore were likely well-matched for unmeasured pre-injury factors such as un-diagnosed dementia. In this prior study, which additionally implemented a required 1-year lag and contributed to our lag sub-group analysis, our risk estimate was indeed near HR of 1.2.[39] Thus, a RR around 1.2 may be considered a very conservative estimate of the residual risk of dementia associated with TBI after aggressively mitigating the possibility of reverse-causation. Of course, by matching to non-TBI trauma, risk estimates may be falsely low as this comparison essentially controls for many other co-occurring exposures such as psychological trauma or systemic inflammation that may contribute to the causal pathway between TBI and dementia.[58] Similarly, by extending the lag out to 30+ years, risk estimates will be stripped of the possibility that a TBI may accelerate a pre-existing neurodegenerative process leading to an earlier age of dementia diagnosis than would have otherwise occurred. Thus, the question of mitigation of reverse-causation in epidemiological studies of TBI and risk of dementia is complex. Individual studies should be designed with special attention to their specific scientific aims rather than a one-size-fits-all methodology.

We found that studies with younger average age reported higher risk of dementia after TBI. The definition of ''age,'' however, is quite heterogeneous across the included studies. Age sometimes refers to age at TBI, sometimes to age at the study baseline (which may be either before or after TBI), and sometimes to age at the time of outcome ascertainment. This finding at first seems contrary to our prior California-wide study of risk of dementia after TBI that identified an interaction with older age and TBI severity such that milder TBIs became increasingly risky with increasing age at the time of injury.[39] It is possible that this discrepancy is due to the dearth of studies investigating risk of dementia after TBI specifically in the oldest-old age-strata, as we did in our prior study.[39] However, it is also possible that our finding was confounded by shorter time since injury in the oldest-old. The study by Fann and colleagues[47] presents, perhaps, the most nuanced treatment of age of any prior study with careful investigations of risk of dementia according to age at time of TBI as well as by time since injury/age at time of outcome ascertainment. Their results suggest that risk estimates go down with increasing time since injury which also means that risk estimates will appear to go up with increasing age at injury.[47]

Six studies in this meta-analysis reported sex-stratified risk estimates for men versus women and of these, four reported higher risk among men [21,24,28,29] while two reported higher risk among women.[25,30] We were able to investigate the effect of sex by categorizing studies as being greater than or less than 50% female. With this novel approach, we were able to include all 39 risk estimates in our sex analysis and determine that sex is a significant contributor to heterogeneity with studies including majority males reporting significantly higher risk. This finding is consistent with the majority of prior studies reporting sex-stratified risk estimates.

We were surprised to find that region was a significant contributor to heterogeneity with studies from Asia reporting significantly higher risk of dementia after TBI. This finding may be due to methodological differences as five of six of these studies had an average age of 40s and five of six of these studies used medical records for diagnosis; both of these factors were found to be associated with higher risk estimates in this meta-analysis. However, whether there may be other region-specific contributors to this finding deserves further study.

This meta-analysis has many strengths. It is the most comprehensive meta-analysis on risk of all-cause dementia after all-severity TBI to date. We only included high quality studies. We were able to carefully explore sources of heterogeneity. However, the study is limited by substantial residual heterogeneity and resultant uncertainty of the final pooled risk estimate, the possibility of exposure misclassification in many included studies, the possibility of under-diagnosis of dementia and reverse-causation in many included studies, the lack of reliable definitions for mild TBI in most studies, and of course, the substantial heterogeneity of methods and definitions used across different studies. Additionally, our PAR of dementia due to TBI estimates may be influenced by additional factors often seen with TBI such as post-traumatic stress disorder and other comorbidities, are a result of many assumptions about prevalence of exposure and outcome, are a result of pooled estimates across very heterogeneous studies, and may not generalize to individuals under 50 given that the TBI prevalence data was taken from the Health and Retirement Study. Thus, the specific estimates of attributable cases of dementia in the U.S. (e.g., $n = 860{,}696$) should be interpreted with all of these limitations in mind and readers are encouraged instead to focus on the relative comparison of PARs across sub-groups.

In conclusion, this meta-analysis found that TBI is a significant risk factor for all-cause dementia, increasing risk by approximately 70%. This finding supports

the importance of continued TBI prevention efforts as well as continued efforts to identify therapeutic targets for post-TBI dementia. Further research is additionally warranted to determine mechanisms of the higher risk observed in younger adults, men, and individuals from Asia. Given the higher prevalence of TBI in men and veterans, in combination with the higher estimated risk of dementia after TBI in these groups, TBI prevention in men and Veterans is of especially high public health importance.

Acknowledgments

We are grateful to Dr. Erin L. Abner for providing us with an adjusted risk estimate to include in this meta-analysis.[18]

Authors' Contributions

RCG led study design, data collection, interpretation of results, and drafting and revising the manuscript. AB contributed to study design, data collection, data analysis, interpretation of results, and drafting and revising the manuscript. ESK contributed to data analysis and drafting and revising the manuscript. IEA contributed to study design, interpretation of results, and revising the manuscript. BLP obtained funding and contributed to interpretation of results and revising the manuscript. KY obtained funding and contributed to study design, interpretation of results, and revising the manuscript.

Funding Information

The authors report funding from Department of Defense (W81XWH-18-1-0692 to KY and BLP) and Department of Veterans Affairs (IK2 RX003073-01A2 to ESK). Also partially supported by NIA R35AG071916 (Yaffe) and the Assistant Secretary of Defense for Health Affairs endorsed by the Department of Defense, through the Psychological Health/Traumatic Brain Injury Research Program Long-Term Impact of Military-Relevant Brain Injury Consortium (LIMBIC) Award/W81XWH-18-PH/TBIRP-LIMBIC under Awards No. W81XWH1920067 and W81XWH-13-2-0095, and by the U.S. Department of Veterans Affairs Awards No. I01 CX002097, I01 CX002096, I01 HX003155, I01 RX003444, I01 RX003443, I01 RX003442, I01 CX001135, I01 CX001246, I01 RX001774, I01 RX 001135, I01 RX 002076, I01 RX 001880, I01 RX 002172, I01 RX 002173, I01 RX 002171, I01 RX 002174, and I01 RX 002170. The U.S. Army Medical Research Acquisition Activity is the awarding and administering acquisition office. Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the Department of Defense.

Author Disclosure Statement

No competing financial interests exist.

Supplementary Material

Supplementary Data

References

1. Huang CH, Lin CW, et al. Is traumatic brain injury a risk factor for neurodegeneration? A meta-analysis of population-based studies. BMC Neurol 2018;18(1):184; doi: 10.1186/s12883-018-1187-0
2. 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(1):e0169650; doi: 10.1371/journal.pone.0169650
3. Perry, D.C., Sturm, V.E., Peterson, et al. Association of traumatic brain injury with subsequent neurological and psychiatric disease: a meta-analysis. J Neurosurg 2016;124(2):511–526; doi: 10.3171/2015.2.JNS14503
4. Fleminger S, Oliver DL, Lovestone S, et al. Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. J Neurol Neurosurg Psychiatry 2003;74(7):857–862; doi: 10.1136/jnnp.74.7.857
5. Mortimer JA, van Duijn CM, Chandra V, et al. Head trauma as a risk factor for Alzheimer's disease: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group. Int J Epidemiol 1991;20 Suppl 2:S28–S35; doi: 10.1093/ije/20.supplement_2.s28
6. Gu D, Ou S, Liu G. Traumatic brain injury and risk of dementia and Alzheimer's disease: a systematic review and meta-analysis. Neuroepidemiology 2022;56(1):4–16; doi: 10.1159/000520966
7. Guo Z, Cupples LA, Kurz A, et al. Head injury and the risk of AD in the MIRAGE study. Neurology 2000;54(6):1316–1323; doi: 10.1212/wnl.54.6.1316
8. Barnes DE, Byers AL, Gardner RC, et al. Association of mild traumatic brain injury with and without loss of consciousness with dementia in US military veterans. JAMA Neurol 2018;75(9):1055–1061; doi: 10.1001/jamaneurol.2018.0815
9. Kornblith ES, Yaffe K, Langa KM, et al. Prevalence of lifetime history of traumatic brain injury among older male veterans compared with civilians: a nationally representative study. J Neurotrauma 37 2020; 37(24):2680–2685; doi: 10.1089/neu.2020.7062
10. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Last accessed November 9, 2022].
11. Stare J, Maucort-Boulch D. Odds ratio, hazard ratio, and relative risk. Metodoloski zvezki 13, 59–67.
12. George A, Stead TS, Ganti L. What's the risk: differentiating risk ratios, odds ratios, and hazard ratios? Cureus 2020;12(8):e10047; doi: 10.7759/cureus.10047
13. Borenstein, M. Introduction to Meta-Analysis. John Wiley and Sons: Chichester, U.K; 2009.
14. Egger, M., Smith, G.D., Schneider, M. et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315(7109):629–634; doi: 10.1136/bmj.315.7109.629
15. National Institutes of Neurological Diseases and Stroke Common Data Elements: Traumatic Brain Injury. Available from: https://www.commondataelements.ninds.nih.gov/Traumatic%20Brain%20Injury [Last accessed November 9, 2022].
16. Ofstedal MB, Weir DR, Chen KT, et al. Updates to HRS Sample Weights. Institute for Social Research, University of Michigan: Ann Arbor, Michigan; 2011.
17. Whiteneck, GG, Cuthbert JP, Corrigan JD, et al. Prevalence of self-reported lifetime history of traumatic brain injury and associated disability: a statewide population-based survey. J Head Trauma Rehabil 2016;31(1): E55–E62; doi: 10.1097/HTR.0000000000000140
18. Abner EL, Nelson PT, Schmitt FA, et al. Self-reported head injury and risk of late-life impairment and AD pathology in an AD center cohort. Dement Geriatr Cogn Disord 2014;37(5-6):294–306; doi: 10.1159/000355478
19. Tsolaki M, Fountoulakis K, Chantzi E, et al. Risk factors for clinically diagnosed Alzheimer's disease: a case-control study of a Greek population. Int Psychogeriatr 1997;9(3):327–341; doi: 10.1017/s104161029700447x
20. Boston PF, Dennis MS, Jagger C. Factors associated with vascular dementia in an elderly community population. Int J Geriatr Psychiatry 1999;14(9):761–766; doi: 10.1002/(sici)1099-1166(199909)14:9<761::aid-gps14>3.0.co;2-h

21. Broe GA, Henderson AS, Creasey H, et al. A case-control study of Alzheimer's disease in Australia. Neurology 1990;40(11):1698–1707; doi: 10.1212/wnl.40.11.1698
22. Ferini-Strambi L, Smirne S, Garancini P, et al. Clinical and epidemiological aspects of Alzheimer's disease with presenile onset: a case control study. Neuroepidemiology 1990;9(1):39–49; doi: 10.1159/000110750
23. Graves, A.B., White, E., Koepsell, T.D., et al. The association between head trauma and Alzheimer's disease. Am J Epidemiol 1990;131(3):491–501; doi: 10.1093/oxfordjournals.aje.a115523
24. van Duijn CM, Tanja TA, Haaxma R, et al. Head trauma and the risk of Alzheimer's disease. Am J Epidemiol 1992;135(7):775–782; doi: 10.1093/oxfordjournals.aje.a116364
25. Mayeux R, Ottman R, Tang MX, et al. Genetic susceptibility and head injury as risk factors for Alzheimer's disease among community-dwelling elderly persons and their first-degree relatives. Ann Neurol 1993;33(5):494–501; doi: 10.1002/ana.410330513
26. (1994). The Canadian Study of Health and Aging: risk factors for Alzheimer's disease in Canada. Neurology 1994;44(11):2073–2080; doi: 10.1212/wnl.44.11.2073
27. Forster DP, Newens AJ, Kay DW, et al. Risk factors in clinically diagnosed presenile dementia of the Alzheimer type: a case-control study in northern England. J Epidemiol Community Health 1995;49(3):253–258; doi: 10.1136/jech.49.3.253
28. O'Meara ES, Kukull WA, Sheppard L, et al. Head injury and risk of Alzheimer's disease by apolipoprotein E genotype. Am J Epidemiol 1997;146(5):373–384; doi: 10.1093/oxfordjournals.aje.a009290
29. Salib E, Hillier V. Head injury and the risk of Alzheimer's disease: a case control study. Int J Geriatr Psychiatry 1997;12(3):363–368; doi: 10.1002/(sici)1099-1166(199703)12:3 <363::aid-gps515>3.0.co;2-f
30. Mehta KM, Ott A, Kalmijn S, et al. Head trauma and risk of dementia and Alzheimer's disease: the Rotterdam Study. Neurology 1999;53(9):1959–1962; doi: 10.1212/wnl.53.9.1959
31. 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(8):1158–1166; doi: 10.1212/wnl.55.8.1158
32. Lindsay J, Laurin D, Verreault R, et al. Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. Am J Epidemiol 2002;156(5):445–453; doi: 10.1093/aje/kwf074
33. Bachman DL, Green RC, Benke KS, et al. and Group, M.S. Comparison of Alzheimer's disease risk factors in white and African American families. Neurology 2003;60(8):1372–1374; doi: 10.1212/01.wnl.0000058751.43033.4d
34. Ogunniyi A, Hall KS, Gureje O, et al. Risk factors for incident Alzheimer's disease in African Americans and Yoruba. Metab Brain Dis 2006;21(2-3):235–240; doi: 10.1007/s11011-006-9017-2.
35. Rippon GA, Tang MX, Lee JH, et al. Familial Alzheimer disease in Latinos: interaction between APOE, stroke, and estrogen replacement. Neurology 2006;66(1):35–40; doi: 10.1212/01.wnl.0000191300.38571.3e
36. Suhanov AV, Pilipenko PI, Korczyn AD, et al. Risk factors for Alzheimer's disease in Russia: a case-control study. Eur J Neurol 2006;13(9):990–995; doi: 10.1111/j.1468-1331.2006.01391.x
37. Wang HK, Lin SH, Sung PS, et al. Population based study on patients with traumatic brain injury suggests increased risk of dementia. J Neurol Neurosurg Psychiatry 2012;83(11):1080–1085; doi: 10.1136/jnnp-2012-302633
38. Lee YK, Hou SW, Lee CC, et al. Increased risk of dementia in patients with mild traumatic brain injury: a nationwide cohort study. PloS One 2013;8(5):e62422; doi: 10.1371/journal.pone.0062422
39. Gardner RC, Burke JF, Nettiksimmon, J, et al. Dementia risk after traumatic brain injury vs nonbrain trauma: the role of age and severity. JAMA Neurol 2014;71(12):1490–1497; doi: 10.1001/jamaneurol.2014.2668
40. Nordstrom P, Michaelsson K, Gustafson Y, et al. Traumatic brain injury and young onset dementia: a nationwide cohort study. Ann Neurol 2014 Mar;75(3):374–381; doi: 10.1002/ana.24101
41. Barnes DE, Kaup A, Kirby KA, et al. Traumatic brain injury and risk of dementia in older veterans. Neurology 2014;83(4):312–319; doi: 10.1212/WNL.0000000000000616
42. Chu SF, Chiu WT, Lin HW. et al. Hazard ratio and repeat injury for dementia in patients with and without a history of traumatic brain injury: a population-based secondary data analysis in Taiwan. Asia Pac J Public Health 2016;28(6):519–527; doi: 10.1177/1010539516662956
43. Crane PK, Gibbons LE, Dams-O'Connor K, et al. Association of traumatic brain injury with late-life neurodegenerative conditions and neuropathologic findings. JAMA Neurol 2016;73(9):1062–1069; doi: 10.1001/jamaneurol.2016.1948
44. Tolppanen AM, Taipale H, Hartikainen S. Head or brain injuries and Alzheimer's disease: A nested case-control register study. Alzheimers Dement 2017;13(12):1371–1379; doi: 10.1016/j.jalz.2017.04.010
45. Lin WC, Hu LY, Tsai SJ, et al. Depression and the risk of vascular dementia: a population-based retrospective cohort study. Int J Geriatr Psychiatry 2017;32(5):556–563; doi: 10.1002/gps.4493
46. Cations M, Draper B, Low LF, et al. Non-Genetic Risk Factors for Degenerative and Vascular Young Onset Dementia: Results from the INSPIRED and KGOW Studies. J Alzheimers Dis 2018;62(4):1747–1758; doi: 10.3233/JAD-171027
47. Fann JR, Ribe AR, Pedersen HS, et al. Long-term risk of dementia among people with traumatic brain injury in Denmark: a population-based observational cohort study. Lancet Psychiatry 2018;5(5):424–431; doi: 10.1016/S2215-0366(18)30065-8
48. Nordstrom A, Nordstrom P. Traumatic brain injury and the risk of dementia diagnosis: A nationwide cohort study. PLoS Med 2018 Jan;15(1):e1002496; doi: 10.1371/journal.pmed.1002496
49. Yaffe K, Lwi SJ, Hoang TD, et al. Military-related risk factors in female veterans and risk of dementia. Neurology 2019;92(3):e205-e211; doi: 10.1212/WNL.0000000000006778
50. 2021 Alzheimer's disease facts and figures. Alzheimers Dement. 2021;17(3):327–406.
51. VA Projections of the Prevalence and Incidence of Dementias Including Alzheimer's Disease for the Total Veteran, Enrolled and Patient Populations Age 65 and Older. 2013. https://www.va.gov/GERIATRICS/docs/Methodology_Paper_Projections_of_the_Prevalence_and_Incidence_of_Dementias_v5_FINAL.pdf. [Last accessed: June 30, 2021].
52. Veitch DP, Friedl KE, Weiner MW. Military risk factors for cognitive decline, dementia and Alzheimer's disease. Curr Alzheimer Res 2013;10(9):907–930; doi: 10.2174/15672050113109990142
53. Greig F, McManus S, Fear NT. 0. Occup Med (Lond) 2021;71(1):34-40. doi: 10.1093/occmed/kqaa213
54. Power MC, Murphy AE, Gianattasio KZ, et al. Association of military employment with late-life cognitive decline and dementia: a population-based prospective cohort study. Mil Med 2021;usab413; doi: 10.1093/milmed/usab413
55. Leung KK, Carr FM, Russell MJ, et al. Traumatic brain injuries among veterans and the risk of incident dementia: a systematic review & meta-analysis. Age Ageing 2022;51(1):afab194; doi: 10.1093/ageing/afab194
56. Gardner RC, Rivera E, O'Grady M, et al. Screening for lifetime history of traumatic brain injury among older American and Irish adults at risk for dementia: development and validation of a web-based survey. J Alzheimers Dis 2020;74(2):699–711; doi: 10.3233/JAD-191138
57. Kornblith ES, Langa KM, Yaffe K, et al. Physical and functional impairment among older adults with a history of traumatic brain injury. J Head Trauma Rehabil 2020 Jul/Aug;35(4):E320–E329; doi: 10.1097/HTR.0000000000000552
58. Albrecht JS, Gardner RC, Wiebe D, et al. Comparison groups matter in traumatic brain injury research: an example with dementia. J Neurotrauma 2022 Nov;39(21-22):1518–1523; doi: 10.1089/neu.2022.010