Evidence Brief: Traumatic Brain Injury and Dementia

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Prepared by:

Evidence Synthesis Program (ESP)
Coordinating Center
Portland VA Health Care System
Portland, OR
Mark Helfand, MD, MPH, MS, Director

Authors:

Kim Peterson, MS
Stephanie Veazie, MPH
Donald Bourne, MPH
Johanna Anderson, MPH

U.S. Department of Veterans Affairs

Veterans Health Administration
Health Services Research & Development Service

PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. These reports help:

- · Develop clinical policies informed by evidence;
- · Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- · Set the direction for future research to address gaps in clinical knowledge.

The program is comprised of four ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program and Cochrane Collaboration. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, and interface with stakeholders. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee comprised of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, Deputy Director, ESP Coordinating Center at Nicole.Floyd@va.gov.

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EXECUTIVE SUMMARY

Key Findings

- Dementia prevalence appears similar in Veteran and non-Veteran populations.
- TBI appears associated with an increased risk of dementia in Veterans.
- Key evidence gaps to consider for future research include direct comparison of dementia rates in Veteran versus non-Veteran populations, the association between TBI and early-onset dementia, and mechanisms of the association between TBI and dementia.

Traumatic brain injury (TBI) is a common condition among both civilian and military populations. In general, military service members are at a higher risk of experiencing a TBI than their civilian counterparts. While some TBIs cause acute symptoms that resolve over several weeks or months, evidence accumulating over nearly 3 decades suggests that TBI may lead to chronic neurodegenerative diseases such as dementia. Increased public awareness of Chronic Traumatic Encephalopathy (CTE) and preliminary reports about TBI in active-duty service members as a risk factor for earlier onset of dementia and/or CTE has increased the urgency to better understand the association of TBI with chronic neurodegenerative conditions. In particular, a better understanding of the link between TBI and dementia among Veterans could help the US Department of Veterans Affairs (VA) develop and provide guidance on new screening, diagnosis, and treatment efforts in the future.

This rapid review builds on previous evidence synthesis work by focusing on Veteran populations and adding a few key studies in Veterans. This review found that although no study has directly compared dementia rates in Veterans and non-Veterans in the same sample, estimates from 2 separate sources suggest that dementia rates appear similar in Veterans (10.7%) and non-Veterans (range, 8.8% to 11.6%) aged 65 years and older. No studies were identified on the comparative prevalence of dementia among younger (< 65 years) Veteran and civilian populations. Findings from studies evaluating the association between TBI and dementia in military and Veteran populations were consistent with findings from a 2017 systematic review suggesting that TBI is associated with increased risks of dementia in a worldwide general community population. Possibly the most interesting contribution from the most recent and largest study in US Veterans is that there may be a dose-response relationship between TBI and dementia diagnosis. Compared to the increased risk of dementia for a mild TBI without loss of consciousness (HR 2.36, 95% CI 1.35 to 1.83), the association between TBI and dementia grew progressively larger with increasing TBI severity (HR 3.77, 95% CI 3.63 to 3.91 for moderate/severe TBI).

Background

The ESP Coordinating Center (ESP CC) is responding to a request from the Office of Research and Development for an evidence brief on the prevalence of dementia in Veterans with and without traumatic brain injury (TBI). Findings from this evidence brief will be used to inform research into early diagnosis and potential treatment of dementia in Veterans with TBI.

Methods

To identify studies, we searched MEDLINE®, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and other sources up to November 2018. We used prespecified criteria for study selection, data abstraction, and rating internal validity and strength of the evidence.

Although the additional studies in Veterans – particularly the 2018 study by Barnes et al – are important additions to the growing literature supporting a consistent association between TBI and dementia, the body of evidence as a whole still has some important limitations that deserve further attention. The main methodologic limitation of existing studies is the continued reliance on retrospective data. This comes with inherent challenges: lack of consistent definitions for TBI and dementia; residual confounding due to lack of adequate information on previously identified genetic, medical, andpsychiatric factors; residual confounding due to lifestyle risk factors for dementia including Apolipoprotein E polymorphisms, hypertension, diabetes, alcohol use, smoking, and prescription opioid misuse.

Remaining key gaps in evidence include that no study has directly compared dementia prevalence in Veteran versus non-Veteran populations, few data are available on the potential role of brain injury severity, mode (blast vs non-blast), single versus repeated injury, setting (*ie*, military deployment or not) on dementia onset, and whether TBI is associated with early-onset dementia. Ongoing retrospective research from the Vietnam Era Health Retrospective Observational Study (VE-HEROeS) and prospective research from the Chronic Effects of Neurotrauma Consortium (CENC) on deployment-related TBI and CTE are anticipated to address some of the major existing gaps. Although there is still room for improvement on methodological limitations inherent to the existing retrospective cohort studies, new research that addresses the potentially bigger gaps in knowledge about mechanism of association and timing of onset of dementia may be of higher priority in informing development of screening, prevention and rehabilitation efforts.

Table 1. Summary of Findings

Key Question	Evidence characteristics	Main findings
KQ1. Dementia prevalence in Veterans vs civilians	1 systematic review in US Veterans (total N=432,461) 3 cross-sectional studies in US civilians (total N>21,913)	Dementia prevalence is likely similar between US Veterans (10.7%) and civilians (range: 8.8% to 11.6%) aged 65 years and older.
KQ1a. Veteran dementia prevalence by combat deployment history	None identified.	More research is needed.
KQ1b. Veteran dementia prevalence by era of conflict	None identified.	More research is needed.
KQ2. Veteran dementia prevalence by TBI history	2 good-quality retrospective cohort studies in US Veterans (total N= 546,322) 1 fair-quality retrospective cohort study in Swedish men conscripted for military service (total N=811,622)	Dementia prevalence is likely higher in those with TBI (range: 6 to 16%) than those without (range: 3 to 10%). There may be a dose-response relationship between TBI and dementia; however, this was not consistently seen across all subtypes of dementia.

KQ2a. TBI+ Veteran dementia prevalence by combat deployment	None identified.	More research is needed.
KQ2b. TBI+ Veteran dementia prevalence by timing of onset	4 fair-quality retrospective cohort studies among: · Swedish men conscripted for military service (N=811,622) · US Veterans (N=948) · US civilians (total N=13,705)	All 4 studies suggest there may be a relationship between TBI and some forms of early-onset dementia. However, our confidence is limited due to some important methodological limitations.

EVIDENCE BRIEF

INTRODUCTION

PURPOSE

The ESP Coordinating Center (ESP CC) is responding to a request from the Office of Research and Development (ORD) for an evidence brief on dementia prevalence in Veterans with and without traumatic brain injury (TBI). Findings from this evidence brief will be used to inform research into early diagnosis and potential treatment of dementia in Veterans with TBI.

BACKGROUND

Traumatic brain injury (TBI) is a common condition among both civilian and military populations. In the United States and Canada, over four million people (1.3% of the population) experience a TBI every year.[1] In general, military service members are at a higher risk of experiencing a TBI than their civilian counterparts. In 2017, the Department of Defense (DOD) reported 15,000 new TBI diagnoses among military service members,[2] and researchers have estimated that 10-20% of Veterans experience a TBI during deployment.[3-5] Most military service members who experience a TBI experience more than one.[5]

While some TBIs cause acute symptoms that resolve over several weeks or months, evidence accumulating over nearly 3 decades suggests that TBI may lead to chronic neurodegenerative diseases, such as dementia.[6] Dementia is a general term used to describe major and often progressive difficulties with various aspects of mental functioning, including memory, thinking, problem-solving, and/or language. Several mechanisms have been proposed to explain how TBI could lead to dementia.[7] One major theory is that TBIs could damage brain structure and the resulting diffuse axonal injury may progress over a period of years and lead to dementia onset. Second, TBIs could cause neuropathological changes, such as the accumulation of the proteins β-amyloid peptide (Aβ) in plaques and tau in neurofibrillary tangles, which are 2 characteristic pathologies of Alzheimer's Disease. Third, TBIs could cause white matter degeneration or neuroinflammation which could lead to dementia. Finally, it is possible that dementia diagnosed many years following TBI reflects ongoing cognitive impairment initiated at the time of their original injury.

Findings from a 2017 systematic review by Li et al of data from 32 studies published between 1990 and 2015 involving over 2 million individuals worldwide suggests that head injury of any type may significantly increase the risk of any dementia (RR 1.63; 95% CI 1.34-1.99).[6] However, the clinical relevance of these findings to the VA is unclear for 3 key reasons: (1) the Li 2017 review did not distinguish military-related from non-military-related TBI types or Veteran populations; (2) it did not include some key studies in Veterans that were either not yet published[7] or that used analytic methods other than a risk ratio (*ie*, hazard ratio, prevalence rates)[7,8]; and (3) it noted that interpretation of their own findings was limited by flaws of previous research that are inherent in TBI research, including lack of use of standardized methods for assessing head injury and dementia and potential residual bias from unmeasured confounding factors. Regarding the variation in use of TBI and dementia assessment methods, in 2016, the Defense and Veterans Brain Injury Center, Armed Forces Health Surveillance Branch, and Centers for Disease Control agreed upon a standard definition of TBI.[7] However, studies

conducted before 2016 or from other agencies may use different definitions, and discrepancies between research and health care organizations in how TBIs are defined and categorized makes it difficult to compare rates of TBIs across studies. Regarding unmeasured confounding of the association between dementia and TBI, many demographic, medical, psychiatric, genetic, and lifestyle risk factors have been reported, including, age, sex, Apolipoprotein E polymorphisms, alcohol use, smoking, prescription opioid misuse, diabetes, hypertension, and others.[9-11] These factors may have an impact on the development of dementia and may vary between TBI and non-TBI groups within studies. Additionally, TBI, dementia, and other mental health disorders have some overlapping symptoms, making it difficult to determine where one condition ends and another begins.

Also, the Li 2017 review did not address other ongoing areas of research interest, including consideration of the role of variation in brain injury severity, mode (blast vs non-blast), single versus repeated injury, whether the injury occurred during military deployment, and timing of dementia onset (early vs late). For example, a recent study found that dementia is diagnosed on average 2.38 years earlier in those with TBIs versus those without, which has led to interest in whether TBIs may lead to e*arlier* onset of neurodegenerative disorders.[12] To address these clinically relevant questions, in 2013, VA, DOD, and other academic and private research entities launched the Chronic Effects of Neurotrauma Consortium (CENC). Major goals of the Consortium include: better understanding the basic science of mild TBI, its potential association with numerous comorbidities including dementia, their diagnostic and prognostic indicators, and developing and advancing methods to treat associated conditions.[13]

TBI management guidelines pre-date this evidence and do not yet discuss the potential risk of dementia following TBI or offer clinicians guidance on dementia screening or risk reduction. Mention of dementia prevention and treatment strategies is absent from both the current Department of Veterans Affairs and Department of Defense (VA/DoD) clinical practice guidelines on the Management of Concussion-mild Traumatic Brain (mTBI) (2016)[14] and the Brain Trauma Foundation's 4th Edition of Guidelines for Management of Severe Traumatic Brain Injury (2016).[15]

Furthermore, increased public awareness and concern about reports of Chronic Traumatic Encephalopathy (CTE) in active-duty service members has heightened the urgency to better understand the potential chronic neurodegenerative risks of TBI.[16,17] CTE is a neurodegenerative condition first recognized in contact sports athletes exposed to frequent blows to the head, such as boxers and football players. Compared to former eras, there is concern that military service members deployed in Afghanistan and Iraq are at higher risk of CTE because they are exposed to multiple blasts over the course of repeated deployments. Survival after these blasts has increased due to the use of modern body armor and helmets, but this means more people are living with head injuries.[18] CTE has been associated with some similar clinical features to dementia – such as memory disturbances, behavior and personality changes, and Parkinsonism – but is currently thought to be a distinct clinical entity with a distinct pattern of brain pathology detectable upon autopsy,[19] including atrophy in the frontal and temporal lobes, widened ventricles, dilated and bifurcated septum pellucidums, and accumulation of proteins such as tau.[20] Research on CTE to date primarily focuses on autopsy examinations, which is outside of this scope of this report on the clinical evidence of the association of TBI and dementia.[21]

A better understanding of the link between TBI and dementia among Veterans could help clinicians discuss potential risks with patients, as well as guide the development of best practices regarding screening, risk reduction, and treatment including rehabilitation post-TBI. Understanding the prevalence and risk factors for development of dementia after TBI could help identify who would benefit most from more intensive screening and treatment efforts. For example, neurorehabilitation, which involves multidisciplinary care teams (*eg*, physical therapist, occupational therapist, speech/language pathologist, neuropsychologist, social worker, and others) providing a range of treatments to maximize patient function, minimize impairments, and prevent complications, has traditionally focused on those with moderate to severe TBIs.[22] However, as new research emerges on the long-term effects of TBIs – especially multiple TBIs – neurorehabilitation and other intensive treatments may become viable options for those with persistent symptoms. Optimally, early identification and management of TBI could help prevent subsequent TBIs or damage from occurring before the brain has healed, which could then prevent the cascade of structural and/or neurophysiological events that may contribute to dementia.

The aim of this rapid review is to summarize the best evidence on the comparative prevalence of dementia between Veterans and civilians, and to assess whether particular risk factors (including previous TBIs, era of conflict, and combat exposure) affect the risk and timing of dementia onset among Veterans.

SCOPE

This evidence brief will address the following key questions and inclusion criteria:

KEY QUESTIONS

Key Question 1: What is the comparative prevalence of dementia between Veterans and the civilian population?

> Key Question 1a: Does the prevalence of dementia in Veterans vary based on combat deployment history?

> Key Question 1b: Does the prevalence of dementia in Veterans vary based on era of conflict?

Key Question 2: What is the comparative prevalence of dementia between Veterans with and without TBI?

> Key Question 2a: Does the prevalence of dementia in Veterans with TBI vary based on combat deployment history?

> Key Question 2b: Does the prevalence of dementia in Veterans with TBI vary based on timing of dementia onset (*ie*, early vs late)?

ELIGIBILITY CRITERIA

The ESP included studies that met the following criteria:

·   **P**opulation: US Veterans or military personnel, or Veterans or military personnel from UK, Canada, New Zealand, or Australia

·   **I**ntervention: None

·   **C**omparator: Civilian population

·   **O**utcomes: Any

·   **T**iming: Any

·   **S**etting: Any

·   **S**tudy design: Any

METHODS

To identify articles relevant to the key questions, our research librarian searched Medline, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, PsycINFO, and Google Scholar using keyword and MESH terms for dementia, Alzheimer's, traumatic brain injury, and prevalence (see Appendix A in Supplemental Materials for complete search strategies). Additional citations were identified from hand-searching reference lists and consultation with content experts. We limited the search to published and indexed articles involving human subjects available in the English language. Study selection was based on the eligibility criteria described above. If no studies met all eligibility criteria, then we used a best-evidence approach in which we ranked studies of indirect evidence into 5 tiers based on relevance to US Veterans: Tier 1 = US Veterans; Tier 2 = Veterans or military personnel from UK, Canada, New Zealand, or Australia; Tier 3 = Veterans or military personnel from all other countries; Tier 4 = Civilians from US, UK, Canada, New Zealand, or Australia; and Tier 5 = Civilians from all other countries. Among the studies from the highest available tier of relevance, we then highlighted the largest and most up-to-date studies as providing the strongest evidence. Titles, abstracts, and full-text articles were reviewed by one investigator and checked by another. All disagreements were resolved by consensus.

We used predefined criteria to rate the internal validity of all studies. We used AMSTAR 2 to rate the internal validity of for systematic reviews.[23] We rated the internal validity of cohort studies using an adapted tool based on the Joanna Briggs Institute Checklist for Prevalence Studies.[24] We evaluated the potential for selection bias, detection bias, and confounding bias, as well as the appropriateness of data analysis. See Supplemental Materials Appendix C for more information on the adapted tool. We abstracted data from all studies and results for each included outcome. All data abstraction and internal validity ratings were first completed by one reviewer and then checked by another. All disagreements were resolved by consensus.

We informally graded the strength of the evidence based on the AHRQ Methods Guide for Comparative Effectiveness Reviews, by considering risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence.[25] Ratings typically range from high to insufficient, reflecting our confidence that the evidence reflects the true effect. As an example for this review, moderate-strength evidence would typically consist of 1 good-quality, direct, and precise cohort study or multiple consistent fair-quality cohort studies.

Where studies were appropriately homogenous, we synthesized outcome data quantitatively using StatsDirect statistical software (StatsDirect Ltd. 2013, Altrincham, UK) to conduct random-effects meta-analysis to estimate pooled effects. We assessed heterogeneity using the Q statistic and the I^2 statistic. Where meta-analysis was not suitable due to limited data or heterogeneity, we synthesized the evidence qualitatively.

The complete description of our full methods can be found on the PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/; registration number CRD42018107926). A draft version of this report was reviewed by peer reviewers as well as clinical leadership. Their comments and our responses are presented in the Supplemental Materials.

RESULTS

LITERATURE FLOW

Figure 1: Literature Flowchart
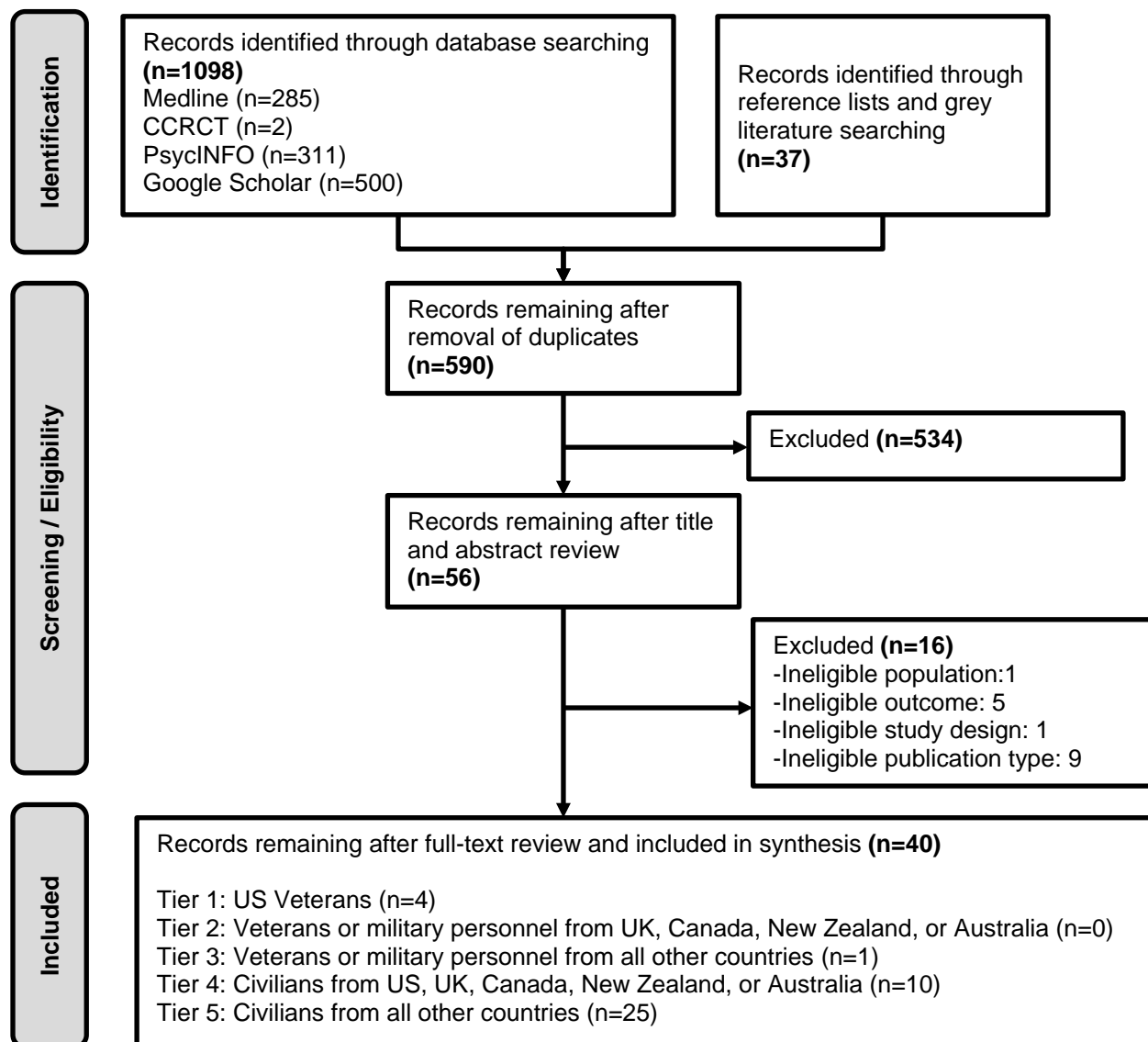
LITERATURE OVERVIEW

Searches resulted in 590 unique potentially relevant articles. We grouped relevant studies into 5 tiers based on how directly they addressed our population of interest (see Supplemental Materials Appendix B for list of excluded studies). In total, we identified 40 studies that addressed our key questions: 4 studies[7,8,26,27] were rated as Tier 1 evidence, no studies were rated as Tier 2 evidence, 1 study[28] was rated as Tier 3 evidence, 10 studies[12,29-37] were rated as Tier 4 evidence, and 25 studies were rated as Tier 5 evidence.[38-62] We then used a best evidence approach, whereby 3 researchers reached consensus, to select studies for qualitative synthesis. Among our

40 included studies, we focused on the strongest evidence from 4 studies[27,33,34,36] for Key Question 1 (see Table 2) and 6 studies[7,8,12,26,28,35] for Key Question 2 (see Table 3). Included studies were observational, due to the epidemiological nature of the key questions.

KEY QUESTION 1: What is the comparative prevalence of dementia between Veterans and the civilian population?

No studies directly compared the prevalence of dementia between Veterans and non-Veteran populations. We therefore used a best-evidence approach to select studies of indirect evidence and included the strongest and most up-to-date studies for our discussion (see Table 2). Overall, we found low-strength evidence that dementia prevalence appears to be similar in US Veterans[27] (10.7%) and non-Veterans[33,34] (range, 8.8% to 11.6%) aged 65 years and older. No studies were identified on the comparative prevalence of dementia among younger (< 65 years) Veteran and civilian populations.

The best available evidence on prevalence in Veterans comes from a systematic review and meta-analysis of 6 studies published between 2001 and 2011.[27] The authors of the review rated 1 study as good quality, and the rest were rated as fair quality using the National Institutes of Health: Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.[63] There was substantial heterogeneity between studies ($I^2 = 99.83$), which may be a product of clinical (*ie*, recruitment after mental health care encounter versus recruitment in nursing homes) or methodologic (*ie*, instrument used for outcome measurement) differences.[27] A random-effects model was used to account for the presence of heterogeneity.

This review[27] concluded that the prevalence of dementia in older Veterans was consistent with a previous study in the general population, which reported a dementia prevalence of 13.93% in people $\geq$ 71 years.[36] We updated these numbers with 2 more recently published studies[33,34] that used data from the Health and Retirement Study (HRS), a nationally representative, biennial, longitudinal survey sponsored by the National Institute on Aging (grant number NIA U01AG009740). These studies used an equivalent cut-off age of $\geq$ 65 years and reported dementia prevalence ranging from 11.6% to 12.0% in 2000 and 8.6% to 10.5% in 2012.[33,34] Even though both studies used the same raw data, there were slight differences in their reported numbers due to methodological decisions. The reported prevalence numbers in non-Veterans are similar to those reported in Veterans.

We rated the strength of this evidence as low because the comparison was indirect – coming from 2 separate bodies of evidence – and there were important methodological limitations (*ie*, differences in outcome measurements) and inconsistency (*ie*, heterogeneity across studies). To further understand the prevalence of dementia, future studies should ideally compare the prevalence of dementia in US Veterans and non-Veterans from the same dataset using a cross-sectional or longitudinal design.

KQ1A: Does the prevalence of dementia in Veterans vary based on combat deployment history?

No studies were identified to address this question.

KQ1B: Does the prevalence of dementia in Veterans vary based on era of conflict?

No studies were identified to address this question.

Table 2. Highlighted Studies Addressing KQ1

Author, Year Country	Study Design Sample Size	Demographics	Ascertainment of Dementia	Data Collection Period	Outcomes
Williamson 2018 US	SR & MA 6 studies N= 432,461	Age: 69.9-73.6 years (avg.) Sex: 96.6% male Race: NR Veterans: Yes	Electronic records at VA health care facilities	Included studies were published between 2001-2011	Dementia Prevalence: 10.1% (95% CI 7.59% to 12.84%; Range: 5.7% to 19.6%)
Hudomiet 2018 US	Cross-sectional N=NR	Age: ≥65 years Sex: NR Race: NR Veterans: No	Health and Retirement Study (HRS) dataset	2000-2012	Dementia Prevalence: 12.0% (95% CI 11.06% to 12.94%) in 2000 10.5% (95% CI 9.54% to 11.46%) in 2012
Langa 2017 US	Cross-sectional N= 21,057	Age: 74.9 years (avg.) Sex: 42.7% male Race: 83.4% white Veterans: No	Health and Retirement Study (HRS) dataset	2000-2012	Dementia Prevalence: 11.6% (95% CI 10.7% to 12.7%) in 2000 8.6% (95% CI 8.2% to 9.4%) in 2012 [age- and sex-standardization]
Plassman 2007 US	Cross-sectional N=856	Age: ≥71 years Sex: 39.3% Race: 87.1% white Veterans: No	Aging, Demographics, and Memory Study (ADAMS) dataset	2001-2003	Dementia Prevalence: 13.9% (95% CI 11.42% to 16.44%)

Abbreviations: CI = Confidence Interval; NR = not reported; SR = systematic review; MA = meta-analysis; VA = Veterans Affairs

KEY QUESTION 2: What is the comparative prevalence of dementia between Veterans with and without TBI?

We identified 2 retrospective cohort studies in US Veterans[7,26] and 1 retrospective cohort study in Swedish men conscripted for military service[28] that compared prevalence of dementia for those with and without a history of TBI (Table 3). Overall, we found the prevalence of dementia was higher in those with TBI than those without. We also found evidence there may be a dose-response relationship between TBIs and dementia; however, this relationship was not consistently seen for all types of dementia.

Two studies[7,26] examined all ages of dementia onset, and 1 study[28] focused on early-onset dementia. The best evidence comes from the 2 US-based studies, both[7,26] of which analyzed data from the National Patient Care Database containing data for all Veterans receiving care at the VA, and one[7] of which also analyzed data from the Traumatic Brain Injury Evaluation database containing data from Veterans who screen positive for TBI. Both studies reported a higher

prevalence of dementia among Veterans with a history of TBI (range: 6% to 16%) than those without (range: 3% to 10%).[7,26] One study also reported a dose-response relationship between TBI and dementia.[7] In adjusted analyses, the risk of developing dementia increased with increased TBI severity (RR: mild TBI without loss of consciousness 2.36 (95% CI 2.10 to 2.66, mild TBI with loss of consciousness 2.51 (95% CI 2.29 to 2.76), moderate to severe TBI 3.77 (95% CI 3.63 to 3.91). Strengths of these studies included the use of nationally representative datasets, valid methods to ascertain dementia cases, and control for several important confounders (including patient demographics, medical comorbidities, and psychiatric conditions). However, we rated these studies[7,26] as fair quality (See Appendix C in Supplemental Materials for complete details), because of a few important limitations that are inherent to their retrospective design, including: (1) that their lack of use of consistent definitions for TBI or dementia comes with an increased risk of bias due to misclassified diagnosis and (2) that we cannot rule out residual confounding due to the lack of data on other unmeasured important genetic and lifestyle risk factors. Because of their consistency, directness, and precision, these studies provide moderate-strength evidence of this association.

The other study[28] conducted in Sweden similarly found in adjusted analyses that the risk of early-onset dementia increased with increased number and severity of TBI (RR: 1 mild TBI 1.5 (95% CI 1.1 to 2.0), > 1 mild TBI 1.8 (95% CI 1.1 to 3.0), 1 severe TBI 2.3 (95% CI 1.5 to 3.6)).[28] However, the clinical importance of these findings is unclear as the effect was not seen in a subgroup analysis of those with Alzheimer's Disease, which is the most common form of dementia among older adults.[64] In addition, it is worth noting the study found the absolute risk of developing dementia after TBI was low (1 in 6,000 men with at least 1 severe TBI was diagnosed with Alzheimer's Disease over > 30 years).[28] We rated this study as fair quality primarily because it was unclear if the sample was nationally representative or geographically diverse and it failed to report how TBIs were ascertained, making it difficult to determine if these patients are similar to patients in other studies or patients currently seen at the VA.

KEY QUESTION 2A: Does the prevalence of dementia in Veterans with TBI vary based on combat deployment history?

No studies were identified to address this question.

KEY QUESTION 2B: Does the prevalence of dementia in Veterans with TBI vary based on timing of dementia onset (*ie*, early vs late)?

We identified no studies that were designed specifically to evaluate the association of TBI and early-onset dementia in US Veterans. We therefore focused on indirect evidence from 4 retrospective cohort studies[8,12,28,35] that assessed the relationship between TBI and early-onset dementia (diagnosis of dementia before age 65), including 1 that involved Swedish men conscripted to military service,[28] 1 among US Veterans that examined a retrospective cohort of those with early or late-onset dementia compared to matched controls ,[8] and 2 others in non-Veterans populations (Table 3). Overall, these studies suggest there may be a relationship between TBI and early-onset dementia, although our confidence in limited due to important methodological limitations of the studies.

The best evidence comes from the previously discussed study of Swedish men conscripted to military service,[28] as this study was conducted in a large population (n=811,622) and adjusted for a variety of potential confounders. As discussed, this study found increasing risk of early-onset dementia with increasing number and severity of TBIs; however, the effect was not seen for those with Alzheimer's Disease, which made up a third of the study population.[28] Study authors could not explain why an effect was not seen for Alzheimer's Disease, although they noted that part of the association between TBI and non-Alzheimer's Disease forms of dementia was likely due to residual confounding (as the effect was attenuated when major comorbidities were controlled for) or through an interaction between TBI and other risk factors.

Another study of Veterans receiving care at a VA memory disorders clinic found that a history of TBI was more likely to be present in those with early-onset dementia than those with late-onset dementia (24% vs 4% respectively).[8] However, this study did not control for any confounders, and even noted that the early-onset group had significantly more cognitive impairment from TBI, alcohol abuse, were more likely to be HIV-positive, and had more frontotemporal lobar degeneration. The study also failed to report how TBIs were ascertained, making it difficult to determine if these patients are similar to patients in other studies or patients currently seen at the VA.

Two additional studies examined civilian data from a national registry of patients seen at Alzheimer's Disease Centers.[12,35] One study[35] found that a history of TBI was more likely to be present in early-onset dementia patients than late-onset dementia patients (OR 1.75, CI 1.47 to 2.07). One additional study paired medical record data with autopsy data to confirm Alzheimer's Disease diagnosis and found that dementia was diagnosed 2.38 years earlier in those with a history of TBI than those without.[12] However, both these studies only controlled for a limited number of confounders (age, sex, and race), so we cannot be certain that the effect is due to TBI rather than other comorbidities. Additionally, in the autopsy-confirmed study, authors note that due to issues in how data were collected in the first 2 years of the study, dementia onset could have preceded TBI.

All 4 studies were rated as fair quality, primarily because they did not adequately control for potential confounders that may contribute to the development of dementia and differ between TBI and non-TBI groups[8,12,35] and because we could not determine if data were nationally representative or geographically diverse.[28]

Table 3. Highlighted Studies Addressing KQ2

Author Year Country	Study Design Sample Size	Demographics	Comparator	Ascertainment of TBI	Ascertainment of Dementia	Follow-up Period	Outcomes
Barnes 2014[26] **US**	Retrospective cohort 188,764	Age: 68 years (avg.) Sex: 96.52% male Race: NR Veterans: Yes	TBI vs no TBI	ICD-9 codes	ICD-9 codes	9 years between 2000-2012	Prevalence of dementia: 16% vs 10% (TBI vs no TBI history) Hazard Ratio for dementia (adjusted): 1.57 (95% CI 1.35 to 1.83) for any TBI
Barnes 2018[7] **US**	Retrospective cohort 357,558	Age: 49.48 (avg.) Sex: 90.7% male Race: 72.48% white Veterans: Yes	TBI (+/- mild, unknown, or moderate/severe) and LOC (+/-, unknown) vs no TBI (propensity matched)	Comprehensive TBI Evaluation database, National Patient Care Database	ICD-9 codes	2001-2014	Prevalence of dementia: 6% vs 3% (TBI vs no TBI history) Hazard Ratio for dementia (adjusted): 3.45 (95% CI 3.33 to 3.57) for any TBI 2.36 (95% CI 2.10-2.66) for mild TBI w/o LOC 2.51 (95% CI 2.29 to 2.76) for mild TBI w/LOC 3.19 (95% CI 3.05 to 3.33) for mild TBI w/unknown LOC 3.77 (95% CI 3.63 to 3.91) for moderate/severe TBI
McMurtray 2006[8] **US**	Retrospective cohort 948	Age: NR Sex: 97.89% male Race: 59.70% white Veterans: Yes	TBI (+/-) and Early- (EOD) vs Late-onset dementia (LOD)	NR	Neurology and psychiatry physicians used MRI results in the process of arriving at the clinical diagnosis	4 years between 2001-2004	Prevalence of TBI: 24% (EOD) vs 4% (LOD), χ^2= 71.60, P<.001

Mendez 2015[35] **US**	Retrospective cohort and matched controls 11,572	Age: 73 (avg.) at initial visit Sex: NR Race: 84% white Veterans: No	TBI (+/-) and Early-onset Alzheimer's Disease (EOAD) vs TBI (+/-) and Late-onset Alzheimer's Disease (LOAD)	National Alzheimer's Coordinating Center Uniform (NACC) database	National Alzheimer's Coordinating Center Uniform (NACC) database	2005-2014	Prevalence of TBI: χ^2= 3.64, P=.056 EOAD vs EOAD matched normal controls: 13.3% vs 11.1% LOAD vs LOAD matched normal controls: 7.7% vs 8.7% Odds ratio of TBI (adjusted): EOAD vs LOAD: 1.75 (95% CI 1.47 to 2.07) EOAD vs EOAD matched normal controls: 1.28 (95% CI 1.00 to 1.57) LOAD vs LOAD matched normal controls: 0.90 (95% CI 0.76 to 1.04)
Nordstrom 2014[28] **Sweden**	Retrospective cohort 811,622	Age: 18 (avg.) at enrollment Sex: 100% male Race: NR Veterans: Yes	TBI (+/-) vs Early-onset dementia (EOD)	ICD-8, 9 and 10 codes	ICD-8, 9 and 10 codes	33 years (median) between 1969-1986	Hazard Ratio for dementia (adjusted): 1.5 (95% CI 1.1 to 2.0) for 1 mild TBI 1.8 (95% CI 1.1 to 3.0) for >1 mild TBIs 2.3 (95% CI 1.5 to 3.6) for 1 severe TBI
Schaffert 2018[12] **US**	Retrospective cohort 2,133	Age: NR Sex: 55% male Race: 95% white Veterans: No	TBI (+/-) and Early-onset Alzheimer's Disease (EOAD)	Self-report	Autopsy-confirmed	2005-2015	Age of dementia symptoms onset (adjusted): 2.35 years earlier in the TBI+ group (P=.01) Age of dementia diagnosis (adjusted): 2.38 years earlier in the TBI+ group (P=.002)

Abbreviations: TBI = EOAD = Early-onset Alzheimer's Disease; EOD = Early-onset dementia; ICD = International classification of diseases; LOAD = Late-onset Alzheimer's Disease; LOC = Loss of consciousness; LOD = Late onset dementia; NACC = National Alzheimer's Coordinating Center; NR = Not reported; TBI = Traumatic brain injury

SUMMARY AND DISCUSSION

This rapid review builds on previous evidence synthesis work[6,27] by focusing on Veteran populations and adding a few key studies in Veterans that were either not yet published[7,33,34] or that used a broader range of analytic methods (*ie*, hazard ratio, prevalence rates).[8,26] Our review found that although no study has directly compared dementia rates in Veterans and non-Veterans in the same sample, estimates from 2 separate sources suggest that dementia rates appear similar in Veterans (10.7%) and non-Veterans (range, 8.8% to 11.6%) aged 65 years and older.[27,33,34] This finding could potentially allay concerns that military service may increase risk of dementia overall. Our review also found that although few studies have focused on evaluating the association between TBI and dementia in military and Veteran populations, findings of those that did[7,26] were consistent with those from a 2017 systematic review by Li et al of worldwide general community studies in suggesting that TBI is associated with increased risk of dementia. Possibly the most interesting contribution from this study is that it observed a dose-response relationship between TBI and dementia diagnosis. Compared to the increased risk of dementia for a mild TBI without loss of consciousness (HR 2.36, 95% CI 1.35 to 1.83), the association between TBI and dementia grew progressively larger with increasing TBI severity to an HR of 3.77 (95% CI 3.63 to 3.91) for moderate/severe TBI. Although the Barnes 2018 study is an important addition to the growing literature supporting a consistent association between TBI and dementia, the body of evidence as a whole still has some remaining important limitations that deserve further attention.

LIMITATIONS

The main methodologic limitation of available evidence is its continued reliance on retrospective data. As noted in these studies themselves, their lack of use of consensus definitions for TBI or dementia due to their retrospective design comes with an increased risk of bias due to misclassified diagnosis.[6,7] Also, although an important strength of the Barnes 2018 study is its use of propensity matching to minimize the potential for confounding based on a large number of key demographic variables and medical and psychiatric comorbidities, we still cannot rule out residual confounding due to the lack of data on other unmeasured important genetic and lifestyle risk factors.

Additionally, there are several important gaps in available evidence. First, no study has directly compared dementia rates in Veteran versus non-Veteran populations. Second, additional research is still critically needed about the potential role of variation in brain injury severity, mode (blast vs non-blast), single versus repeated injury, setting (*ie*, military deployment or not), and dementia onset, and whether TBI is more likely to lead to early-onset dementia than other etiologies. However, in the most recent and largest study to date in Veterans,[7] despite providing the best available evidence about the association between mild TBI and dementia, one of their challenges – inherent to retrospective database analyses – is that they lacked the data necessary to quantify the number, types, or causes of TBIs experienced. The previous gap in data on combat-related TBI may have been due at least in part to TBI reporting, which may be seen as inconsistent with traditional and strong core military culture that promotes values such as a strong commitment to the mission and self-sacrifice.[65,66]

The primary limitations of our findings related to our review methods include (1) our literature search and (2) our scope. First, although our search included multiple databases, our shortened

timeframe precluded searching a more exhaustive range of gray literature sources. Therefore, there is a risk that we may have missed additional relevant studies that have not yet or will not be fully published in peer-reviewed journals. Regarding our scope, our focus on studies of Veterans may limit the generalizability of our findings to a broader range of patients.

CLINICAL AND FUTURE RESEARCH IMPLICATIONS

In addition to the evidence that TBI may increase the risk of dementia in general, some reports have emerged based on civilian data[12] suggesting that the onset of dementia may be accelerated in those with a TBI history. As no study has directly and adequately evaluated the association between TBI and early-onset dementia in US Veterans, this may be one of the highest-priority areas for future research efforts.

As of yet, there is no specific guidance on screening, prevention, and rehabilitation of TBI-associated dementia. A critical area of research to support efforts to develop effective treatment and prevention strategies is to better understand the underlying mechanisms of the observed association between TBI and dementia. Although several plausible mechanisms have been proposed, their evidence has been mixed and inconclusive. [7]

Additionally, to further understand the comparative prevalence of dementia in Veteran and non-Veteran populations, future studies should ideally directly compare prevalence rates from the same population using a cross-sectional or longitudinal design. To improve on the above-described methodological limitations of the studies examining the association between TBI and dementia that are inherent to their retrospective design, future research should use a prospective design that could consistently use consensus definitions for TBI and dementia and account for a broader range of potential confounders.

Although we found no evidence to address the question of whether the association of TBI and dementia varies based on combat deployment history, we are aware of at least 1 ongoing study which is anticipated to begin to address this important gap in knowledge. The Vietnam Era Health Retrospective Observational Study (VE-HEROeS)[67] on lifetime brain injury and dementia diagnosis that is categorized by deployment status plans to analyze existing self-report data from approximately 18,000 Vietnam Veterans, Blue Water Navy Veterans, and Veterans who served elsewhere during the Vietnam Era (1961-1975) (see Appendix D in Supplemental Materials for more details on this and other ongoing studies). Media reports about cases of Chronic Traumatic Encephalopathy (CTE) in active-duty service members[68] have heightened public awareness and concern about risk and raised questions about if/how CTE is related to early-onset dementia and other chronic neurodegenerative diseases. This has increased the urgency to better understand how TBI may increase risk of CTE specifically, as well for other neurodegenerative conditions in general.[17,69] Although this report did not formally evaluate the literature on CTE, we can confirm that we did not identify any studies that have evaluated CTE in relation to TBI. Also, although CTE has been characterized as sharing some clinical similarities with Alzheimer's Disease, it is currently thought to be a distinct clinical entity from Alzheimer's Disease, either early- or late-onset, with a unique pattern of brain pathology detectable upon autopsy.[19] We are aware of a CENC observational study in progress on late neurologic effects of OEF/OIF/OND combat (CENC0001C) that plans to evaluate laboratory, neuroimaging, and electrophysiological testing to determine the role of mTBI in late outcomes

including CTE and other illnesses. Hopefully this and other studies over the next 5-10 years will address knowledge gaps about CTE and their clinical implications. As additional research emerges on the relationships between TBI and CTE, dementia and other clinical neurodegenerative syndromes, including Mild Cognitive Impairment (MCI), consideration of an updated systematic review that covers a broader scope of neurodegenerative syndromes may be warranted.

CONCLUSIONS

Findings from this rapid evidence brief indicate that dementia prevalence is likely similar in Veteran and non-Veteran populations and that risk of dementia is likely increased by TBI. Although there is still room to improve upon persistent methodological limitations inherent to the existing retrospective cohort studies, new research to address the potentially bigger gaps in knowledge about mechanism of association and timing of dementia onset may be of higher priority in informing development of screening, prevention, and rehabilitation efforts.

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Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center and the ESP Center work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Supplemental Materials

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Prepared by:
Evidence Synthesis Program (ESP)
Coordinating Center
Portland VA Health Care System
Portland, OR
Mark Helfand, MD, MPH, MS, Director

Authors:
Kim Peterson, MS
Stephanie Veazie, MPH
Donald Bourne, MPH
Johanna Anderson, MPH

U.S. Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service

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APPENDIX A. SEARCH STRATEGIES

1. Search for current systematic reviews Date Searched: 10/18/18	
Sources:	**Strategy:**
AHRQ	Search: dementia; Alzheimer's; traumatic brain injury; TBI; Veteran
CADTH	Search: dementia; Alzheimer's; traumatic brain injury; TBI; Veteran
NICE (NHS Evidence)	Search: Veteran AND dementia; Veteran AND Alzheimer's; traumatic brain injury AND dementia; TBI AND dementia; traumatic brain injury AND Alzheimer's; TBI AND Alzheimer's
NLM	Search: Veteran AND dementia; Veteran AND Alzheimer's; traumatic brain injury AND dementia; TBI AND dementia; traumatic brain injury AND Alzheimer's; TBI AND Alzheimer's
ECRI Institute	Search: Veteran AND dementia; Veteran AND Alzheimer's; traumatic brain injury AND dementia; TBI AND dementia; traumatic brain injury AND Alzheimer's; TBI AND Alzheimer's
VA Products: VATAP, PBM, HSR&D publications, VA ART Database	A. http://www.hsrd.research.va.gov/research/default.cfm B. http://www.research.va.gov/research_topics/ C. http://art.puget-sound.med.va.gov/default.cfm Search: dementia; Alzheimer's; traumatic brain injury; TBI
MEDLINE: Systematic Reviews KQ1	Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to October 17, 2018> Search Strategy: -- 1 exp Veterans/ (14461) 2 veteran$.ti,ab,kw. (31720) 3 exp Veterans Health/ (1006) 4 (active duty or military or service member$ or soldier$ or national guard or reserv$).ti,ab,kw. (173489) 5 or/1-4 (202846) 6 exp Dementia/ (149164) 7 (dementia or Alzheimer$).ti,ab,kw. (188667) 8 6 or 7 (225955) 9 5 and 8 (2013) 10 (systematic review.ti. or meta-analysis.pt. or meta-analysis.ti. or systematic literature review.ti. or this systematic review.tw. or pooling project.tw. or (systematic review.ti,ab. and review.pt.) or meta synthesis.ti. or meta-analy*.ti. or integrative review.tw. or integrative research review.tw. or rapid review.tw. or umbrella review.tw. or consensus development conference.pt. or practice guideline.pt. or drug class reviews.ti. or cochrane database syst rev.jn. or acp journal club.jn. or health technol assess.jn. or evid rep technol assess summ.jn. or jbi database system rev implement rep.jn. or (clinical guideline and management).tw. or ((evidence based.ti. or evidence-based medicine/ or best practice*.ti. or evidence synthesis.ti,ab.) and (((review.pt. or diseases category/ or behavior.mp.) and behavior mechanisms/) or therapeutics/ or evaluation studies.pt. or validation studies.pt. or guideline.pt. or pmcbook.mp.)) or (((systematic or systematically).tw. or critical.ti,ab. or study selection.tw. or ((predetermined or inclusion) and criteri*).tw. or exclusion criteri*.tw. or main outcome measures.tw. or standard of care.tw. or standards of care.tw.) and ((survey or surveys).ti,ab. or overview*.tw. or review.ti,ab. or reviews.ti,ab. or search*.tw. or handsearch.tw. or analysis.ti. or critique.ti,ab. or appraisal.tw. or (reduction.tw. and (risk/ or risk.tw.) and (death or recurrence).mp.)) and ((literature or articles or publications or publication or bibliography or bibliographies or published).ti,ab. or pooled data.tw. or unpublished.tw. or citation.tw. or citations.tw. or database.ti,ab. or internet.ti,ab. or textbooks.ti,ab. or references.tw. or scales.tw. or papers.tw. or datasets.tw. or trials.ti,ab. or meta-analy*.tw. or (clinical and studies).ti,ab. or treatment

	outcome/ or treatment outcome.tw. or pmcbook.mp.))) not (letter or newspaper article).pt. (326420) 11 9 and 10 (71) 12 limit 11 to english language (69) *******************************
PsycINFO: Systematic Reviews KQ1	Database: PsycINFO <1806 to October Week 2 2018> Search Strategy: --- 1 exp Veterans/ (11834) 2 veteran$.ti,ab,kw. (19086) 3 exp Veterans Health/ (0) 4 (active duty or military or service member$ or soldier$ or national guard or reserv$).ti,ab,kw. (4302981) 5 or/1-4 (4303324) 6 exp Dementia/ (70632) 7 (dementia or Alzheimer$).ti,ab,kw. (89329) 8 6 or 7 (92597) 9 5 and 8 (91857) 10 (systematic review.ti. or meta-analysis.pt. or meta-analysis.ti. or systematic literature review.ti. or this systematic review.tw. or pooling project.tw. or (systematic review.ti,ab. and review.pt.) or meta synthesis.ti. or meta-analy*.ti. or integrative review.tw. or integrative research review.tw. or rapid review.tw. or umbrella review.tw. or consensus development conference.pt. or practice guideline.pt. or drug class reviews.ti. or cochrane database syst rev.jn. or acp journal club.jn. or health technol assess.jn. or evid rep technol assess summ.jn. or jbi database system rev implement rep.jn. or (clinical guideline and management).tw. or ((evidence based.ti. or evidence-based medicine/ or best practice*.ti. or evidence synthesis.ti,ab.) and (((review.pt. or diseases category/ or behavior.mp.) and behavior mechanisms/) or therapeutics/ or evaluation studies.pt. or validation studies.pt. or guideline.pt. or pmcbook.mp.)) or (((systematic or systematically).tw. or critical.ti,ab. or study selection.tw. or ((predetermined or inclusion) and criteri*).tw. or exclusion criteri*.tw. or main outcome measures.tw. or standard of care.tw. or standards of care.tw.) and ((survey or surveys).ti,ab. or overview*.tw. or review.ti,ab. or reviews.ti,ab. or search*.tw. or handsearch.tw. or analysis.ti. or critique.ti,ab. or appraisal.tw. or (reduction.tw. and (risk/ or risk.tw.) and (death or recurrence).mp.)) and ((literature or articles or publications or publication or bibliography or bibliographies or published).ti,ab. or pooled data.tw. or unpublished.tw. or citation.tw. or citations.tw. or database.ti,ab. or internet.ti,ab. or textbooks.ti,ab. or references.tw. or scales.tw. or papers.tw. or datasets.tw. or trials.ti,ab. or meta-analy*.tw. or (clinical and studies).ti,ab. or treatment outcome/ or treatment outcome.tw. or pmcbook.mp.))) not (letter or newspaper article).pt. (116195) 11 9 and 10 (3125) 12 limit 11 to english language (2927) 13 ((prevalence or frequency or cause$ or incidence) adj6 (dementia or Alzheimer$)).ti,ab. (5761) 14 12 and 13 (263) *******************************
Cochrane Database of Systematic Reviews KQ1	Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to October 17, 2018> Search Strategy: --- 1 veteran$.ti,ab,kw. (4) 2 (active duty or military or service member$ or soldier$ or national guard or reserv$).ti,ab,kw. (51)

	3 1 or 2 (54) 4 (dementia or Alzheimer$).ti,ab,kw. (222) 5 3 and 4 (0) ***************************
Systematic Reviews (Journal)	Search: dementia; Alzheimer's; traumatic brain injury; TBI; Veteran

2. Systematic reviews currently under development (forthcoming reviews & protocols) **Date Searched: 10/18/18**	
Sources:	**Strategy:**
PROSPERO (SR registry)	Search: Veteran AND dementia; Veteran AND Alzheimer's; traumatic brain injury AND dementia; TBI AND dementia; traumatic brain injury AND Alzheimer's; TBI AND Alzheimer's
DoPHER (SR Protocols)	Search: dementia; Alzheimer's; traumatic brain injury; TBI; Veteran

3. Current Guidelines **Date Searched: 10/18/18**	
Sources:	**Strategy:**
VA/DoD Clinical Practice Guidelines	Relevant Results: Management of Concussion-mild Traumatic Brain Injury (mTBI) (2016)

4. Current primary literature **Date Searched: 10/18/18**	
Sources:	**Strategy:**
MEDLINE: non SR KQ2	Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to October 17, 2018> Search Strategy: -- 1 (((traumatic brain injury or TBI) and (onset or early-onset)) adj6 (dementia or Alzheimer$)).mp. (67) 2 limit 1 to english language (66) 3 limit 2 to humans (46) ***************************
PsycINFO KQ2	Database: PsycINFO <1806 to October Week 2 2018> Search Strategy: -- 1 (((traumatic brain injury or TBI) and (onset or early-onset)) adj6 (dementia or Alzheimer$)).mp. (49) 2 limit 1 to english language (48) ***************************
CCRCT	Database: EBM Reviews - Cochrane Central Register of Controlled Trials <June 2018> Search Strategy: -- 1 (((traumatic brain injury or TBI) and (onset or early-onset)) adj6 (dementia or Alzheimer$)).mp. (5) 2 limit 1 to english language (2) ***************************
Google Scholar	Search: prevalence of dementia in veterans; prevalence of Alzheimer's in veterans; dementia risk in Veterans; Alzheimer's risk in Veterans; traumatic brain injury AND

	dementia; TBI AND dementia; traumatic brain injury AND Alzheimer's; TBI AND Alzheimer's (limited review to first 500 results)

5. Supplemental Searching	
Date Searched: 10/18/18	
Sources:	**Strategy:**
MEDLINE: KQ1	Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to December 06, 2018> Search Strategy: -- 1 exp Dementia/ (149916) 2 (dementia or Alzheimer$).ti,ab,kw. (190779) 3 1 or 2 (228177) 4 prevalence.ti,ab,kw. (551575) 5 exp PREVALENCE/ (260209) 6 4 or 5 (630516) 7 (systematic review.ti. or meta-analysis.pt. or meta-analysis.ti. or systematic literature review.ti. or this systematic review.tw. or pooling project.tw. or (systematic review.ti,ab. and review.pt.) or meta synthesis.ti. or meta-analy*.ti. or integrative review.tw. or integrative research review.tw. or rapid review.tw. or umbrella review.tw. or consensus development conference.pt. or practice guideline.pt. or drug class reviews.ti. or cochrane database syst rev.jn. or acp journal club.jn. or health technol assess.jn. or evid rep technol assess summ.jn. or jbi database system rev implement rep.jn. or (clinical guideline and management).tw. or ((evidence based.ti. or evidence-based medicine/ or best practice*.ti. or evidence synthesis.ti,ab.) and (((review.pt. or diseases category/ or behavior.mp.) and behavior mechanisms/) or therapeutics/ or evaluation studies.pt. or validation studies.pt. or guideline.pt. or pmcbook.mp.)) or (((systematic or systematically).tw. or critical.ti,ab. or study selection.tw. or ((predetermined or inclusion) and criteri*).tw. or exclusion criteri*.tw. or main outcome measures.tw. or standard of care.tw. or standards of care.tw.) and ((survey or surveys).ti,ab. or overview*.tw. or review.ti,ab. or reviews.ti,ab. or search*.tw. or handsearch.tw. or analysis.ti. or critique.ti,ab. or appraisal.tw. or (reduction.tw. and (risk/ or risk.tw.) and (death or recurrence).mp.)) and ((literature or articles or publications or publication or bibliography or bibliographies or published).ti,ab. or pooled data.tw. or unpublished.tw. or citation.tw. or citations.tw. or database.ti,ab. or internet.ti,ab. or textbooks.ti,ab. or references.tw. or scales.tw. or papers.tw. or datasets.tw. or trials.ti,ab. or meta-analy*.tw. or (clinical and studies).ti,ab. or treatment outcome/ or treatment outcome.tw. or pmcbook.mp.))) not (letter or newspaper article).pt. (331841) 8 3 and 6 and 7 (565) 9 limit 8 to english language (541) 10 limit 9 to yr="2016 -Current" (170) ***************************

APPENDIX B. LIST OF EXCLUDED STUDIES

Exclude reasons: 1 = Ineligible population, 2 = Ineligible intervention, 3 = Ineligible comparator, 4 = Ineligible outcome, 5 = Ineligible setting (*eg,* inpatient), 6 = Ineligible study design (*eg,* case report, qualitative methods), 7 = Ineligible publication type (*eg,* abstract, editorial, letter, narrative review, *etc*) 8 = Outdated or ineligible systematic review, 9 = Non-English language, 10 = Critique or rebuttal of paper

#	Citation	Exclude reason
1.	Blakemore A, Kenning C, Mirza N, Daker-White G, Panagioti M, Waheed W. Dementia in UK South Asians: a scoping review of the literature. BMJ Open. 2018;8(4):e020290.	E6
2.	Brayne C. Traumatic brain injury and dementia. The Lancet Psychiatry. 2018;5(5):383-384.	E7
3.	Elder GA. Update on TBI and cognitive impairment in military veterans. Curr Neurol Neurosci Rep. 2015;15(10):68.	E7
4.	Gardner RC, Yaffe K. Traumatic brain injury may increase risk of young onset dementia. Annals of Neurology. 2014;75(3):339-341.	E7
5.	Kenney K, Diaz-Arrastia R. Risk of dementia outcomes associated with traumatic brain injury during military service. JAMA Neurol. 2018.	E7
6.	Kiejna A, Frydecka D, Adamowski T, et al. Epidemiological studies of cognitive impairment and dementia across eastern and middle European countries (epidemiology of dementia in eastern and middle European countries). International Journal of Geriatric Psychiatry. 2011;26(2):111-117.	E7
7.	Kiraly M, Kiraly SJ. Traumatic brain injury and delayed sequelae: a review--traumatic brain injury and mild traumatic brain injury (concussion) are precursors to later-onset brain disorders, including early-onset dementia. Thescientificworldjournal. 2007;7:1768-1776.	E7
8.	Lang L, Clifford A, Wei L, et al. Prevalence and determinants of undetected dementia in the community: a systematic literature review and a meta-analysis. BMJ Open. 2017;7(2):e011146.	E1
9.	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.	E4
10.	LoBue C, Cullum C, Didehbani N, et al. Neurodegenerative dementias after traumatic brain injury. The Journal of Neuropsychiatry and Clinical Neurosciences. 2018;30(1):7-13.	E7
11.	McKee AC, Robinson ME. Military-related traumatic brain injury and neurodegeneration. Alzheimers Dement. 2014;10(3 Suppl):S242-253.	E7
12.	Prince M, Ali GC, Guerchet M, Prina AM, Albanese E, Wu YT. Recent global trends in the prevalence and incidence of dementia, and survival with dementia. Alzheimer's Research & Therapy. 2016;8(1):23.	E4
13.	Sansoni J, Duncan C, Grootemaat P, Capell J, Samsa P, Westera A. Younger onset dementia. American Journal of Alzheimer's Disease & Other Dementias. 2016;31(8):693-705.	E4
14.	Stephan BCM, Birdi R, Tang EYH, et al. Secular trends in dementia prevalence and incidence worldwide: a systematic review. Journal of Alzheimer's Disease. 2018;66(2):653-680.	E4
15.	Weiner MW, Harvey D, Hayes J, et al. Effects of traumatic brain injury and	E4

#	Citation	Exclude reason
	posttraumatic stress disorder on development of Alzheimer's disease in Vietnam veterans using the Alzheimer's disease neuroimaging initiative: Preliminary report. Alzheimers Dement (NY). 2017;3(2):177-188.	
16.	Weiner MW, Veitch DP, Hayes J, et al. Effects of traumatic brain injury and posttraumatic stress disorder on Alzheimer's disease in veterans, using the Alzheimer's disease neuroimaging initiative. Alzheimer's & dementia: the journal of the Alzheimer's Association. 2014;10(3):S226-S235.	E7

APPENDIX C. QUALITY ASSESSMENT OF INCLUDED STUDIES

Quality Assessment of Systematic Reviews

AMSTAR 2 Tool[1]

Williamson 2018[2]

1. **Did the research questions and inclusion criteria for the review include the components of PICO?**

For Yes:	Optional (recommended)	
☑ Population	☑ Timeframe for follow-up	☑ Yes
(NA) ☐ Intervention		☐ No
(NA) ☐ Comparator group		
☑ Outcome		

2. **Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?**

For Partial Yes:	For Yes:	
The authors state that they had a written protocol or guide that included ALL the following:	As for partial yes, plus the protocol should be registered and should also have specified:	☐ Yes
		☐ Partial Yes
☐ review question(s)	☐ a meta-analysis/synthesis plan, if appropriate, *and*	☑ No
☐ a search strategy		
☐ inclusion/exclusion criteria	☐ a plan for investigating causes of heterogeneity	
☐ a risk of bias assessment	☐ justification for any deviations from the protocol	

3. **Did the review authors explain their selection of the study designs for inclusion in the review?**

For Yes, the review should satisfy ONE of the following:	
☐ *Explanation for* including only RCTs	☑ Yes
☑ OR *Explanation for* including only NRSI	☐ No
☐ OR *Explanation for* including both RCTs and NRSI	

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):

- ☑ searched at least 2 databases (relevant to research question)
- ☑ provided key word and/or search strategy
- ☑ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):

- ☑ searched the reference lists / bibliographies of included studies
- ☐ searched trial/study registries
- ☑ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☑ conducted search within 24 months of completion of the review

☐ Yes
☑ Partial Yes
☐ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:

- ☑ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

☑ Yes
☐ No

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:

☑ at least two reviewers achieved consensus on which data to extract from included studies

☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

☑ Yes

☐ No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:

☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:

☐ Justified the exclusion from the review of each potentially relevant study

☐ Yes

☐ Partial Yes

☑ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):

☑ described populations

(NA) ☐ described interventions

(NA) ☐ described comparators

☑ described outcomes

☑ described research designs

For Yes, should also have ALL the following:

☑ described population in detail

(NA) ☐ described intervention in detail (including doses where relevant)

(NA) ☐ described comparator in detail (including doses where relevant)

(NA) ☐ described study's setting

☐ timeframe for follow-up

☐ Yes

☑ Partial Yes

☐ No

9. **Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?**

RCTs

For Partial Yes, must have assessed RoB from

- ☐ unconcealed allocation, *and*
- ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)

For Yes, must also have assessed RoB from:

- ☐ allocation sequence that was not truly random, *and*
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

- ☐ Yes
- ☐ Partial Yes
- ☐ No
- ☑ Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:

- ☑ from confounding, *and*
- ☑ from selection bias

For Yes, must also have assessed RoB:

- ☑ methods used to ascertain exposures and outcomes, *and*
- ☑ selection of the reported result from among multiple measurements or analyses of a specified outcome

- ☑ Yes
- ☐ Partial Yes
- ☐ No
- ☐ Includes only RCTs

10. **Did the review authors report on the sources of funding for the studies included in the review?**

For Yes

- ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

- ☐ Yes
- ☑ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs
For Yes:

☐ The authors justified combining the data in a meta-analysis

    ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.

    ☐ AND investigated the causes of any heterogeneity

☐ Yes
☐ No
☑ No meta-analysis conducted

For NRSI
For Yes:

☑ The authors justified combining the data in a meta-analysis

    ☑ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present

    ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available

(NA) ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

☐ Yes
☑ No
☐ No meta-analysis conducted

12. **If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?**

For Yes:	
☐ included only low risk of bias RCTs	☑ Yes
☑ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☐ No ☐ No meta-analysis conducted

13. **Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?**

For Yes:	
☐ included only low risk of bias RCTs	☑ Yes
☑ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☐ No

14. **Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?**

For Yes:	
☐ There was no significant heterogeneity in the results	
☑ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☑ Yes ☐ No

15. **If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?**

For Yes:

☑ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

    ☑ Yes

    ☐ No

    ☐ No meta-analysis conducted

16. **Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?**

For Yes:

☐ The authors reported no competing interests OR

☐ The authors described their funding sources and how they managed potential conflicts of interest

    ☐ Yes

    ☑ No

Quality Assessment of Observational Studies

Author Year	Selection bias 1. Was the sample frame appropriate to address the target population? 2. Were study participants sampled in an appropriate way? 3. Was the sample size adequate (nationally representative or geographically diverse)? 4. Were the study subjects and the setting described in detail?	Detection bias 5. Were valid methods used for the identification of the condition (dementia)? 6. Was the condition (dementia) measured in a standard, reliable way for all participants?	Confounding bias 7. Is confounding of the effect of intervention unlikely in this study? 8. Are groups balanced in terms of factors that might bias the exposure and outcome association? 9. Are the appropriate confounding factors reported and adjusted for in study design or analysis? 10. Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	Appropriateness of data analysis 11. Was the data analysis conducted with sufficient coverage of the identified sample? 12. Was there appropriate statistical analysis? 13. Was the response rate adequate, and if not, was the low response rate managed appropriately?	Overall Rating
KQ1					
Hudomiet, 2018[3]	Yes Nationally representative sample.	Unclear Telephone Interview for Cognitive Status (TICS) a 27-point cognitive scale that included an immediate and delayed 10-noun free recall test, a serial seven subtraction test, and a backwards count from 20 test.	NA	Yes	Fair
Langa, 2017[4]	Yes Nationally representative sample.	Unclear Telephone Interview for Cognitive Status (TICS) a 27-point cognitive scale that included an immediate and delayed 10-noun free recall test, a serial seven subtraction test, and a backwards count from 20 test.	NA	Yes	Fair

Author Year	Selection bias 1. Was the sample frame appropriate to address the target population? 2. Were study participants sampled in an appropriate way? 3. Was the sample size adequate (nationally representative or geographically diverse)? 4. Were the study subjects and the setting described in detail?	Detection bias 5. Were valid methods used for the identification of the condition (dementia)? 6. Was the condition (dementia) measured in a standard, reliable way for all participants?	Confounding bias 7. Is confounding of the effect of intervention unlikely in this study? 8. Are groups balanced in terms of factors that might bias the exposure and outcome association? 9. Are the appropriate confounding factors reported and adjusted for in study design or analysis? 10. Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	Appropriateness of data analysis 11. Was the data analysis conducted with sufficient coverage of the identified sample? 12. Was there appropriate statistical analysis? 13. Was the response rate adequate, and if not, was the low response rate managed appropriately?	Overall Rating
Plassman, 2007[5]	Yes Nationally representative sample.	Yes A 3-4 hour in-home neuropsychological and clinical assessment as well as expert clinician adjudication	NA	Yes	Fair
KQ2					
Barnes, 2014[6]	Yes National VHA database, random sample of 200,000 Veterans aged 55 and older, no dementia at baseline.	Yes ICD-9 codes.	Yes Adjusted for demographics, medical comorbidities, and psychiatric conditions.	Yes	Fair
Barnes, 2018[7]	Yes All VHA pts from 1 TBI and 1 general patient database.	Yes ICD-9 codes.	Yes Adjusted for demographics, medical comorbidities, and psychiatric conditions.	Yes	Fair

Author Year	Selection bias 1. Was the sample frame appropriate to address the target population? 2. Were study participants sampled in an appropriate way? 3. Was the sample size adequate (nationally representative or geographically diverse)? 4. Were the study subjects and the setting described in detail?	Detection bias 5. Were valid methods used for the identification of the condition (dementia)? 6. Was the condition (dementia) measured in a standard, reliable way for all participants?	Confounding bias 7. Is confounding of the effect of intervention unlikely in this study? 8. Are groups balanced in terms of factors that might bias the exposure and outcome association? 9. Are the appropriate confounding factors reported and adjusted for in study design or analysis? 10. Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	Appropriateness of data analysis 11. Was the data analysis conducted with sufficient coverage of the identified sample? 12. Was there appropriate statistical analysis? 13. Was the response rate adequate, and if not, was the low response rate managed appropriately?	Overall Rating
McMurtray, 2006[8]	No Sampling appropriate (all patients in 4-year period at memory clinic). Study was only conducted in 1 VA. Not a lot of descriptive data of patient comorbidities etc.	Yes Patients had impairment in 2 or more areas of cognition that caused social/occupational functioning.	No Almost no data on comorbidities, no adjustment for confounders in data analyses.	Yes	Fair
Mendez, 2015[9]	Yes National Alzheimer's database (populated from NIA-funded Alzheimer's Disease Centers).	Yes "Clinically probable AD dementia" diagnosed at an Alzheimer's center seems appropriate.	No Matched controls on gender and years of education (within three years), but no data on comorbidities.	No They didn't statistically compare EOD vs LOD on baseline characteristics or control for confounders. Hard to say what's driving the difference in TBI between those groups.	Fair
Nordstrom, 2014[10]	Unclear Large sample, but not enough information to determine if it's nationally representative.	Yes ICD 8, 9, 10 codes for vascular dementia, alcohol dementia, and dementia of unspecified type but not Lewy bodies, etc.	Yes Adjusted for demographics, medical comorbidities, psychiatric conditions, and family history.	Yes	Fair

Author Year	Selection bias 1. Was the sample frame appropriate to address the target population? 2. Were study participants sampled in an appropriate way? 3. Was the sample size adequate (nationally representative or geographically diverse)? 4. Were the study subjects and the setting described in detail?	Detection bias 5. Were valid methods used for the identification of the condition (dementia)? 6. Was the condition (dementia) measured in a standard, reliable way for all participants?	Confounding bias 7. Is confounding of the effect of intervention unlikely in this study? 8. Are groups balanced in terms of factors that might bias the exposure and outcome association? 9. Are the appropriate confounding factors reported and adjusted for in study design or analysis? 10. Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	Appropriateness of data analysis 11. Was the data analysis conducted with sufficient coverage of the identified sample? 12. Was there appropriate statistical analysis? 13. Was the response rate adequate, and if not, was the low response rate managed appropriately?	Overall Rating
Schaffert, 2018[11]	Yes National Alzheimer's database (populated from NIA-funded Alzheimer's Disease Centers).	Yes Diagnoses made by team of physicians and autopsy-confirmed	No Adjusted for sex, education, and race, but not comorbidities.	Yes	Fair

Abbreviations: TBI = traumatic brain injury; EOD = early-onset Alzheimer's; LOD = late-onset Alzheimer's; ICD = International Classification of Disease; VA = Veterans Affairs; Veterans Health Administration; NIA = National Institute on Aging

APPENDIX D. ONGOING STUDIES/EXISTING REGISTRIES

PI or Researcher Institution	Study Title Identifier	Population	Comparator	Outcomes of Interest	Estimated completion
William Walker[12,13] Virginia Commonwealth University; McGuire VA Medical Center	Chronic Effects of Neurotrauma Consortium (CENC) Multi-Centre Observational Study	US Veterans who served in recent military conflicts	TBI vs no TBI	Chronic and late-life effects of mild traumatic brain injury (mTBI), including those that may stem from neurodegeneration such as dementia or CTE.	NA: objective is to create a comprehensive database for researchers.
Rudy Rull[14] Naval Health Research Center	Millennium Cohort Study	US military service members	TBI vs no TBI	Collected information on TBIs, but not on dementia. However, dementia outcomes could be added.	Enrollment ended in 2014 and participants will be followed for 21 years.
David Weir[15] University of Michigan	Health and Retirement Study (HRS) and the Aging, Demographics, and Memory Study (ADAMS)	US civilians	NA	Prevalence of dementia.	NA: objective is to create a comprehensive database for researchers.
Raymond Rosen[16] VA Boston Healthcare System; New England Research Institutes; Department of Defense	Project VALOR (Veterans' After-discharge Longitudinal Registry)	US Veterans from Operation Iraqi Freedom/ Operation Enduring Freedom	TBI vs no TBI	Collected information on TBIs, but not on dementia. However, dementia outcomes could be added.	NA: objective is to create a comprehensive database for researchers.
Mohammed Ahmed[17] University of California, San Diego	National Alzheimer's Coordinating Center (NACC) Database	US civilians	TBI vs no TBI	Collected information on the progression and diagnosis of dementia.	NA: objective is to create a comprehensive database for researchers.
Victoria Davey[18] Veteran Affairs Office of Patient Care Services	Vietnam Era Health Retrospective Observational Study (VE-HEROeS) NCT02825602	US Veterans who served during the Vietnam era	TBI vs no TBI	Dementia	TBD: Study is active, not recruiting.

APPENDIX E. PEER REVIEW COMMENT TABLE

Comment #	Reviewer #	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1	1	Yes	*None*
2	2	Yes	*None*
3	3	Yes	*None*
4	4	Yes	*None*
5	5	Yes	*None*
Is there any indication of bias in our synthesis of the evidence?			
6	1	No	*None*
7	2	No	*None*
8	3	No	*None*
9	4	No	*None*
10	5	No	*None*
Are there any published or unpublished studies that we may have overlooked?			
11	1	Yes - Most recent K Yaffe on sex differences might be cconsidered	*Thank you. We have added the following reference to the background section where we had already identified sex as a potential confounder of the relationship between TBI and dementia.* *Snyder HM, Asthana S, Bain L, et al. Sex biology contributions to vulnerability to Alzheimer's disease: A think tank convened by the Women's Alzheimer's Research Initiative. Alzheimer's & dementia: the journal of the Alzheimer's Association. 2016;12(11):1186-1196.*
12	2	No	*None*
13	3	No	*None*
14	4	Yes - They are embedded in my comments	*See comments in "additional suggestions or comments" section.*
15	5	No	*None*
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.			
16	1	Accept as is	*None*
17	2	None, this report includes all of the relevant references and presents the material in the appropriate scientific manner. Highly readable format and clear conclusions.	*None*

18	3	Page 1 line 46 How about the rate of EOD	*We added the sentence "No studies were identified on the comparative prevalence of dementia among younger (<65 years) Veteran and civilian populations" to both the Executive Summary and Findings sections.*
19	3	Page 2 line 19 and the Prospective Chronic Effects (instead of "and the Chronic Effects of Neurotrauma Consortium (CENC))	*We clarified that research from VE-HEROeS is retrospective and research from CENC is prospective.*
20	3	Page 2 line 46 6 to 16%	*Corrected so this says "6 to 16%."*
21	3	Page 5 line 13 delete "such as PTSD"	*PTSD is one example of a mental health condition whose symptoms overlap with TBI. However, we deleted the specific mention of it here as the important point is that TBI and dementia have overlapping symptoms.*
22	3	Page 5 line 25 along with academic and private entities	*Changed "partners" to "entities."*
23	3	Page 5 lines 43-45 Incorrect, CTE goes back to the 1920's	*Deleted "relatively newly identified."*
24	3	Page 17 lines 27-28 Amyloid is not associated with TBI dementia or the loosely described condition of CTE. This study has many problems and probably should be avoided.	*We deleted this sentence and instead reference the Barnes 2018 study, which describes other potential causal pathways.*
25	3	Page 17 57-60 (the two mentions of "dementia") Should read Alzheimer's Disease, not dementia	*Changed to "Alzheimer's Disease."*
26	3	Page 18 line 5 CENC0001	*Changed to "CENC0001"*
27	4	Given the study limitations, the report could include MCI and other clinical neurodegenerative syndromes in relation to TBI.	*To the "Clinical and Future Research Implications" section of the Discussion, we added a sentence suggesting the need for an updated systematic review in the future that has a broader scope of neurodegenerative syndromes, including MCI.*
28	4	It would also be informative for the authors to extract the confounding variables of most concern.	*We reported information on which confounders were controlled for in each study in "Appendix C: Quality Assessment of Included Studies" which appears in the Supplementary Materials. In cases where authors did not adequately control for confounders, we noted which of these confounders were of most concern.*
29	5	excellent report	*None*

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