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14. ABSTRACT

Up to 20% of young veterans have had a traumatic brain injury (TBI), with many older veterans having TBI as well. Some epidemiological studies have reported a link between TBI and increased risk of dementia even after years of active life post injury, however, few have examined what factors may increase or decrease the risk of dementia after TBI. In recent decades, as the country has become more racially and ethnically diverse, so has the U.S. military. However, no studies have examined how race and ethnicity may influence the TBI outcomes and risk of developing dementia. Findings have linked TBI with negative socioeconomic, medical and psychiatric consequences. Yet, these factors also have been identified independently as risk factors for cognitive impairment. This new and unique research collaboration will leverage two established epidemiological datasets to investigate factors associated with adverse cognitive outcomes among veterans with head injuries. Our overall hypothesis is that veterans who are non-white, have lower socioeconomic status and education, and those with greater psychiatric and medical comorbidities will have a higher risk of dementia after TBI. Further, we hypothesize that these differences will still be present after accounting for early life exposures and genetics by studying a large cohort of 3000 twin pairs. Finally, we will determine the population attributable risk (PAR) or proportion of dementia attributable to TBI, both among Veterans and non-veterans. This estimate will allow us to compare TBI to other important risk factors in order to design better prevention and intervention strategies and help highlight the public health significance of TBI.

15. SUBJECT TERMS

Dementia, aging, cognitive impairment (CI), Alzheimer's disease (AD), traumatic brain injury (TBI)

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- **INTRODUCTION:** Up to 20% of young veterans have had a traumatic brain injury (TBI), with many older veterans having TBI as well. Some epidemiological studies have reported a link between TBI and increased risk of dementia even after years of active life post injury, however, few have examined what factors may increase or decrease the risk of dementia after TBI. In recent decades, as the country has become more racially and ethnically diverse, so has the U.S. military. However, no studies have examined how race and ethnicity may influence the TBI outcomes and risk of developing dementia. Findings have linked TBI with negative socioeconomic, medical and psychiatric consequences. Yet, these factors also have been identified independently as risk factors for cognitive impairment. This new and unique research collaboration will leverage two established epidemiological datasets to investigate factors associated with adverse cognitive outcomes among veterans with head injuries. Our overall hypothesis is that veterans who are non-white, have lower socioeconomic status and education, and those with greater psychiatric and medical comorbidities will have a higher risk of dementia after TBI. Further, we hypothesize that these differences will still be present after accounting for early life exposures and genetics by studying a large cohort of 3000 twin pairs. Finally, we will determine the population attributable risk (PAR) or proportion of dementia attributable to TBI, both among Veterans and non-veterans. This estimate will allow us to compare TBI to other important risk factors in order to design better prevention and intervention strategies and help highlight the public health significance of TBI.

- **KEYWORDS:** Dementia, aging, cognitive impairment (CI), Alzheimer's disease (AD), traumatic brain injury (TBI)

- **ACCOMPLISHMENTS:**

  - **What were the major goals of the project?**

    - Task 1: Planning and Regulatory Review (Months 1-5)
    - Task 2: Aim 1 - To determine the contribution of sociodemographic factors such as race, ethnicity, education, and socioeconomic status (SES) to the association between TBI and dementia in the VA TBI Cohort. (Months 5-15)
    - Task 3: Aim 2 - Determine the contribution of medical and psychiatric conditions to the association between TBI and dementia in the VA TBI Cohort. (Months 8-24)
    - Task 4: Aim 3 - Capitalizing on the twin design, determine the contribution of sociodemographic factors such as SES and education to the association between TBI and risk of cognitive decline and dementia in the Twin Registry. (Months 6-15)
    - Task 5: Aim 4 - Using the Twin Registry, to determine the contribution of medical and psychiatric conditions to the association between TBI and cognitive decline/dementia. (Months 9-24)
    - Task 6: Aim 5 - Estimate the attributable risk of TBI on dementia among veterans and the portion of that risk attributable to each of the mediating or moderating variables including medical and psychiatric comorbidities. (Months 22-36)

  - **What was accomplished under these goals?**

    This project was extremely productive, and we had an excellent working partnership between the UCSF and Duke groups. Over the course of this project, we examined many factors that affect the relationship between traumatic brain injury (TBI) and late-life dementia, described in six peer-reviewed publications.

    - Aim 1: In our first study (Kornblith et al., 2020; Appendix 1) we examined the effects of sex, and race on risk of dementia after TBI, finding that in a large, nation-wide cohort of older Veterans, all race groups with TBI had increased risk of dementia diagnosis, but there was an interaction with White Veterans at greatest risk for dementia following TBI.

    - Aim 3: The next study (Plassman et al., 2022; Appendix 2) was completed in a cohort of older Veteran twins. The findings suggest that non-AD mechanisms may underlie the association between TBI and dementia, potentially providing insight into inconsistent results from prior studies.

- Aim 2: Another manuscript (Kornblith et al., 2022; Appendix 3) studied the relationship between TBI, cardiovascular disease (CVD) and dementia in older Veterans, finding that TBI and CVD increase dementia risk in an additive manner, but CVD does not explain much of the association between TBI and dementia.

- Aim 2: The fourth manuscript (Albrecht et al., 2022; Appendix 4) compared different control groups and risk of dementia, showing that the estimated effect of TBI on incident dementia was strongly impacted by the choice of the comparison group.

- Aim 5: The fifth study was a systematic review and meta-analysis (Gardner et al., 2023; Appendix 5) of risk of post-TBI dementia with the aim of specifically investigating contributors to heterogeneity including age, sex, and veteran status. Overall, age, sex, region, TBI exposure ascertainment method, and dementia outcome ascertainment method all contributed to heterogeneity.

- Aim 4: The most recent publication (Chanti-Ketterl et al., 2023; Appendix 6) from this project examined the association between TBI and cognitive performance in older male veteran twins accounting for medical and psychiatric conditions. The findings support an association on the impact of TBI on lower cognitive score and the rapidity of cognitive decline in later life. The results in monozygotic pairs, who share all genes and many exposures particularly in early life, provide additional evidence of a causal relationship between TBI and poorer late life cognitive outcomes.

- **What opportunities for training and professional development has the project provided?**
  - Dr. Marianne Chanti-Ketterl, a junior investigator at Duke, conducted the analyses examining lifetime history of TBI and cognitive change over time, then drafted and published the manuscript. Her work on this project in risk factors for late life cognitive impairment led to her appointment as a RCMAR scientist for the USC-AD cohort 2021-2022. Dr. Erica Kornblith, a junior investigator at UCSF and the SFVAMC, published two manuscripts in well-respected journals. During this project she collaborated with this group's experienced team of researchers, gaining knowledge about traumatic brain injury, Veteran's health, and working with large administrative datasets.
- **How were the results disseminated to communities of interest?**
  - For this project we selected national and international meetings to disseminate our work through poster and oral presentations in which a broad range of multidisciplinary researchers and clinicians invested in reducing the effects of traumatic brain injury on cognitive aging and improving Veterans' health would be present. We submitted our manuscripts to journals that also target multidisciplinary researchers and clinicians who are invested in improving TBI outcomes and Veterans' health.
- **What do you plan to do during the next reporting period to accomplish the goals?**
  - N/A Final Report

- **IMPACT:**
  - **What was the impact on the development of the principal discipline(s) of the project?**
    - Nothing to report
  - **What was the impact on other disciplines?**
    - Nothing to report
  - **What was the impact on technology transfer?**
    - Nothing to report

- **What was the impact on society beyond science and technology?**
    - Nothing to report

- **CHANGES/PROBLEMS:**
    - **Changes in approach and reasons for change**
        - Nothing to report
    - **Actual or anticipated problems or delays and actions or plans to resolve them**
        - Nothing to report
    - **Changes that had a significant impact on expenditures**
        - Nothing to report
    - **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
        - N/A

- **PRODUCTS:**
    - **Publications, conference papers, and presentations**
        - **Journal publications.**

          Kornblith, E., Peltz, C., Xia, F., Plassman, B., Novakovic-Apopain, T., Yaffe, K. Sex, Race, and Risk of Dementia after Traumatic Brain Injury among Older Veterans. *Neurology*, 2020, 95(13).

          Plassman, BL., Chanti-Ketterl, M., Pieper, CF, Yaffe, K. Traumatic Brain Injury and Dementia Risk in Twins - Controlling for Genetic and Early Life Non-Genetic Factors. *Alzheimer's and Dementia*, 2022, 1-9.

          Kornblith E, Bahorik A, Li Y, Peltz CB, Barnes DE, Yaffe K. Traumatic Brain Injury, Cardiovascular Disease, and Risk of Dementia among Older US Veterans. Brain Injury, 2022. (https://doi.org/10.1080/02699052.2022.2033842).

          Albrecht JS, Gardner RC, Weibe D, Bahorik A, Xia F, Yaffe K. Comparison Groups Matter in Traumatic Brain Injury Research: An Example with Dementia. Journal of Neurotrauma, 2022; 39:1-6. (DOI: 10.1089/neu.2022.010).

          Gardner R, Bahorik A, Kornblith E, Allen I, Plassman B, Yaffe K. Systematic review, meta-analysis, and population attributable risk of dementia associated with traumatic brain injury in Civilians and Veterans. *Journal of Neurotrauma,* 2023; 40(7-8):620-634.

          Chanti-Ketterl, M., Pieper, CF, Yaffe, K., Plassman, BL. Traumatic Brain Injury and Cognitive Aging Trajectories Among Older Veteran Men – A Twin Study Accounting for Genetics and Medical Conditions. Neurology, 2023; 101(18):e1761-e1770.

        - **Books or other non-periodical, one-time publications.**

          Nothing to report

- **Other publications, conference papers, and presentations.**

  Chanti-Ketterl, M., Pieper, CF, Yaffe, K., Plassman, BL. Traumatic Brain Injury and Cognitive Aging Among Older Veteran Men – A Twin Study Accounting for Genetics and Medical Conditions. Accepted for presentation at the 2023 Alzheimer's Association International Conference, Amsterdam, The Netherlands.

  Gardner RC, Bahorik AL, Mangal P, Allen IE, Yaffe K. Novel insights into risk of dementia after traumatic brain injury: a systematic review, meta-analysis, and heterogeneity analysis. Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 16 (S110). 2020 Alzheimer's Association International Conference.

  Chanti-Ketterl, M., Pieper, CF, Yaffe, K, Plassman, BL. (2020) TBI and Increased Risk of Non-Alzheimer's disease dementia in older male twins. Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 16 (S110). 2020 Alzheimer's Association International Conference.

- **Website(s) or other Internet site(s)**

  Nothing to report

- **Technologies or techniques**
  Nothing to report

- **Inventions, patent applications, and/or licenses**
  Nothing to report

- **Other Products**

  - Duke compiled approximately 20 years of longitudinal data collection for analyses for this project. The researchers have cleaned and finalized data containing information on demographics, cognitive screening scores traumatic brain injuries, and diagnoses of dementia for over 15,000 twins. UCSF utilized a database containing demographic, psychiatric, medical information, etc., for nearly 2 million veterans who received healthcare in the VA from 2005-2015. The project researchers have used this database for analyses, selected subsamples, and created variables as appropriate for each project.

- **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

  - **What individuals have worked on the project?**

Name:	Kristine Yaffe
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	KYAFFE
Nearest person month worked:	1
Contribution to Project:	Dr. Yaffe, in coordination with Dr. Plassman, provides scientific leadership and input on the analyses and interpretation of results
Funding Support:	n/a

Name:	Carrie Peltz
Project Role:	Project Coordinator
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	5
Contribution to Project:	Dr. Peltz coordinates the project and assists with data analysis and publication
Funding Support:	n/a

Name:	Feng Xia
Project Role:	Programmer
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	6
Contribution to Project:	Ms. Xia performs statistical analyses for this project.
Funding Support:	n/a

Name:	Tamar Simone
Project Role:	Research Associate
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	5
Contribution to Project:	Ms. Simone assists with project coordination, scheduling meetings, assisting with reporting requirements, etc.
Funding Support:	n/a

Name:	Adrita Chatterjee
Project Role:	Research Associate
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	2
Contribution to Project:	Ms. Chatterjee assists with reporting requirements, project coordination, and presentations.
Funding Support:	n/a

Name:	Julia Cheunkarndee
Project Role:	Research Associate
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	2
Contribution to Project:	Ms. Cheunkarndee assists with reporting requirements, analyses, and presentations.
Funding Support:	n/a

Name:	Brenda L. Plassman
Project Role:	Co-Principal Investigator
Researcher Identifier (e.g. ORCID ID):	000-0003-2867-7198
Nearest person month worked:	1
Contribution to Project:	Dr. Plassman, in coordination with Dr. Yaffe, provides scientific leadership and input on the analyses and interpretation of results
Funding Support:	n/a

Name:	Marianne Chanti-Ketterl
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	000-002-0438-676X
Nearest person month worked:	2
Contribution to Project:	Dr. Chanti-Ketterl performs statistical analyses for the project
Funding Support:	n/a

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

  Nothing to report

- **What other organizations were involved as partners?**
  - Nothing to report

- **SPECIAL REPORTING REQUIREMENTS**
  - Not Applicable

- **APPENDICES:**

  Appendix 1. Kornblith et al., 2020

  Appendix 2. Plassman et al., 2022

  Appendix 3. Kornblith et al., 2022

  Appendix 4. Albrecht et al., 2022

  Appendix 5. Gardner et al., 2023

  Appendix 6. Chanti-Ketterl et al., 2023

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Sex, Race, and Risk of Dementia Diagnosis after Traumatic Brain Injury among Older Veterans

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Search terms: traumatic brain injury, dementia, sex, race, Veterans

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Statistical Analysis conducted by Feng Xia, MS, MPH, SFVA/NCIRE

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Erica Kornblith: Reports no disclosures relevant to the manuscript.

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Feng Xia: Reports no disclosures relevant to the manuscript.

Brenda Plassman: Reports no disclosures relevant to the manuscript.

Tatjana Novakovic-Agopian: Reports no disclosures relevant to the manuscript.

Kristine Yaffe: Dr. Yaffe serves on Data Safety Monitoring Boards for Eli Lilly and several National Institute on Aging-sponsored studies, serves on the board of directors for Alector, Inc, and is member of the Beeson Scientific Advisory Board.

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ABSTRACT

Objective: To investigate whether sex and race differences exist in dementia diagnosis risk associated with TBI among older Veterans.

Methods: Using Fine-Gray regression models, we investigated incident dementia diagnosis risk with TBI exposure by sex and race.

Results: After excluding baseline prevalent dementia, the final sample (all Veterans 55+ diagnosed with TBI during the 2001-2015 study period and a random sample of all Veterans receiving Veterans Health Administration care) included nearly one million Veterans (4.3% female and 81.8% White, 11.5% Black and 1.25% Hispanic), 96,178 with TBI and 903,462 without TBI. Compared to those without TBI, Hispanic Veterans with TBI were almost two times more likely (17.0% vs. 10.3%; HR: 1.74, 95% CI: 1.51-2.01), Black Veterans with TBI were over two times more likely (11.2% vs. 6.4%; HR=2.15, 95% CI: 2.02-2.30), and White Veterans with TBI were nearly three times more likely to receive a dementia diagnosis (12.0% vs. 5.9%; HR=2.71, 95% CI: 2.64-2.77). A significant interaction between TBI and race for dementia diagnosis was observed (p<0.001). Both male and female Veterans with TBI were more than twice as likely (males: 11.8% vs 5.9%, HR: 2.60; 95% CI 2.54-2.66; females 6.3% vs 3.1%, HR: 2.36; 95% CI 2.08, 2.69) to receive a diagnosis of dementia compared to those without. There was a significant interaction effect between sex and TBI (p=0.02), but the magnitude of differences was small.

Conclusions: In this large, nation-wide cohort of older Veterans, all race groups with TBI had increased risk of dementia diagnosis, but there was an interaction effect such that White Veterans were at greatest risk for dementia following TBI. Further research is needed to understand

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mechanisms for this discrepancy. Differences in dementia diagnosis risk for males and females after TBI were significant but small, and male and female Veterans had similarly high risk of dementia diagnosis after TBI.

INTRODUCTION

Traumatic brain injury (TBI), including mild TBI [1], is a well-known risk factor for dementia [2-8]. Veterans are particularity at risk for TBI and therefore may be more vulnerable to developing dementia [9]. Most existing research on TBI and risk of dementia diagnosis in Veterans has been conducted with predominately male and White participants. As the U.S. military becomes more diverse, understanding the outcomes that females and non-white service members may face after TBI is essential. Females are increasingly involved in combat and at risk for TBI [10], and the number of female Veterans, particularly those over 55, is expected to rise sharply in the coming years [11]. The proportion of Black, Hispanic, and other (including American Indian/Alaska native, Asian, and Pacific Islander) minority Veterans is also expected to climb [12].

The few studies which directly examine the effect of sex on risk of dementia diagnosis after TBI ([2] [13] [14] have shown small increases in risk for males but not females. Most existing studies of risk for dementia diagnosis after TBI do not directly examine race differences, and many do not report the racial makeup of their samples [15]. Understanding the possible impact of sex- and race-based health differences on dementia diagnosis risk is key to improving care for the growing population of diverse older Veterans with TBI.

The goal of our study was to examine whether differences in TBI-associated risk of dementia diagnosis by sex and race exist among a large cohort of older Veterans, and to evaluate

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the impact of other demographic factors, medical comorbidities, and psychiatric conditions on this relationship.

METHODS

Standard Protocol Approvals

All study procedures were approved by institutional review boards and the University of California, San Francisco and San Francisco Veterans Affairs Medical Center, and US Army Medical Research and Material Command, Office of Research Protections, Human Research Protection Office. Informed consent was waived because of the use of deidentified archival data. Additionally, many participants were deceased or no longer receiving medical care through VA at the time of study completion.

Study Population

We identified all Veterans Health Administration (VHA) patients 55 years of age or older who received a TBI diagnosis between October 1, 2001 and September 30, 2015 and a 2% random sample of patients who received VHA care within the same time frame (n=1,024,601). Data were sourced from two nationwide VHA system databases: the inpatient and outpatient visits database (National Patient Care Database [NPCD]) and the Vital Status File. We excluded Veterans with prevalent dementia during the 2-year baseline period (defined as within 2 years prior to the index date; i.e., the date of TBI diagnosis or random selection date) (n=24,959). The final sample size was 999,642.

We identified all VHA patients who received an inpatient or outpatient TBI diagnosis using the Defense and Veterans Brain Injury Center list of International Classification of Disease, Ninth Revision (ICD-9) Codes for TBI surveillance [data available from Dryad

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(Appendix 1) https://doi.org/10.7272/Q6V69GSD]. We next identified prevalent dementia at baseline using the VA Dementia Steering Committee's recommended list of ICD-9 codes (2016 version)[16]; data available from Dryad (Appendix 2): https://doi.org/10.7272/Q6V69GSD. For incident dementia diagnoses during the follow-up period, we used a modified version of the same list that excluded prion disease and alcohol or drug-induced dementia.

Biological sex data were also taken from VHA inpatient or outpatient files in which each Veteran was coded as male or female. Two participants had missing sex data, and the final sample size was 999,640 for sex analyses. Race and ethnicity were retrieved from VHA inpatient and outpatient files (supplemented with Medicare data after 2004). Veterans were coded as Non-Hispanic Black, Non-Hispanic White, Hispanic, or Other/Unknown. The Other/Unknown race category was removed from the final unadjusted and adjusted race models because of the likelihood of missing data in the unknown group confounding interpretation of information about respondents in the "other" category. These codes are based on self-report of patient sex and race. The final sample size was 937,380 for race analyses, reflecting 62,262 participants with missing data ("other/unknown") for race.

We obtained data on demographics, medical comorbidities, health care visits, and psychiatric conditions using VHA inpatient and outpatient files. Zip codes and 2016 American Community Survey data were used to categorize Veterans' residences into educational and income categories (for education, less than or equal to 25% of the adult population has a bachelor's degree or higher vs. more than 25%; income was categorized into median income tertiles). Medical and psychiatric comorbidities as identified by ICD-9 codes were assessed during the 2-year baseline. Comorbidities included hypertension, diabetes mellitus, myocardial infarction, transient ischemic attack (TIA)/stroke, chronic pain, posttraumatic stress disorder

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(PTSD), depression, drug/alcohol abuse, and tobacco use or smoking. Health care visits were defined as any inpatient or outpatient visit from VA medical records, and included information regarding date of visit and diagnosis.

Baseline characteristics of Veterans in each race and sex group were compared by TBI status using *t* tests for continuous variables and *chi square* tests for categorical variables. Although TBI prevalence by race and sex is reported, these data points represent estimates only; because of the oversampling of TBI patients in our sample, these figures lack precision. We used Fine-Grey proportional hazards regression models, accounting for the competing risk of death, to examine time to dementia diagnosis according to TBI status for each sex and race group with age as the timescale. Models were unadjusted and adjusted for demographics and medical/psychiatric comorbidities that significantly differed between sex/race groups at $p<.01$ (age, race or sex, education, income, hypertension, diabetes, myocardial infarction, TIA/stroke, chronic pain, PTSD, depression, drug/alcohol abuse, and tobacco use/smoking). For cumulative incidence graphs (Figures 1 and 2), we used age 95 as a cutoff point, and 1% of data (n=9751) were truncated. Assumptions of the Fine-Gray models were examined and found to be satisfied. We used the cumulative residuals with respect to time (ASSESS statement) to test the proportional hazards assumption.

We also separately examined the interaction effect of TBI with sex and with race on risk of dementia diagnosis in adjusted models and subsequently conducted stratified analyses to examine the interactions. Finally, in sensitivity analyses we a) conducted models in which we excluded Veterans receiving a dementia diagnosis within 1 year of TBI diagnosis for a "washout period" in order to address concerns about reverse causation and etiology (TBI vs. neurodegenerative) and b) examined the impact of number of health care visits during the

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follow-up period to determine whether increased involvement in/access to health care accounted for some of the race-based differences in dementia diagnoses we identified. Statistical significance was set at $p<.05$ (two-sided). SAS version 9.4 was used for all analyses.

Data Availability Statement

The data are derived from VHA electronic health records and contain protected health information; therefore, the data cannot be placed in a public repository. Please contact the authors for additional details regarding the process of accessing these data.

RESULTS

The final analytic cohort (all Veterans 55+ with TBI during the study period and a 2% random sample of all Veterans in the VHA) included 96,178 Veterans with TBI and 903,464 Veterans without (4.3% female; 81.8% White, 11.5% Black and 1.25% Hispanic). Median follow-up was 4.3 years (interquartile range 1.9-7.6).

TBI Risk for Dementia Diagnosis by Sex

Table 1 shows characteristics of male and female Veterans with and without TBI. Male Veterans were older ($p<0.001$). All Veterans with TBI regardless of sex had higher prevalence of medical and psychiatric comorbidities compared to those without TBI history. Among male Veterans, those with TBI were more than twice as likely to receive a dementia diagnosis (HR: 2.87, 95% CI 2.81-2.94) compared to those without a TBI diagnosis. Among females, those with TBI vs. no TBI were more than twice as likely to receive a dementia diagnosis (HR: 2.51, 95% CI 2.22-2.84). The difference lessened somewhat after adjustment for demographics and comorbid conditions: (male HR=2.60; 95% CI=2.54-2.66; female HR=2.36; CI: 2.08-2.69). There was a significant interaction effect of sex and TBI on dementia diagnosis risk ($p=.02$) such

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that males with TBI demonstrated slightly increased risk of receiving a dementia diagnosis compared to females. The interaction between sex and TBI on dementia diagnosis risk remained significant after adjustment (p=.03). Adjusted cumulative incidence curves for age at dementia diagnosis, accounting for competing risk of mortality are shown in Figure 1 for male and female Veterans.

TBI Risk for Dementia Diagnosis by Race

Table 2 shows characteristics of White, Black, and Hispanic Veterans with and without TBI. Across all race groups, those with TBI were generally younger, more likely to be female, better educated, more likely to fall in the low-income group, and were less likely to be diagnosed with hypertension and diabetes but otherwise had more health and psychological comorbidities compared to those without TBI history. The Hispanic group was unique, however, in that Hispanic Veterans with TBI were older ($p<0.001$) and did not differ from Hispanic Veterans without TBI on sex ($p=0.78$). All Veterans with TBI were much more likely to fall in the low-income group, but low income group membership was most likely in the Black and Hispanic groups (31.6% of White Veterans with TBI compared to 58.1% of Black Veterans and 70.1% of Hispanic Veterans with TBI).

White Veterans with TBI had an almost 3-fold increased risk of dementia diagnosis (HR=2.93, 95% CI 2.86-3.00) compared to those without TBI while Black and Hispanic Veterans with TBI had about a two-fold increased risk (Black: HR=2.27, 95% CI 2.13-2.41 and Hispanic: HR= 1.98, 95% CI 1.74-2.24). There was a significant interaction between TBI and race on risk of receiving a dementia diagnosis ($p<.001$), such that White Veterans with TBI were at highest risk for dementia diagnosis with similar risks for Blacks and Hispanics. After adjustment for demographics, medical and psychiatric conditions, White Veterans with TBI

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remained at higher risk (HR=2.71; 95% CI: 2.64-2.77) compared to Black and Hispanic veterans with TBI (Black, HR= 2.15; 95% CI 2.02-2.30 and Hispanic, HR= 1.74; 95% CI 1.51-2.01). The interaction between TBI and race on risk of dementia diagnosis remained after full adjustment (p<.001). Adjusted cumulative incidence curves for age at dementia diagnosis, accounting for competing risk of mortality are shown in Figure 2 for White, Black, and Hispanic Veterans. Results of one-year lag "washout" sensitivity analyses showed slightly attenuated HRs but the pattern of sex and race results was identical. Additional adjustment for number of clinic visits slightly attenuated risk estimates but did not change the pattern of results (White HR=2.33; 95% CI 2.26-2.39, Black HR= 1.94; 95% CI 1.82-2.08, and Hispanic HR=1.63; 95% CI 1.41-1.89).

DISCUSSION

In this diverse sample of older Veterans, we show an increased risk of dementia diagnosis with a diagnosis of TBI compared to those without for Veterans of both sexes and all major race groups, consistent with previous work on this topic in the Veteran population [9]. We also identified differences in the risk of dementia diagnosis after TBI based on race. Specifically, older White Veterans appear to have an elevated risk of receiving a dementia diagnosis after TBI compared to Blacks and Hispanics. Sex differences in dementia diagnosis risk after TBI observed in this large sample, although statistically significant, were small and of unclear clinical significance.

The limited available data about the effect of sex on dementia risk after TBI show increased risk for males but not females. For example, an older meta-analysis of 11 case control studies conducted before 1991 suggested that there is an increased risk of dementia (specifically AD) after TBI for males, but not females [2]; another metanalysis published in 2003 examining 7 additional studies replicated that finding [13]. A recent population-based study in Denmark

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conducted in 2018 similarly found slightly increased risk of dementia after TBI in males compared to females (30% vs. 19% increased risk) [14]. Our results showing a similarly high risk for both males and females are novel and inconsistent with this prior work. Therefore, further exploration of sex-based differences in dementia risk after TBI for Veterans is indicated. For example, it is possible that although the TBIs suffered by civilian females may be less severe on average than those suffered by civilian males, male and female Veterans may suffer TBIs of similar severity. Additionally, military females may experience a unique profile of injuries in which repeated injuries caused by intimate partner violence (IPV) are superimposed on single or multiple concussive or sub-concussive head injuries, conferring elevated dementia risk compared to civilian females.

Most existing studies of risk for dementia after TBI do not directly examine race differences, and many do not report the racial makeup of their samples [15]. For example, in a recent review of the evidence for the association between TBI and dementia, race was not listed as a known demographic factor impacting that relationship [17]. Our finding that White Veterans may be at increased risk for dementia after TBI, therefore, is novel. Our findings stand in contrast to previous research which has shown that Black and Hispanic adults have worse functional outcomes (as defined by standardized measures such as the Disability Rating Scale, Functional Independence Measure, and the Community Integration Questionnaire) compared to White adults one year after moderate-severe TBI [18]. However, the different methodological approach in our work, which utilizes medical record data including diagnostic codes rather than standardized measures of functional outcome, may account for some of these discrepancies. Our results may also be explained by race-based differences in the documentation of dementia diagnoses by health care providers; if providers are, for example, more likely to consider

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dementia as a diagnosis for white patients, that could account for our findings of increased dementia diagnosis risk for white Veterans.

It is clear that more research is needed to understand the impact of race on dementia diagnosis risk after TBI. Differential risk for dementia by race among Veterans is unknown, and a topic of current ongoing research, and it may be the case that non-white Veterans have higher baseline risk, such that having a TBI may not lead to increased risk for these race groups, as it does for Whites. Health disparities research suggests that White individuals may be more likely to interact with health care and receive a diagnosis [19, 20], which may result in inflated rates of TBI and dementia diagnoses for white Veterans compared to other groups. However, in our sample White veterans had fewer follow-up visits compared to Black and Hispanic Veterans, and after adjustment for number of visits, the increased risk of dementia after TBI for White Veterans persisted. It is also possible that Black and Hispanic individuals, who are significantly more likely to live in multigenerational households with high levels of family support compared to White individuals [21], may function well independently in the community for longer because of this increased support and therefore delay receiving a dementia diagnosis. However, all Veterans were followed at VA and cognitive problems therefore were likely to have been detected, even in the absence of concern from patients and/or families. Additionally and importantly, there may be unmeasured and unrecognized social factors impacting differences in medical care and driving differences in outcomes between race groups that deserve further study in the future.

Furthermore, we did not measure Apolipoprotein e4 (APOE e4) allele status, which differs by race and increases risk for dementia [22]. Although the allele is more common among individuals of African descent [23], White individuals have a greater increased risk for dementia

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with APOE e4, compared to other racial groups [24]. These findings support our results showing increased risk for White Veterans. There is also some evidence that APOE e4 increases risk for negative outcome, including dementia, after TBI [25-27], which may be related to its decreased ability to effectively protect and repair neural tissue after trauma, compared to APOE e3 [28]. Other unknown and unmeasured genetic factors may play a role in the race differences and the increased risk of dementia diagnosis for White Veterans after TBI seen here, and further research is required to identify such mechanisms.

Although our study was not designed to precisely measure prevalence of TBI among older Veterans, the TBI prevalence estimates we report suggest differential patters in prevalence of TBI by both sex and race in our sample that are clinically interesting and bear further study. Our results suggest a greater prevalence of TBI in female Veterans compared to male Veterans. These results may reflect a departure from civilian findings, which generally show higher rates of TBI in males [29]. Our results also suggest the possibility of increased prevalence of TBI among Hispanic Veterans compared to Black and White Veterans. This pattern may represent a novel finding, and in fact there is a dearth of research available on the prevalence or risk of TBI by race among Veterans and Civilians, an area clearly requiring further study. Existing VA research shows that Hispanic Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Veterans are less likely to receive care for a TBI, and that Hispanic Veterans of all eras are at higher risk for mortality after a TBI [30, 31], but these studies do not report prevalence of TBI among Hispanic Veterans. In contrast, our results suggest that Hispanic Veterans receive more follow-up care compared to White Veterans but less than Black Veterans. These patterns demonstrate that further research specifically focused on investigating race and sex differences in TBI prevalence among Veterans is clearly indicated.

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There are some important limitations to our study which impact the interpretation and generalizability of our results. For example, sex and race were based on self-report, and sex was coded as a binary variable only (i.e., transgender individuals were not captured), likely excluding some of the true complexity of this variable. Furthermore, our sample had some limitations: we were unable to examine Asian Veterans and Veterans identifying their race/ethnicity as "other" because of small sample size. Further research focused on Asian Veteran samples and those that identify their race as "other" would be helpful and provide insights for treatment planning and prevention as this growing cohort of Veterans ages. Moreover, because of oversampling of TBI patients, we are unable precisely measure TBI prevalence in veterans. Although TBI prevalence by race and sex is reported, these data points represent estimates only. Additionally, because of our use of medical record data, there are likely to be differences between the sex and race groups studied that we were not able to measure but which are driving differences in risk of dementia after TBI. Also, we used ICD-9 codes in existing medical records for dementia diagnoses, which may result in less accurate categorization of participants compared to studies in which participants were given a comprehensive dementia examination. Because we included Veterans in our sample who may have received a dementia diagnosis shortly after their TBI diagnosis, we are not able to draw conclusions about causality of dementia diagnoses or make inferences about neurodegenerative vs. traumatic etiology. Finally, results may not generalize to Veterans who do not receive VA health care.

This is one of the first studies to examine differential risk for dementia diagnosis after TBI based on sex and race. This study is novel because of the large sample size and the direct, explicit consideration of race and sex and their impact on dementia risk following TBI among Veterans. Our results show a doubling of dementia diagnosis risk after TBI for both males and

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females, and an interesting difference by sex which is small and of unclear clinical significance. Risk of dementia diagnosis was also approximately doubled for all Veterans across race categories after TBI, with White Veterans showing an even greater increased risk. These findings suggest that understating the possible differential impact of TBI on dementia diagnosis risk based on race is worth exploring. This is of particular importance given the increasing diversity and rapid aging of our military and Veteran populations, and may provide the VA with an important opportunity to identify and correct possible health disparities in TBI and dementia identification and care.

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Appendix. Authors

Name	Location	Contribution
Erica Kornblith, PhD	SFVA/NCIRE, San Francisco	Designed and conceptualized study; interpreted data; prepared initial manuscript draft
Carrie B. Peltz, PhD	SFVA/NCIRE, San Francisco	Acquired and interpreted data; contributed to preparation, review, and revision of manuscript
Feng Xia, MS, MPH	SFVA/NCIRE, San Francisco	Analyzed the data; contributed to preparation, review, and revision of manuscript
Brenda Plassman, PhD	Duke University, Durham, NC	Contributed to preparation, review, and revision of manuscript
Tatjana Novakovic-Agopian, PhD	SFVA/UCSF, San Francisco	Contributed to preparation, review, and revision of manuscript
Kristine Yaffe, MD	SFVA/UCSF, San Francisco	Obtained funding; designed and conceptualized study; interpreted data; contributed to preparation, review, and revision of manuscript

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Table 1
Baseline characteristics of male and female Veterans with and without TBI

Values n (%) unless otherwise stated	**Male (n=956,622)**		**Female (n=43,018)**	
	No TBI (n=866,208)	TBI (n=90,414)[1]	No TBI (n=37,254)	TBI (n=5,764)[2]
Age, years [mean (SD)]	70.03 (9.53)	68.76 (10.43)	65.07 (9.86)	65.63 (10.53)
Race				
Non-Hispanic White	719,105 (83.0)	69,860 (77.3)	24,641 (66.1)	3,954 (68.6)
Non-Hispanic Black	90,589 (10.5)	11,860 (13.1)	4,847 (13.0)	766 (13.3)
Hispanic	9,250 (1.1)	2,182 (2.4)	265 (0.7)	60 (1.0)
>25% college ed. in zip code	355,716 (42.2)	38,466 (44.1)	16,755 (46.9)	2,673 (48.1)
Low income tertile (<$43,018)	277,115 (33.0)	31,432 (36.3)	11,684 (33.4)	1,770 (32.5)
Follow-up time, years [Mean (SD)]	5.06 (3.69)	3.65 (3.19)	4.01 (3.47)	3.31 (3.03)
Total follow-up visits	60.96 (83.86)	88.54 (114.61)	46.00 (75.56)	80.20 (115.91)
Follow-up visits/yr.	15.23 (28.42)	34.09 (50.02)	17.80 (45.10)	34.89 (63.79)
Hypertension	161,449 (18.6)	14,024 (15.5)	4,356 (11.7)	724 (12.6)
Diabetes	74,690 (8.6)	7,252 (8.0)	1,873 (5.0)	350 (6.1)
Myocardial infarction	19,428 (2.2)	3,162 (3.5)	286 (0.8)	90 (1.6)
TIA/stroke	33,166 (3.8)	11,402 (12.6)	778 (2.1)	410 (7.1)
Chronic Pain	2,452 (0.3)	1,094 (1.2)	167 (0.5)	120 (2.1)
PTSD	21,699 (2.5)	6,027 (6.7)	652 (1.8)	347 (6.0)
Depression	47,416 (5.5)	10,629 (11.8)	2,152 (5.8)	599 (10.4)
Drug/alcohol abuse	27,678 (3.2)	7,525 (8.3)	511 (1.4)	217 (3.8)
Tobacco use/smoking	58,787 (6.8)	7,754 (8.6)	1,512 (4.1)	297 (5.2)

Abbreviations: SD = standard deviation; TIA: transient ischemic attack; PTSD: posttraumatic stress disorder
[1] *p* values for all comparisons TBI vs. no TBI: <0.001
[2] *p* values for all comparisons TBI vs. no TBI <0.001 except age (*p*=0.07); >25% college ed. in zip code (*p*=0.09); low income tertile (<$43,018) (*p*=0.35); and HTN (*p*=0.06).

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Table 2
Characteristics of Veterans with and without TBI by race

Values are n (%) unless otherwise stated	**Non-Hispanic White (n=817,561)**		**Non-Hispanic Black (n=108,062)**		**Hispanic (n=11,757)**	
	No TBI (n=743,747)	TBI[1] (n=73,814)	No TBI (n=95,436)	TBI [1] (n=12,626)	No TBI (n=9,515)	TBI[2] (n=2,242)
Age, years [mean(SD)]	70.74 (9.42)	69.55 (10.43)	66.45 (8.90)	66.21 (9.63)	70.91 (10.61)	72.69 (11.64)
Female	24,641 (3.3)	3,954 (5.4)	4,847 (5.1)	766 (6.1)	265 (2.8)	60 (2.7)
>25% college ed. in zip code	314,585 (43.4)	32,598 (45.6)	31,135 (33.8)	4,418 (36.4)	2,953 (33.3)	830 (41.0)
Low income tertile (<$43,018)	215,604 (29.9)	22,430 (31.6)	51,410 (56.1)	7,015 (58.1)	5,455 (62.1)	1,404 (70.1)
Follow-up time, years [mean(SD)]	5.15 (3.70)	3.68 (3.21)	4.91 (3.67)	3.73 (3.26)	4.89 (3.76)	3.47 (3.14)
Total follow-up visits	58.61 (79.12)	87.68 (111.10)	83.13 (114.24)	103.55 (141.07)	77.87(101.98)	88.96 (124.60)
Follow-up visits/yr.	14.34 (27.00)	33.76 (50.63)	20.33 (32.01)	36.52 (49.13)	19.55 (29.10)	35.74 (46.30)
Hypertension	139,748 (18.8)	11,256 (15.3)	16,890 (17.7)	2,024 (16.0)	1,479 (15.5)	296 (13.2)
Diabetes	62,412 (8.4)	5,801 (7.9)	9,344 (9.8)	1,102 (8.7)	940 (9.9)	171 (7.6)
Myocardial infarction	16,969 (2.3)	2,716 (3.7)	1,744 (1.8)	320 (2.5)	236 (2.5)	76 (3.4)
TIA/stroke	28,786 (3.9)	9,117 (12.4)	3,653 (3.8)	1,646 (13.0)	395 (4.2)	384 (17.1)
Chronic pain	2,054 (0.3)	950 (1.3)	332 (0.4)	142 (1.1)	22 (0.2)	17 (0.8)

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PTSD	16,813 (2.3)	4,661 (6.3)	3,679 (3.9)	944 (7.5)	267 (2.8)	108 (4.8)
Depression	40,448 (5.4)	8,634 (11.7)	5,682 (6.0)	1,411 (11.2)	586 (6.2)	239 (10.7)
Drug/alcohol abuse	20,344 (2.7)	5,519 (7.5)	5,190 (5.4)	1,263 (10.0)	319 (3.4)	170 (7.6)
Tobacco/smoking	49,132 (6.6)	6,083 (8.2)	7,247 (7.6)	1,133 (9.0)	490 (5.2)	155 (6.9)

Abbreviations: SD = standard deviation; TIA: transient ischemic attack; PTSD: posttraumatic stress disorder
[1]*p* values for all comparisons TBI vs. no TBI <0.001
[2]*p* values for all comparisons TBI vs. no TBI p<0.001 except Female (*p*=0.78); hypertension (*p*=0.01); diabetes (*p*=0.001); myocardial infarction (*p*=0.02); and tobacco use/smoking (*p*=0.001)

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Figure Legends

Figure 1. Adjusted* cumulative incidence of dementia: age at dementia diagnosis with and without TBI, accounting for mortality in male and female Veterans
*Adjusted for demographic and health characteristics

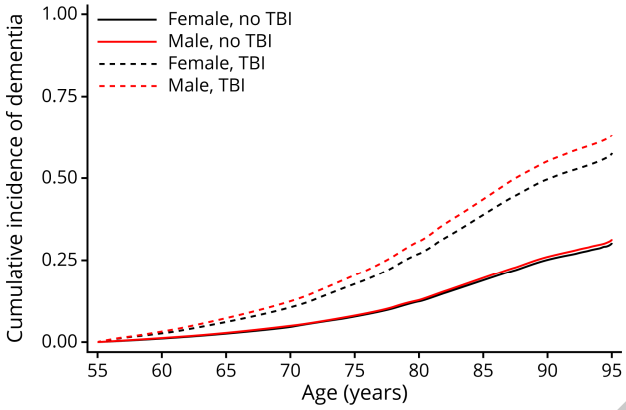
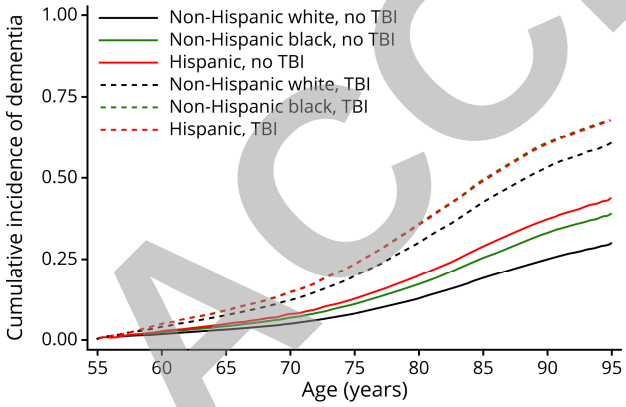


Figure 2. Adjusted* cumulative incidence of dementia: age at dementia diagnosis with and without TBI, accounting for mortality in White, Black, and Hispanic Veterans
*Adjusted for demographic and health characteristics



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References

1. Barnes, D.E., et al., *Association of mild traumatic brain injury with and without loss of consciousness with dementia in US military veterans.* JAMA neurology, 2018. **75**(9): p. 1055-1061.
2. Mortimer, J., et al., *Head trauma as a risk factor for Alzheimer's disease: a collaborative re-analysis of case-control studies.* International journal of epidemiology, 1991. **20**(Supplement_2): p. S28-S35.
3. Plassman, B.L., et al., *Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias.* Neurology, 2000. **55**(8): p. 1158-1166.
4. Guo, Z., et al., *Head injury and the risk of AD in the MIRAGE study.* Neurology, 2000. **54**(6): p. 1316-1323.
5. Wang, H.-K., et al., *Population based study on patients with traumatic brain injury suggests increased risk of dementia.* J Neurol Neurosurg Psychiatry, 2012. **83**(11): p. 1080-1085.
6. Gardner, R.C., et al., *Dementia risk after traumatic brain injury vs nonbrain trauma: the role of age and severity.* JAMA neurology, 2014. **71**(12): p. 1490-1497.
7. Lee, Y.-K., et al., *Increased risk of dementia in patients with mild traumatic brain injury: a nationwide cohort study.* PloS one, 2013. **8**(5): p. e62422.
8. Nordström, P., et al., *Traumatic brain injury and young onset dementia: a nationwide cohort study.* Annals of neurology, 2014. **75**(3): p. 374-381.
9. Barnes, D.E., et al., *Traumatic brain injury and risk of dementia in older veterans.* Neurology, 2014. **83**(4): p. 312-319.
10. Amoroso, T. and K.M. Iverson, *Acknowledging the risk for traumatic brain injury in women veterans.* The Journal of nervous and mental disease, 2017. **205**(4): p. 318-323.
11. *National Center for Veterans Analysis and Statistics. Living veterans by age, group, gender, 2015-2045*. Online, Retrieved from: https://www.va.gov/vetdata/veteran_population.asp.
12. *National Center for Veterans Analysis and Statistics. 2014 mintory veterans report.* Online, Retrieved from: https://www.va.gov/vetdata/docs/SpecialReports/Minority_Veterans_2014.pdf.
13. Fleminger, S., et al., *Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication.* Journal of Neurology, Neurosurgery & Psychiatry, 2003. **74**(7): p. 857-862.
14. Fann, J.R., et al., *Long-term risk of dementia among people with traumatic brain injury in Denmark: a population-based observational cohort study.* The Lancet Psychiatry, 2018. **5**(5): p. 424-431.
15. Bazarian, J.J., et al., *Diffusion tensor imaging detects clinically important axonal damage after mild traumatic brain injury: a pilot study.* J Neurotrauma, 2007. **24**(9): p. 1447-59.
16. *US Department of Veterans Affiars (VA) Veterans Health Administration (VHA) Dementia Steering Committee (DSC). VHA dementia steering committee recommendations for dementia care in the VHA healthcare system 2016.* 2016 [cited 2019 September 3]; Available from: https://www.va.gov/GERIATRICS/docs/VHA_DSC_RECOMMENDATIONS_SEPT_2016_9-12-16.pdf.
17. Peterson, K., et al., *Evidence Brief: Traumatic Brain Injury and Dementia.* 2019.

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18. Arango-Lasprilla, J.C., et al., *Traumatic brain injury and functional outcomes: does minority status matter?* Brain Injury, 2007. **21**(7): p. 701-708.
19. Hall, W.J., et al., *Implicit racial/ethnic bias among health care professionals and its influence on health care outcomes: a systematic review.* American journal of public health, 2015. **105**(12): p. e60-e76.
20. Boulware, L.E., et al., *Race and trust in the health care system.* Public health reports, 2016.
21. Taylor, P., et al., *The return of the multi-generational family household.* Pew Research Center, 2010. **18**.
22. Bookheimer, S. and A. Burggren, *APOE-4 genotype and neurophysiological vulnerability to Alzheimer's and cognitive aging.* Annual review of clinical psychology, 2009. **5**: p. 343-362.
23. Kuller, L.H., et al., *Relationship between ApoE, MRI findings, and cognitive function in the Cardiovascular Health Study.* Stroke, 1998. **29**(2): p. 388-398.
24. Bretsky, P., et al., *The role of APOE-ε4 in longitudinal cognitive decline: MacArthur Studies of Successful Aging.* Neurology, 2003. **60**(7): p. 1077-1081.
25. Verghese, P.B., J.M. Castellano, and D.M. Holtzman, *Apolipoprotein E in Alzheimer's disease and other neurological disorders.* The Lancet Neurology, 2011. **10**(3): p. 241-252.
26. Zhou, W., et al., *Meta-analysis of APOE 4 allele and outcome after traumatic brain injury.* Journal of neurotrauma, 2008. **25**(4): p. 279-290.
27. Magnoni, S. and D.L. Brody, *New perspectives on amyloid-β dynamics after acute brain injury: moving between experimental approaches and studies in the human brain.* Archives of neurology, 2010. **67**(9): p. 1068-1073.
28. Bu, G., *Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy.* Nature Reviews Neuroscience, 2009. **10**(5): p. 333.
29. Taylor, C.A., et al., *Traumatic brain injury–related emergency department visits, hospitalizations, and deaths—United States, 2007 and 2013.* MMWR Surveillance Summaries, 2017. **66**(9): p. 1.
30. Arriola, V. and J. Rozelle, *Traumatic brain injury in United States Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Hispanic Veterans—a review using the PRISMA method.* Behavioral Sciences, 2016. **6**(1): p. 3.
31. Egede, L.E., C. Dismuke, and C. Echols, *Racial/ethnic disparities in mortality risk among US veterans with traumatic brain injury.* American journal of public health, 2012. **102**(S2): p. S266-S271.

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FEATURED ARTICLE

Traumatic brain injury and dementia risk in male veteran older twins—Controlling for genetic and early life non-genetic factors

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Abstract

Introduction: This study leveraged the twin study design, which controls for shared genetic and early life exposures, to investigate the association between traumatic brain injury (TBI) and dementia.

Methods: Members of the National Academy of Sciences–National Research Council's Twins Registry of World War II male veterans were assigned a cognitive outcome based on a multi-step assessment protocol. History of TBI was obtained via interviews.

Results: Among 8302 individuals, risk of non-Alzheimer's disease (non-AD) dementia was higher in those with TBI (hazard ratio [HR] = 2.00, 95% confidence interval [CI], 0.97–4.12), than for AD (HR = 1.23, 95% CI, 0.76–2.00). To add more control of genetic and shared environmental factors, we analyzed 100 twin pairs discordant for both TBI and dementia onset, and found TBI-associated risk for non-AD dementia increased further (McNemar odds ratio = 2.70; 95% CI, 1.27–6.25).

Discussion: These findings suggest that non-AD mechanisms may underlie the association between TBI and dementia, potentially providing insight into inconsistent results from prior studies.

KEYWORDS
Alzheimer's disease, dementia, traumatic brain injury, twin studies

1 | INTRODUCTION

Traumatic brain injury (TBI) has been reported as a risk factor for Alzheimer's disease (AD),[1–3] non-AD dementia,[4] and all-cause dementia[1,3,5] by a number of studies, but not by all.[6–8] The inconsistent results may be due to differences in study design, but may also be due to the many potentially confounding factors occurring that manifest during the decades in a person's life prior to the onset of dementia that may lead to analytic under-control of the confounders. AD and other types of dementia have complex etiologies influenced by multiple genetic and non-genetic factors occurring throughout the lifespan.[9] Several childhood adversities such as parental death, family violence, economic hardship, poor quality education, and poor nutrition have been linked to increased risk of dementia.[10,11] However, it is difficult to obtain reliable information about early life environmental exposure because the data are often collected decades after exposure and thus are prone to recall error.[12] Twins studies have significant advantages in addressing this limitation because genetic and early life exposures shared by the members of the twin pair, even those not identified, are controlled.[13] Monozygotic (MZ) twins share all of their genetic material, whereas dizygotic (DZ) twins, on average, share 50% of their genes, and both MZ and DZ twin pairs exactly share many early life influences such as socioeconomic status or upbringing that can affect later life outcomes and cognition. Differences in an outcome between genetically identical pairs are presumed to reflect a difference in an environmental influence that occur in only one member of the twin pair, such as TBI. Twin studies use within-twin-pair differences in an exposure to evaluate its impact on the outcome of interest, such as dementia, and thus provide greater confidence in the causal nature of the association.

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We examined the association between TBI and subsequent risk for dementia in members of the National Academy of Sciences–National Research Center (NAS-NRC) Twin Registry of male World War II veterans. In this study, TBI was defined as a reported blow to the head, a head injury, or head trauma that was severe enough to require medical attention, to cause loss of consciousness, or memory loss for a period of time. Leveraging the twins methodology, which allowed within-twin-pair control of many unmeasured genetic and environmental factors, we aimed to better understand the association between TBI and later risk of AD and non-AD dementias.

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors reviewed the literature indexed on PubMed. Several prior studies, but not all, have reported that traumatic brain injury (TBI) is linked to increased risk of Alzheimer's disease (AD) or other dementias. The reason for these discrepant findings is not understood.
2. **Interpretation**: Risk for AD and other dementias accumulates throughout the lifespan. Yet, identifying risk exposures that have occurred years prior to onset of symptoms in late life is fraught with challenges. To address this issue, we leveraged the twin study design, which controls for many shared genetic and early life exposures. In this sample of twins, we found that the association between TBI was most consistently associated with non-AD dementia.
3. **Future Directions**: Based on the evidence amassed to date, future studies are needed to investigate mechanisms underlying the association between TBI and non-AD dementia while controlling for other potentially confounding factors occurring throughout the lifespan.

2 | METHODS

Participants were enrolled in the Duke Twins Study of Memory in Aging, and were members of the NAS-NRC registry of World War II veteran male twins born between 1917 and 1927. As part of the study, surviving and consenting individuals were administered a cognitive status measure every 3 to 4 years beginning in 1990 as part of a screening and assessment protocol for dementia. Participants completed up to four waves of cognitive screening. All procedures were approved by the Duke University Medical Center Institutional Review Board and written consent was obtained from participants or their legal representatives.

2.1 | Sample

The full sample included all participants with information available on both TBI and dementia status (7870 non-demented and 481 demented). The sample included 3210 complete twin pairs (6420 individuals) in which both members were included and 1931 individuals in which only one member of the twin pair was available (henceforth called singletons) or zygosity was missing, resulting in a total of 8351 individuals. The co-twin control sample is a subset of the full sample and included all 100 twin pairs who were discordant for TBI and for dementia or age of onset of dementia. For a twin pair to be discordant for dementia or age of onset of dementia, we required that the current age, age at death, or age of onset of dementia of the co-twin be at least 3 years greater than the age of onset of the proband (i.e., the twin with the earliest age of onset within a pair), to account for the imprecision in estimating age at onset of dementia. Eligibility criteria included completed questions about TBI, and known cognitive status at time of censoring due to dementia, drop out, death, or end of data collection. For participants with dementia, only TBI occurring before the onset of dementia was considered. Figure 1 shows the flowchart of the study population. We excluded participants who did not complete targeted telephone cognitive screening interviews or in-person clinical assessments ($N = 474$, 5.4% of cohort sample). We also excluded 41 individuals who had been given a diagnosis of cognitive impairment, not demented, based on the multi-step screening and assessment procedures described below, because these individuals were more likely to be on the trajectory toward dementia but did not yet meet criteria for the diagnosis.

Information about TBI was collected by trained interviewers during telephone interviews at either Wave 3 (1996–1998) or Wave 4 (2000–2001) for all non-demented pairs, and for those pairs in which a twin was identified as demented in Waves 3 or 4. For individuals who were identified as demented prior to Wave 3 (and their co-twins), information about TBI was collected during in-person or telephone interviews administered by trained interviewers. This information was obtained directly from the participant in most cases, and from a proxy informant if the participant was unable to complete the interview. TBI information collected included (1) history of occurrence of TBI severe enough to require medical attention or cause loss of consciousness (LOC), (2) presence and duration of LOC, (3) number of TBIs, and (4) age(s) of TBI.

2.2 | Other variables

Zygosity was determined by DNA for a subset of twin pairs. For 87% of individuals, zygosity was determined by questionnaire, from military records (physical characteristics such as height, weight, eye and hair color), fingerprint records, and (for a small sample) blood group testing.[14,15] This method of establishing zygosity has been estimated by cross-validation with DNA to be 97% accurate.[16] Years of education completed was collected at the telephone interviews beginning in 1990. History of cigarette smoking and alcohol use was collected at in-person and telephone interviews beginning in 1990. Cigarette smoking was categorized into four groups: never smoked, smoked in the past but quit, current smoker, and missing. Alcohol overuse was defined as

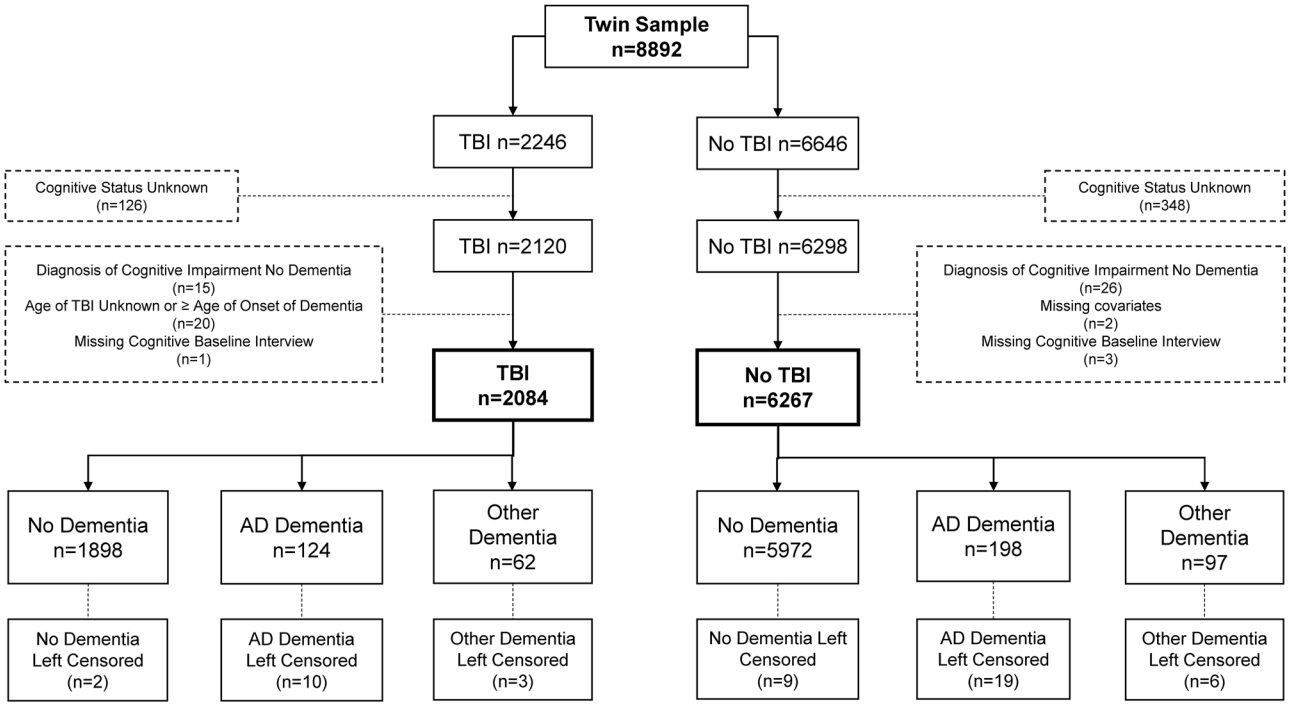

FIGURE 1 Flowchart of study population. AD, Alzheimer's disease; TBI, traumatic brain injury

reporting a problem drinking more alcohol than he should or drinking 12 or more drinks per day at some time. Alcohol use was categorized into three groups: alcohol overuse present, alcohol overuse absent, or missing.

2.3 | Assessment of cognition

The diagnosis of dementia was determined based on the outcome of a multistep screening and assessment protocol that has been described previously.[17] Individuals completed up to four waves of screening for cognitive impairment with the modified Telephone Interview for Cognitive Status (TICS-m).[18] Individuals who were unable to complete the TICS-m were screened by proxy with the Informant Questionnaire on Cognitive Decline in the Elderly[19] or another brief proxy interview. For study participants scoring in the suspected impaired range on the TICS-m or the proxy screening instrument, the Dementia Questionnaire (DQ)[20] was then administered to a proxy informant. Individuals whose DQ indicated possible dementia were scheduled for an in-home evaluation by a research nurse and a neuropsychology technician. As part of the evaluation, the participants completed: (1) a battery of neuropsychological tests, (2) a standardized neurological examination, (3) blood-pressure readings, (4) collection of blood or buccal DNA samples for determination of zygosity, and (5) a brief videotaped segment of cognitive status items. Information collected from the informant included: (1) a chronological history of cognitive function, (2) medical and neuropsychiatric history and current medications, and (3) measures of severity of cognitive and functional symptoms. When possible, we attempted to obtain medical records for neuroimaging and laboratory results that might be relevant to the diagnosis. All available information was reviewed and final diagnoses were assigned by an expert consensus panel of psychologists, neuropsychologists, neurologists, and psychiatrists with expertise in dementia. For a minority of participants (about 8%), an in-person evaluation was not possible due to refusal or death; thus, the dementia diagnosis was based on all available data, including telephone interviews, medical records, and neuropathological examination. The diagnostic guidelines in place during the years of the study were used for dementia,[21] AD,[22] vascular dementia,[23] frontal lobe dementia,[24] and dementia with Lewy bodies.[25,26] We assigned a diagnosis of dementia, unknown etiology, to individuals who met criteria for dementia, but did not fit other criteria. Age of onset for dementia was assigned based on the age at which an individual unambiguously met Diagnostic and Statistical Manual of Mental Disorders, 3rd edition revised criteria for dementia. This methodology of assessment and diagnosis has been used successfully in several other epidemiological studies of dementia,[1,27,28] and resulted in good agreement between clinical and neuropathological diagnoses.[29]

2.4 | Data analyses

Two sets of analyses were performed. First, the analyses of the full sample used the Cox proportional hazard regression model[30] to estimate the risk of dementia within the twin pair, adjusting for correlation in risk within the twin pair using stratification, and with age of onset of dementia, as the outcome variable. The sample was left-censored, using the later of the twin pairs' initial interview date in the Duke Twins Study as the starting age for complete pairs or the initial interview date for singletons. Subjects were censored at the point of death, onset

of dementia, or 1 year after last contact. Singletons were included in the analyses as these individuals contribute to the estimation of risk of dementia and thus increase the precision and statistical power of the analyses. Each proportional hazards regression model assessed risk for AD and other dementias combined, AD only (censoring for other dementia), and non-AD dementia (censoring for AD). We then ran the triad of models separately for MZ and DZ complete twin pairs. Additional proportional hazards models examined whether TBI with LOC, time since TBI, or multiple TBIs increased dementia risk over and above the risk of TBI overall. To assess whether risk for dementia differs based on age of TBI, we re-ran the main models categorizing initial TBI as occurring before age 25 versus age 25 and older. Age 25 was the point at which the occurrence of TBI events at younger ages tapered off, providing a data-driven distinction between the young and not-young groups. In the main model, we also assessed the impact of control for education, smoking, and alcohol over use on the association between TBI and dementia. The viability of the proportionality assumption was tested by inspection of the log(-log[S]) plots.

Finally, for the main models using left-censoring, we excluded 49 individuals who had a dementia event or death prior to the second member of the twin pair's initial interview. However, to assess the impact of excluding these individuals from the analyses, we conducted a sensitivity analysis removing left censoring, continuing use of TBI as a time-varying covariate so that all individuals with dementia could be included in the analysis.

Second, we then analyzed the data using the co-twin control method. These analyses include twin pairs who are discordant for both TBI exposure and dementia onset, thus one twin is used as the matched control for the other twin. The benefit of using a co-twin control design is that it allows the most control of confounding from genetic as well as early environmental factors, as most twins share a common environment during their childhood and adolescence. Prior to conducting the co-twin control analyses, we used logistic regression models to compare the association between TBI and dementia in MZ pairs to that among DZ pairs. Justification for combining the MZ and DZ pairs in the co-twin control analyses is provided by the lack of a significant difference in the association between TBI and dementia in MZ and DZ pairs. The co-twin control analysis combined MZ and DZ pairs and used logistic regression models dependent on twin pair to assess risk of all-cause dementia (or AD or non-AD dementia) within twin pairs who were discordant for both TBI and onset of dementia. The metric of risk was the McNemar odds of the twin with the TBI being the first or only twin in the pair to develop dementia. All analyses were run using SAS statistical software 9.4. The sample characteristics for those with dementia were compared to those without dementia, using Chi-squares for categorical variables, paired *t*-tests for continuous variables, and analyses of variance for the number of head injuries.

Post hoc power analyses for the McNemar odds was calculated using the binomial test. Under the null hypothesis, among discordant pairs, the probability of dementia in the TBI twin is 50% (odds = 1.0). For a given number of discordant twins, the detectable proportion in (or odds of) membership in either the TBI or non-TBI group rejecting the null can be calculated. The power of declaring for the alternative hypothesis was computed using SAS onesamplefreq power, using the normal approximation, power = 80% with level alpha = 0.05 (two-tailed). These analyses estimated that 100 discordant twin pairs could detect an odds of 1.78 and 50 discordant pairs could detect an odds of 2.23 with 80% power.

3 | RESULTS

Participant characteristics for the entire sample are provided in Table 1 and for the co-twin control group in Table 2. TBIs were more common among those who later developed dementia (38.5%) compared to those who did not have dementia (24.1%; $P < .001$). TBI with loss of consciousness was more frequent among those who later developed dementia (31.0%) compared to those who did not develop dementia (17.0%; $P < .001$). For those with both TBI and dementia, participants incurred their first TBIs an average of 39.02 (standard deviation [SD] = 22.42) years prior to the onset of dementia. Among the 2036 who reported having had a TBI and with information on the number of TBIs, 388 (19.0%) reported having more than one TBI; those with at least one TBI had an average of 1.26 (SD = 0.64) injuries (range 1–10).

3.1 | Full sample analyses

Proportional hazard models indicate that a history of TBI was not significantly associated with higher risk of all-cause dementia or AD, but TBI tended to be higher among those with non-AD dementia (hazard ratio [HR] = 2.00; 95% confidence interval [CI] = 0.97–4.12; $P = .06$) compared to those with AD (HR = 1.23; 95% CI = 0.76–2.00; $P = .39$; Table 3). Analyses of the complete twin pairs found that in MZ complete twin pairs that TBI was associated with all-cause dementia (HR = 1.71; 95% CI: 1.00–2.94; $P = .05$; Table 3) and the HR increased for AD among the MZs. In contrast, among the DZ complete pairs, the HR for TBI and risk of non-AD increased (HR = 3.33; 95% CI = 0.92–12.11; $P = .07$). However, the interaction for zygosity and TBI only approached significance for AD ($P = .08$), suggesting that TBI was less associated with AD in DZ pairs. LOC did not contribute significantly above the effect of TBI when added to the model. The number of TBIs, the time since TBI for 10-year intervals, and whether the TBI was before age 25 each also did not contribute significantly to the models over and above the TBI effects.

Adding the covariates of education, smoking, and alcohol overuse had little effect on the HR for TBI and dementia (Table 4). When the 49 individuals with an event prior to their baseline interview were included in sensitivity analyses, the association between TBI and non-AD dementia increased from HR = 2.00 to HR = 2.23, but the association between TBI and AD did not change.

3.2 | Co-twin control analysis

The association between TBI and dementia was similar for MZ and DZ pairs (McNemar odds ratio [OR] = 1.3; 95% CI = 0.58–2.93; $P = .52$)

TABLE 1 Sample characteristics for full sample

	All sample N = 8351	No dementia n = 7870 (94.24%)	All dementia n = 481 (5.76%)	Alzheimer's disease[a] n = 322 (3.86%)	Non-Alzheimer's disease dementia[b] n = 159 (1.90%)	P-value No dementia versus All dementia
Baseline age Mean (SD)	67.1 (3.0)	67.0 (3.0)	68.4 (3.2)	68.4 (3.2)	68.3 (3.2)	<.001
MZ twins[c] DZ twins	66.8 (3.0) 66.9 (3.0)					
Age of onset or censoring age[d] Mean (SD)	75.2 (4.1)	75.3 (3.9)	73.9 (5.8)	73.9 (6.0)	73. 9 (5.5)	<.001
MZ twins DZ twins	75.5 (4.0) 75.1 (4.1)					
TBI = Yes N (%)	2084 (23.0)	1898 (24.1)	186 (38.7)	124 (38.5)	62 (39.0)	<.001
MZ twins[e] DZ twins	994 (25.8) 985 (24.6)					
TBI with LOC[f] = Yes N (%)	1455 (17.8)	1314 (17.0)	141 (29.3)	94 (31.0)	47 (30.7)	<.001
Age of first TBI N[g] Mean (SD)	2041 32.6 (23.1)	1857 32.4 (23.1)	184 35.0 (22.4)	122 34.0 (22.4)	62 36.9 (22.3)	.142
Number of TBI N (%) One More than one	1648 (19.9) 388 (4.7)	1518 (81.5) 345 (18.5)	130 (75.1) 43 (24.8)	87 (75.0) 29 (25.0)	43 (75.4) 14 (24.5)	<.001
Education Mean years (SD)	13.2 (3.2)	13.2 (3.2)	13.1 (3.3)	13.1 (3.2)	13.0 (3.5)	.207

Abbreviations: AD, Alzheimer's disease; DZs, dizygotic; LOC , loss of consciousness; MZs, monozygotic; SD, standard deviation; TBI, traumatic brain injury.
[a]63 of those with an AD diagnosis had a neuropathologically confirmed diagnosis.
[b]Among the non-AD dementias, 64 had vascular dementia; 58 had dementia of unknown etiology; 36 had frontotemporal dementia, Lewy body dementia, or a range of other types of dementia. Twenty-four of those with non-AD diagnosis had a neuropathologically confirmed diagnosis. Among the entire group of non-AD dementias, 64 had vascular dementia, 58 had dementia of unknown etiology, 11 had frontotemporal dementia, 11 Parkinson's disease dementia, 8 had Lewy body dementia, and the remaining 7 had a range of other types of dementia.
[c]All values reported in this table by zygosity are both complete and incomplete twin pairs with known zygosity (those with unknown zygosity are excluded). Baseline age did not differ between MZs and DZs ($P = .07$).
[d]Age of onset for those with dementia. For those without dementia, censoring age was age at death, 1 year after last contact by study, or age lost to follow-up. MZs and DZs differed significantly on this variable ($P < .05$).
[e]MZs and DZs did not differ on the proportion with a history of TBI ($P = .23$).
[f]Information on LOC was unknown for 145 with no dementia and 25 with dementia.
[g]Information for age of first TBI was unknown for 43 men.

providing justification for analyzing all pairs together. Logistic regression models among the 100 twin pairs (45 MZ and 55 DZ pairs) discordant for both TBI and onset of dementia showed that the twin with a TBI had an increased risk of all-cause dementia (McNemar OR = 1.56; 95% CI = 1.03–2.40; $P = .04$; Figure 2). This association appeared to be due mainly to twin pairs with non-AD dementia (McNemar OR = 2.70; 95% CI = 1.27–6.25; $P = 0.01$) and was attenuated in those with AD (McNemar OR = 1.17; 95% CI = 0.69–2.00; $P = .61$).

When the co-twin control analysis was limited to the MZ pairs ($n = 45$ pairs) to more fully control for genetic influences, the McNemar ORs increased for all-cause dementia (OR = 1.81; 95% CI = 0.95–3.57; $P = .07$) and for AD (McNemar OR = 1.60; 95% CI = 0.68–3.94; $P = .33$), but decreased for non-AD dementia (OR = 2.17; 95% CI = 0.77–6.95; $P = .17$), albeit none of the results reached statistical significance.

4 | DISCUSSION

The current study leveraged the twin method to investigate the association between TBI and dementia in twin pairs, thus providing inherent control for many genes and early life experiences that may contribute to risk of late life dementia, but yet cannot typically be measured in other studies. We found in the full sample that a history of TBI showed a trend toward increased risk of non-AD dementia, but not AD. This pattern remained when adding covariates of years of education, smoking, and overuse of alcohol. This association seemed to be primarily driven by the DZ twins in both the analyses of the full sample and the co-twin control sample. However, because DZ twins share fewer genes than MZ twins, unidentified genetic factors cannot be ruled out as a contributing factor to the association between TBI and non-AD dementia.

TABLE 2 Sample characteristics for co-twin control sample

	Demented first *N* = 100	Not demented or demented last *N* = 100	*P*-value
Age of onset or censoring age[a] Mean (SD)	71.01 (6.78)	77.85 (5.09)	<.001
Number with TBI N (%)	55 (55)	42 (42)	.07
Age of first TBI Mean (SD)	36.47 (21.08)	40.0 (23.64)	.44
Number with LOC n (%)[b]	37 (37)	31 (31)	.13
Education Mean years (SD)	13.34 (3.33)	12.77 (3.58)	.25

Abbreviations: LOC, loss of consciousness; SD, standard deviation; TBI, traumatic brain injury.
[a]Age of onset for those with dementia. For those without dementia, censoring age was age at death, 1 year after last contact by study, or age lost to follow-up.
[b]LOC was unknown for 11 of those with dementia first and 5 who were not demented or demented last.

TABLE 3 HRs for TBI and risk of dementia in full sample

	All dementia HR (95% CI), *P*-value	Alzheimer's disease HR (95% CI),*P*-value	Non-Alzheimer's disease dementia HR (95% CI), *P*-value
TBI = yes[a]	1.44 (0.97–2.14), *P* = .07	1.23 (0.76–2.00), *P* = .39	2.00 (0.97–4.12), *P* = .06
Monozygotic twins[b] *n* = 1618 pairs	TBI 1.71 (1.00–2.94), *P* = .05	TBI 1.85 (0.94–3.63), *P* = .08	TBI 1.50(0.61–3.67), *P* = .37
Dizygotic twins *n* = 1592 pairs	TBI 1.15 (0.63–2.09), *P* = .21	TBI 0.77 (0.37–1.57), *P* = .47	TBI 3.33 (0.92–12.11), *P* = .07
Age of TBI < 25 years old	TBI 1.31 (0.81–2.12), *P* = .28 TBI ≤ 25 years old 1.23 (0.68–2.22), *P* = .49	TBI 1.20 (0.68–2.12), *P* = .54 TBI ≤ 25 years old 1.07(0.52–2.01), *P* = .86	TBI 1.60 (0.65–3.95), *P* = .31 TBI ≤ 25 years old 1.53(0.53–4.36), Pp = .43
Time since TBI (per 10 years)	TBI 1.40(0.73–2.68), *P* = .31 Time since TBI 1.07 (0.88–1.15), *P* = .92	TBI 1.40 (0.65–3.02), *P* = .39 Time since TBI 0.97(0.82–1.14), *P* = .68	TBI 1.52 (0.45–5.15), *P* = .50 Time since TBI 1.07 (0.85–1.34), *P* = .59
TBI with LOC	TBI 2.31 (0.98–5.46), *P* = .06 TBI with LOC 0.55 (0.23–1.32), *P* = .18	TBI 2.48 (0.76–8.10), *P* = .13 TBI with LOC 0.40 (0.12–1.32), *P* = .13	TBI 2.20 (0.62–7.85), *P* = .22 TBI with LOC 1.00 (0.25–3.95), *P* = 1.00
Number of TBIs	TBI 1.39 (0.91–2.14), *P* = .14 ≥ 1 TBI 1.07(0.77–1.49), *P* = .68	TBI 1.18(0.70–1.97), *P* = .54 ≥ 1 TBI 1.12(0.74–1.69), *P* = .61	TBI 2.03(0.92–4.50), *P* = .08 ≥ 1 TBI 0.98(0.57–1.67), *P* = .93

Note: Some variables do not equal the total number of TBIs due to missing data.
Abbreviations: CI, confidence interval; HR, hazard ratio; LOC , loss of consciousness; TBI, traumatic brain injury.
[a]Analysis excluded 49 individuals who had an event prior to their baseline interview date or their twin's baseline interview date. *N* = 8302.
[b]The number of monozygotic twins and dizygotic twins includes in which both members of the twin pair.

Due to the limited number of twins with apolipoprotein E (*APOE*) genotype, we were not able to examine whether controlling for *APOE* contributed to this finding. Combined, these results support an increased risk for non-AD dementia associated with TBI, but not with AD.

Others have proposed that although long-term outcomes of TBI share neuropathological features and clinical symptoms of some classically defined neurodegenerative disorders, they are heterogeneous and have polypathologies making them difficult to categorize as a single neurodegenerative disorder.[31] Our results reflect this heterogeneity in that the non-AD dementia most strongly associated with TBI was dementia of unknown etiology, a category of dementia not phenotypically characteristic of any specific type of dementia. Without neuropathological evidence, clinical subtypes of dementia cannot be confirmed. But among those in our cohort with neuropathological confir-

TABLE 4 Covariate models and sensitivity analyses for HRs for TBI and risk of dementia

	All dementia HR (95% CI), *P*-value	Alzheimer's disease HR (95% CI), *P*-value	Non-Alzheimer's disease dementia HR (95% CI), *P*-value
TBI	1.50 (0.98–2.27) *P* = .06	TBI 1.39 (0.83–2.31) *P* = .21	TBI 2.13 (0.97–4.68) *P* = .06
Years of education	1.01 (0.92–1.10), *P* = .92	0.92 (0.80–1.06), *P* = .24	1.077 (0.92–1.26), *P* = .36
Alcohol overuse past or present (reference = no)	Overall *P* = .75	Overall *P* = .99	Overall *P* = .14
Yes	1.20 (0.75–1.92)	Yes = 1.04 (0.59–1.83)	Yes = 1.95 (0.79–4.81)
Smoking (reference = never)	Overall *P* = .25	Overall *P* = .48	Overall *P* = .22
Current	1.36 (0.65–2.82)	1.74 (0.65–4.66)	1.24 (0.39–3.92)
Past	0.79 (0.48–1.31)	1.18 (0.61–2.26)	0.44 (0.18–1.06)
Missing[a]	1.69 (0.53–5.46)	2.51 (0.56–11.29)	0.81(0.11–6.05)
Sensitivity analyses without left censoring			
TBI = yes	1.48 (1.03–2.12) *P* = .03	1.22 (0.79–1.88) *P* = .38	2.23 (1.16–4.29) *P* = .02

Abbreviation: CI, confidence interval; HR, hazard ratio; TBI, traumatic brain injury.
[a]The HR for missing for smoking applies to both smoking and alcohol overuse because individuals missing smoking were also missing alcohol overuse.

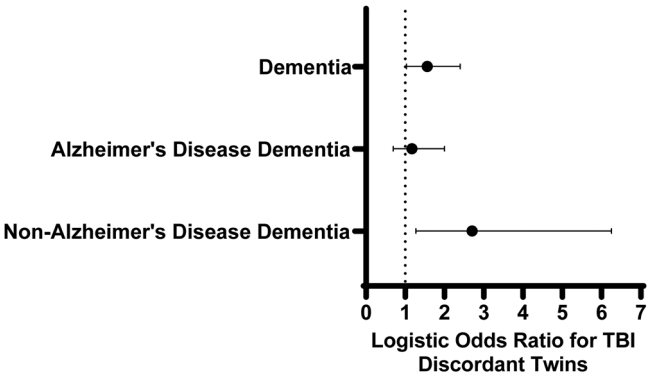

FIGURE 2 Logistic odds ratios for traumatic brain injury (TBI) and all-cause dementia, Alzheimer's disease dementia, and non-Alzheimer's disease dementia in twin pairs discordant for both TBI and dementia. Bars represent 95% confidence intervals

mation of the diagnosis, the clinical diagnosis showed high correlation with the neuropathology.[29] Others have also found that TBI is associated with increased risk of multiple types of dementia[32–34] and some have also not found an association between AD and TBI.[34–36] Adding further support to an association between TBI and non-AD dementia is a recent study that reported higher levels of a common AD biomarker, amyloid beta 42, were not detected among those with TBI and cognitive impairment, but rather blood-based neurodegenerative proteins and inflammatory cytokines were elevated among those with TBI and cognitive impairment, even decades after the TBI.[37]

There has been much interest in the long-term effects of multiple TBIs, particularly sports- and military-related injuries. Numerous studies have reported that such repetitive injuries lead to cognitive, functional, and psychiatric problems associated with a specific pathological pattern that has been termed chronic traumatic encephalopathy.[38] Our findings are consistent with the risk of dementia increasing further with more than one TBI; however, the HRs were not significant.

Our study has some limitations. We relied on self or proxy report for the history of TBI and LOC. Our prior work[1] showed that both individuals and their proxies tend to under-report lifetime history of TBI with the less severe TBIs under-reported at a higher rate. However, our prior work provided no evidence that under-reporting occurred more frequently among individuals who eventually developed dementia, thus such under-reporting was unlikely to bias our results.[1] We note that even studies using medical records to identify TBI are typically limited to relatively few years within the total lifespan, thus they too have errors in classification of exposure to TBI. In contrast to findings from other studies,[1] self-reported LOC did not increase the associated risk between TBI and dementia. This raises questions about the rate of accuracy of self-reported LOC. Another consideration is that we used diagnostic criteria current during the period of data collection, thus amyloid and tau biomarkers were not available. In addition, consistent with other epidemiological studies with geographically dispersed samples, standardized neuroimaging was not available for all participants as part of the dementia evaluation. However, when possible we did obtain medical records, including neuroimaging reports, to review as part of our diagnostic adjudication procedures. Typically multiple pathologies are present in the brains of individuals with dementia, but for the present analyses, including the subset with neuropathological examinations, we used the primary diagnosis to categorize dementia type. Even when multiple neuropathologies are identified it would be difficult to parse the impact of each on the association between TBI and dementia. It is also noted that although co-twin control analyses have more statistical power than non-twin samples of comparable size, the power for some analyses was limited as evidenced by the relatively

wide CIs around some of the risk estimates. This suggests that these results should be confirmed in other samples. Finally, the NAS-NRC Twin Registry is limited to males, thus our results do not directly generalize to females. However other studies have reported that female veterans with a history of TBI also have a higher risk of dementia in later life.[39]

Despite these limitations, twin studies have significant advantages over standard epidemiologic case-control designs by minimizing confounding by both genetic and environmental factors, thereby reducing the likelihood of spurious associations. The twin study design allows for control of a multitude of shared factors when estimating an effect, without a requirement for inclusion of a large number of control variables in the model. Furthermore, this design controls for these shared factors even when they have not been identified, meaning they have unique benefit when genetic testing and information on exposures throughout the lifespan are not available. Combined, these points highlight the unique value of the twin design when studying late-life complex diseases that result from accumulated risk through the lifespan, such as dementia. In addition, our use of a standardized, comprehensive, in-person dementia evaluation that has been validated with neuropathology, and used in multiple large epidemiological studies, strengthened the investigation of the association between TBI and various types of dementia.

The twins in these analyses were veterans of World War II and the Korean War, although only some of the injuries were incurred during their war-time service. Decades pass before those injured during military service reach the age of risk for dementia, thus highlighting the value of this registry, which is the only US twin registry in which all members have reached the age of dementia risk. Recent military conflicts have resulted in an alarming increase of TBIs with an estimated 10% to 20% of veterans from the wars in Iraq and Afghanistan having suffered TBI.[40–42] This large number of aging veterans at increased risk of dementia due to TBI will add substantially to the projected growing number of individuals with dementia. Thus, the importance of understanding the long-term impact of TBI will only increase as the veterans of recent conflicts reach the age of risk of dementia.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. 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.
2. Barnes DE, Byers AL, Gardner RC, Seal KH, Boscardin WJ, Yaffe K. Association of mild traumatic brain injury with and without loss of consciousness with dementia in US military veterans. *JAMA Neurol*. 2018;75(9):1055-1061.
3. 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.
4. Huang CH, Lin CW, Lee YC, et al. Is traumatic brain injury a risk factor for neurodegeneration? A meta-analysis of population-based studies. *BMC Neurol*. 2018;18(1):184.
5. 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.
6. 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.
7. Julien J, Joubert S, Ferland MC, et al. Association of traumatic brain injury and Alzheimer disease onset: a systematic review. *Ann Phys Rehabil Med*. 2017;60(5):347-356.
8. Dams-O'Connor K, Gibbons LE, Bowen JD, McCurry SM, Larson EB, Crane PK. Risk for late-life re-injury, dementia and death among individuals with traumatic brain injury: a population-based study. *J Neurol Neurosurg Psychiatry*. 2013;84(2):177-182.
9. Launer LJ. The epidemiologic study of dementia: a life-long quest?. *Neurobiol Aging*. 2005;26(3):335-340.
10. Seifan A, Schelke M, Obeng-Aduasare Y, Isaacson R. Early life epidemiology of Alzheimer's disease—a critical review. *Neuroepidemiology*. 2015;45(4):237-254.
11. Tani Y, Fujiwara T, Kondo K. Association between adverse childhood experiences and dementia in older Japanese adults. *JAMA Netw Open*. 2020;3(2):e1920740.
12. McGue M, Osler M, Christensen K. Causal inference and observational research: the utility of twins. *Perspect Psychol Sci*. 2010;5(5):546-556.
13. Godbolt AK, Cancelliere C, Hincapie CA, et al. Systematic review of the risk of dementia and chronic cognitive impairment after mild traumatic brain injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch Phys Med Rehabil*. 2014;95:S245-S256.
14. Hrubec Z, Neel JV. The National Academy of Sciences—National Research Council Twin Registry: ten years of operation. *Prog Clin Biol Res*. 1978;24:153-172.
15. Jablon S, Neel JV, Gershowitz H, Atkinson GF. The NAS-NRC twin panel: methods of construction of the panel, zygosity diagnosis, and proposed use. *Am J Hum Genet*. 1967;19(2):133-161.
16. Reed T, Plassman BL, Tanner CM, Dick DM, Rinehart SA, Nichols WC. Verification of self-report of zygosity determined via DNA testing in a subset of the NAS-NRC twin registry 40 years later. *Twin Res Hum Genet*. 2005;8(4):362-367.
17. Plassman BL, Steffens DC, Burke JR, et al. Duke twins study of memory in aging in the NAS-NRC twin registry. *Twin Res Hum Genet*. 2006;9(6):950-957.
18. Welsh KA, Breitner JC, Magruder-Habib KM. Detection of dementia in the elderly using telephone screening of cognitive status. *Neuropsychiatry Neuropsychol Behav Neurol*. 1993;6:103-110.
19. Jorm AF, Jacomb PA. The informant questionnaire on cognitive decline in the elderly (IQCODE): socio-demographic correlates, reliability, validity and some norms. *Psychol Med*. 1989;19(4):1015-1022.
20. Silverman JM, Keefe RS, Mohs RC, Davis KL. A study of the reliability of the family history method in genetic studies of Alzheimer disease. *Alzheimer Dis Assoc Disord*. 1989;3(4):218-223.
21. American Psychiatric Association. (1987). *Diagnostic and Statistical Manual of Mental Disorder*. (3rd ed., revised), Washington, DC.
22. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34(7):939-944.

23. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology*. 1993;43(2):250-260.
24. Lund and Manchester Groups. Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. *J Neurol Neurosurg Psychiatry*. 1994;57(4):416-418.
25. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology*. 1996;47(5):1113-1124.
26. McKeith IG, Perry EK, Perry RH. Report of the second dementia with Lewy body international workshop: diagnosis and treatment. Consortium on Dementia with Lewy Bodies. *Neurology*. 1999;53(5):902-905.
27. Plassman BL, Langa KM, Fisher GG, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. *Neuroepidemiology*. 2007;29(1-2):125-132.
28. Breitner JC, Wyse BW, Anthony JC, et al. APOE-epsilon4 count predicts age when prevalence of AD increases, then declines: the Cache County Study. *Neurology*. 1999;53(2):321-331.
29. Plassman BL, Khachaturian AS, Townsend JJ, et al. Comparison of clinical and neuropathologic diagnoses of Alzheimer's disease in 3 epidemiologic samples. *Alzheimers Dement*. 2006;2(1):2-11.
30. Kleinbaum D, Klein M. *Survival Analysis: A Self-Learning Text*. 2nd ed.. Springer; 2005.
31. Washington PM, Villapol S, Burns MP. Polypathology and dementia after brain trauma: does brain injury trigger distinct neurodegenerative diseases, or should they be classified together as traumatic encephalopathy?. *Exp Neurol*. 2016;275:381-388.
32. Gardner RC, Burke JF, Nettiksimmons J, Kaup A, Barnes DE, Yaffe K. Dementia risk after traumatic brain injury vs nonbrain trauma: the role of age and severity. *JAMA Neurol*. 2014;71(12):1490-1497.
33. Rosso SM, Landweer EJ, Houterman M, Donker Kaat L, van Duijn CM, van Swieten JC. Medical and environmental risk factors for sporadic frontotemporal dementia: a retrospective case-control study. *J Neurol Neurosurg Psychiatry*. 2003;74(11):1574-1576.
34. Kalkonde YV, Jawaid A, Qureshi SU, et al. Medical and environmental risk factors associated with frontotemporal dementia: a case-control study in a veteran population. *Alzheimers Dement*. 2012;8(3):204-210.
35. Weiner MW, Crane PK, Montine TJ, Bennett DA, Veitch DP. Traumatic brain injury may not increase the risk of Alzheimer disease. *Neurology*. 2017;89(18):1923-1925.
36. Weiner MW, Harvey D, Hayes J, et al. Effects of traumatic brain injury and posttraumatic stress disorder on development of Alzheimer's disease in Vietnam Veterans using the Alzheimer's Disease Neuroimaging Initiative: preliminary report. *Alzheimers Dement (N Y)*. 2017;3(2):177-188.
37. Peltz CB, Kenney K, Gill J, Diaz-Arrastia R, Gardner RC, Yaffe K. Blood biomarkers of traumatic brain injury and cognitive impairment in older veterans. *Neurology*. 2020;95(9):e1126-e1133.
38. McKee AC, Daneshvar DH. The neuropathology of traumatic brain injury. *Handb Clin Neurol*. 2015;127:45-66.
39. Kornblith E, Peltz CB, Xia F, Plassman B, Novakovic-Apopain T, Yaffe K. Sex, race, and risk of dementia diagnosis after traumatic brain injury among older veterans. *Neurology*. 2020;95(13):e1768-e1775.
40. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. Soldiers returning from Iraq. *N Engl J Med*. 2008;358(5):453-463.
41. Elder GA, Cristian A. Blast-related mild traumatic brain injury: mechanisms of injury and impact on clinical care. *Mt Sinai J Med*. 2009;76(2):111-118.
42. Wojcik BE, Stein CR, Bagg K, Humphrey RJ, Orosco J. Traumatic brain injury hospitalizations of U.S. army soldiers deployed to Afghanistan and Iraq. *Am J Prev Med*. 2010;38:S108-S116.

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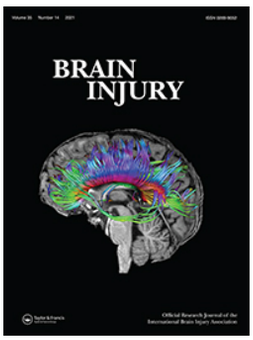

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Traumatic brain injury, cardiovascular disease, and risk of dementia among older US Veterans

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ABSTRACT

Objective: Traumatic brain injury (TBI) is associated with elevated rates of cardiovascular disease (CVD), and both CVD and TBI are risk factors for dementia. We investigated whether CVD and its risk factors underlie the association between TBI and dementia.

Materials and Methods: Cox proportional hazards models among 195,416 Veterans Health Administration patients age 55+ with TBI and a non-TBI, age/sex/race-matched comparison sample.

Results: Veterans +TBI were more likely to have any CVD diagnosis (24% vs 36% p = <0.001) or risk factor (83 vs. 90% p < .001) compared to -TBI. During follow-up (mean ~7 years), 12.0% of Veterans with TBI only (HR: 2.17 95% CI 2.09–2.25), and 10.3% with CVD only developed dementia (HR 1.21 95% CI 1.15–1.28), compared to 6.5% with neither. There was an additive association between TBI and CVD on dementia risk (HR 2.51, 95% CI 2.41–2.61). Among those +TBI (±CVD), risk was minimally attenuated by adjustment for CVD/CVD risk factors (unadjusted HR: 2.38, 95% CI: 2.31–2.45; adjusted HR: 2.17, 95% CI 2.10–2.23).

Conclusions: Older veterans TBI have increased prevalence of CVD/CVD risk factors. TBI and CVD had an additive statistical association, with dementia risk increased by ~2.5-fold. However, CVD accounted for little of the association between TBI and dementia. More research is needed to understand mechanisms of TBI-dementia and inform clinical guidelines post-TBI.

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Introduction

Traumatic brain injury (TBI) is common and debilitating (1,2), and is associated with several adverse outcomes, particularly among older adults (3,4). Of particular public health significance, TBI, including mild TBI (5), is a risk factor for dementia (6–12). However, the etiology and mechanisms underlying the relationship between TBI and dementia risk are largely unknown. One possible link between TBI and increased risk for dementia is cardiovascular disease (CVD) as individuals with a history of TBI have a higher burden of CVD (13–15), and CVD is a well-documented risk factor for dementia (16–18).

However, the relationship between TBI and CVD is not yet well understood. Older adults who experience a TBI have high rates of preexisting CVD and CVD risk factors (15), which may increase TBI risk through vulnerability to falls (19). TBI may also increase the risk for, or even cause, CVD: TBI exposure has been shown to increase the risk for subsequent CVD compared to individuals without TBI (14), and vascular damage is a commonly reported outcome of TBI due to molecular changes causing chronic inflammation and damage to the blood-brain barrier (13,20).

Although CVD is an established risk factor for cognitive decline and dementia (16–18), it is unknown how CVD and TBI together may contribute to the risk of dementia. CVD may explain the association between TBI and dementia; exacerbate the effects of TBI, including dementia risk; or could have an effect on dementia risk independent of TBI (i.e., additive effect). In addition to addressing possible mechanisms linking TBI to dementia, understanding how TBI and CVD together increase the risk for dementia has important implications for the clinical management of patients with TBI.

Veterans are a group at high risk for TBI and may be particularly vulnerable to developing dementia (21). Therefore, our objective was to study a large, diverse, nationally representative cohort of older veterans to investigate whether CVD explains the association between TBI and dementia or whether they have additive or synergistic effects.

Methods

Standard protocol approvals

All study procedures were approved by institutional review boards at the University of California, San Francisco, San Francisco Veterans Affairs Medical Center, and US Army Medical Research and Materiel Command Human Research Protection Office. Informed consent was waived because of the use of deidentified archival data.

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Study population

We sourced data from two nationwide Veterans Health Administration (VHA) system databases: the inpatient and outpatient visits database (National Patient Care Database [NPCD]) and the Vital Status File. Using these databases, we identified all VHA patients 55 years of age or older who received a TBI diagnosis between October 1, 2002 and September 30, 2019. TBI was defined using the Defense and Veterans Brain Injury Center list of International Classification of Disease, Ninth and Tenth Revisions (ICD-9 and 10) Codes for TBI surveillance coded in inpatient or outpatient visits.

To identify a comparison sample of veterans without TBI, we first selected all veterans aged 55 years and older evaluated at VHA facilities during the study period. We excluded veterans with prevalent dementia during the 2-year baseline period (defined as 2 years prior to TBI diagnosis or a randomly selected date within the study period for Veterans without TBI) and those with less than 1 year of follow-up. We then performed 1:1 matching based on age, sex, and race (white vs. nonwhite), resulting in 97,708 veterans with TBI and 97,708 veterans without TBI. Dementia was defined using the VA Dementia Steering Committee's recommended list of ICD-9 and 10 codes (2016 version) (22) or a prescription for dementia medication (donepezil, memantine, rivastigmine, and galantamine).

Demographic information (age, sex, and race/ethnicity) was collected from VHA inpatient or outpatient files. Zip codes and 2012 US Census data were used to categorize veterans' residences into educational and income categories (for education, 25% or less of the adult population has a bachelor's degree or higher vs. more than 25%; income was categorized into median income tertiles). Post-traumatic stress disorder (PTSD), depression, and cardiovascular risk factors (diabetes mellitus, obesity/overweight, current tobacco use, hypertension, and hypercholesteremia) were defined using ICD-9 and 10 codes assessed during the 2-year period prior to the TBI diagnosis or random selection date. Cardiovascular disease (CVD) was defined as having an ICD 9 or 10 code for any of the following: heart failure, atrial fibrillation, stroke/transient ischemic attack or coronary artery disease (using the VA Informatics and Computing Infrastructure [VINCI] phenotype library definition of myocardial infarction, cardiac arrest, coronary arteriosclerosis, or coronary artery bypass grafting procedure codes).

Baseline characteristics of the age, sex, and race matched veterans with and without TBI were compared using *t* tests for continuous variables and *chi-square* tests for categorical variables. We used Cox proportional hazard regression models to determine whether TBI was associated with greater risk of dementia by censoring at the date of the last medical encounter and age as a timescale. Models were unadjusted and then adjusted for confounding factors selected a priori in steps for 1) education, depression, and PTSD; and 2) education, depression, PTSD, any cardiovascular risk factor, and any CVD diagnosis. We also completed a sensitivity analysis additionally adjusting for incident CVD risk factors and diagnoses occurring during follow-up. We also repeated our analyses using Fine-Gray proportional hazards models to account for the competing risk of death. Results are reported as hazard ratios (HR) with 95% confidence intervals (CI). We separately tested for the presence of an interaction between TBI and any CVD at risk of dementia. Additionally, we examined whether TBI and any CVD only, or TBI and any CVD in combination, were associated with greater risk of dementia. Cumulative incidence of dementia as a function of TBI and CVD diagnoses was examined graphically.

Standard statistical and graphical techniques were used to assess proportional hazards assumptions for all final models. Statistical significance was set at $p < .05$ (two-sided). SAS version 9.4 and STATA/MP version 16.1 were used for all analyses. The data are derived from VHA electronic health records and contain protected health information; therefore, the data cannot be placed in a public repository. Please contact the authors for additional details regarding the process of accessing these data.

Results

Veterans had a mean age of 67 years (SD 9.31) at baseline; 6% were female, and 80% were white. Although we included veterans with TBIs across the severity spectrum, approximately 80% of participants had injuries categorized as mild. Baseline characteristics of veterans with and without TBI are shown in Table 1. Veterans with TBI were much more likely than those without TBI to have any CVD diagnosis (36% vs 24%, p < .001) or any cardiovascular risk factors (90% vs 83%). Thirty-two percent of veterans with TBI had a diagnosis of diabetes mellitus compared to 28% without TBI, and 78% with TBI had a diagnosis of hypertension compared to 70% without TBI (p < .001 for both). Additionally, 22% of veterans with TBI compared to 15% of veterans without TBI currently used tobacco at baseline, and 21% of veterans with TBI vs. 17% of those without were categorized as overweight or obese (p < .001 for both). Veterans with TBI were also almost twice as likely than those without TBI to have depression (29% vs. 15%, p < .001) and PTSD (19% vs. 10%). Moreover, education and income differed

Table 1. Baseline characteristics based on traumatic brain injury (TBI) status among older veterans.

	No TBI (n = 97,708)	Any TBI (n = 97,708)	P
Demographic			
Age, y, mean (SD)	66.91 (9.3)	66.91 (9.3)	–
Female, n (%)	5,690 (5.8)	5,690 (5.8)	–
White	77,372 (79.2)	77,372 (79.2)	–
>25% college-educated zip code	46,034 (47.1)	46,953 (48.1)	<.001
Low median income tertile	32,349 (33.1)	33,107 (33.9)	<.001
Any CVD Risk Factor	81,553 (83.5)	87,921 (90.0)	<.001
Current tobacco use	14,334 (14.7)	21,320 (21.8)	<.001
Diabetes mellitus	26,993 (27.6)	30,744 (31.5)	<.001
Obesity/overweight	16,087 (16.5)	20,012 (20.5)	<.001
Hypertension	68,772 (70.4)	76,528 (78.3)	<.001
Hypercholesterolemia	59,744 (61.2)	64,044 (65.6)	<.001
Any CVD Diagnosis	23,184 (23.7)	34,794 (35.6)	<.001
Coronary artery disease (CAD)	15,598 (16.0)	19,275 (19.7)	<.001
Heart Failure	4,252 (4.4)	8,049 (8.2)	<.001
Atrial Fibrillation	4,821 (4.9)	9,135 (9.4)	<.001
Stroke/transient ischemic attack	5,634 (5.8)	15,816 (16.2)	<.001
Psychiatric			
Depression	14,311 (14.7)	28,273 (28.9)	<.001
Post-traumatic stress disorder	9,232 (9.5)	18,756 (19.2)	<.001

SD, standard deviation, CVD, cardiovascular disease.

between veterans with and without TBI, such that those with TBI were slightly better educated and more likely to live in less wealthy ZIP codes compared to those without TBI.

Overall, 10.8% of veterans developed a dementia diagnosis over follow-up (mean 6.6 years, range 1–18 years) with veterans with TBI developing dementia at a higher rate (14.3%) compared to those without TBI (7.4%). The unadjusted risk of dementia was almost two and a half times as high for veterans with TBI compared to those without TBI (HR: 2.38, 95% CI: 2.31–2.45). After adjustment for education, depression and PTSD, the HR was slightly attenuated to 2.21 (95% CI 2.15–2.28). After further adjustment for any CVD diagnoses and any CVD risk factor, the adjusted hazard for dementia was 2.17 (95%, CI 2.10–2.23). Results were similar using Fine-Gray proportional hazards models accounting for the competing risk of death (unadjusted, HR: 2.29, 95% CI 2.23–2.36; fully adjusted HR: 2.08, 95% CI 2.02–2.14). About 33% of veterans who did not have CVD risk factors or a CVD diagnosis at baseline developed incident CVD or risk factors during follow-up; 35% of those with TBI and 31% of those with no TBI. Our sensitivity analysis adjusting for incident CVD risk factors and diagnoses led to similar results (fully adjusted HR: 2.18, 95% CI 2.12–2.25).

There was no evidence of an interaction between TBI and any CVD diagnosis of dementia risk (p for interaction, 0.12). Table 2 shows the unadjusted and adjusted associations between TBI only and dementia, any CVD diagnosis only and dementia, or TBI in addition to any CVD diagnosis with dementia. Compared with Veterans with neither exposure (6.5%), veterans with TBI only, CVD only, or both TBI and CVD had higher rates of incident dementia during follow-up (with incident dementia rates ranging from 12.0% for TBI only to 18.4% for both diagnoses). TBI and CVD were both associated with an increased risk of dementia in a model adjusted for education, depression, PTSD and cardiovascular risk factors (TBI only HR: 2.17, 95% CI 2.09–2.25; CVD only HR: 1.21, 95% CI 1.15–1.28). Veterans with TBI plus any CVD diagnosis had the highest risk of dementia (HR: 2.51, 95% CI 2.41–2.61), suggesting the presence of an independent, additive statistical association. Results of sensitivity analyses adjusting for both baseline and incident CVD and CVD risk factors were very similar: TBI only HR 2.23, 95% CI 2.12–2.35; CVD only HR 1.08, 95% CI 1.02–1.13; TBI plus CVD HR 2.33, 95% CI 2.22–2.43). The cumulative incidence of dementia diagnosis among veterans with TBI, any CVD diagnosis, or both is shown in Figure 1.

Discussion

In this large, diverse, nationally representative cohort of older US veterans, we observed an increased prevalence of both CVD and cardiovascular risk factors among older veterans with TBI compared to those without TBI. Moreover, we found that TBI exposure was associated with more than a 2-fold increase in the risk for dementia, and CVD was also associated with increased dementia risk. However, the statistical association between TBI and dementia remained elevated after adjusting for CVD diagnoses and risk factors, suggesting that CVD and its risk factors do not account for much of the increased risk of dementia with TBI.

Despite the documented connections between TBI and CVD and risk factors (13–15,19), little prior research has explicitly addressed the impact of CVD on risk for dementia after TBI. Here, our results suggest a large increased risk of dementia after TBI (6–12) as well as a modest increase in dementia risk associated with CVD (16,17). However, we did not find that CVD or risk factors accounted for the association between TBI and risk for dementia, nor did we find an interaction between TBI and CVD on dementia risk. Instead, we observed an additive statistical association between TBI and CVD on the risk of dementia. It is clear that more research is needed to understand the mechanisms and causal pathways underlying the increased dementia diagnosis risk after TBI.

The reason for the elevated prevalence of CVD and CVD risk factors among those with TBI is unclear. Our results constitute a statistical association and do not establish a causal relationship between CVD and TBI. However, there are multiple pathways by which CVD and TBI appear to be related. For example, TBI may trigger a complex molecular cascade that is not yet fully understood but that may lead to a number of central nervous system changes including arterial stiffness, chronic inflammation, and damage to the blood-brain barrier (23). These neurovascular changes also increase the risk for stroke (23). TBI also increases the risk of incident CVD, including coronary artery disease, arrhythmias, heart failure, and stroke (14), perhaps by disturbing hemodynamics and interfering with coagulation pathways (24).

Besides CVD, there are several additional proposed mechanistic pathways for the association between TBI and dementia. TBI appears to trigger neuropathological changes, which may lead to dementia, through multiple pathways including the deposition of both tau and amyloid (25), and biomarkers of neuronal damage have been observed in the blood of TBI patients even many years after injury (26). However, one study with brain autopsies has shown that individuals with TBI are at higher risk for Lewy body

Table 2. The association between TBI and CVD and risk of dementia from Cox proportional hazards models.

	No. (%)	HR (95% CI)		
	Dementia	Unadjusted	Adjusted	
			Model 1	Model 2
Neither	4,864 (6.5)	ref	ref	ref
TBI only	7,555 (12.0)	2.35 (2.27–2.44)	2.19 (2.11–2.27)	2.17 (2.09–2.25)
CVD only	2,378 (10.3)	1.26 (1.20–1.32)	1.23 (1.17–1.29)	1.21 (1.15–1.28)
TBI and CVD	6,398 (18.4)	2.83 (2.72–2.94)	2.59 (2.49–2.69)	2.51 (2.41–2.61)

TBI, traumatic brain injury, CVD, cardiovascular disease, HR, hazard ratio, CI, confidence interval, PTSD, post-traumatic stress disorder. Unadjusted and adjusted analyses included Veterans with TBI matched 1:1 on age, race, and sex. Model 1 adjusted for education, PTSD, and depression. Model 2 adjusted for education, PTSD, depression, and CVD risk factors (diabetes mellitus, obesity/ overweight, current tobacco use, hypertension, and hypercholesterolemia).

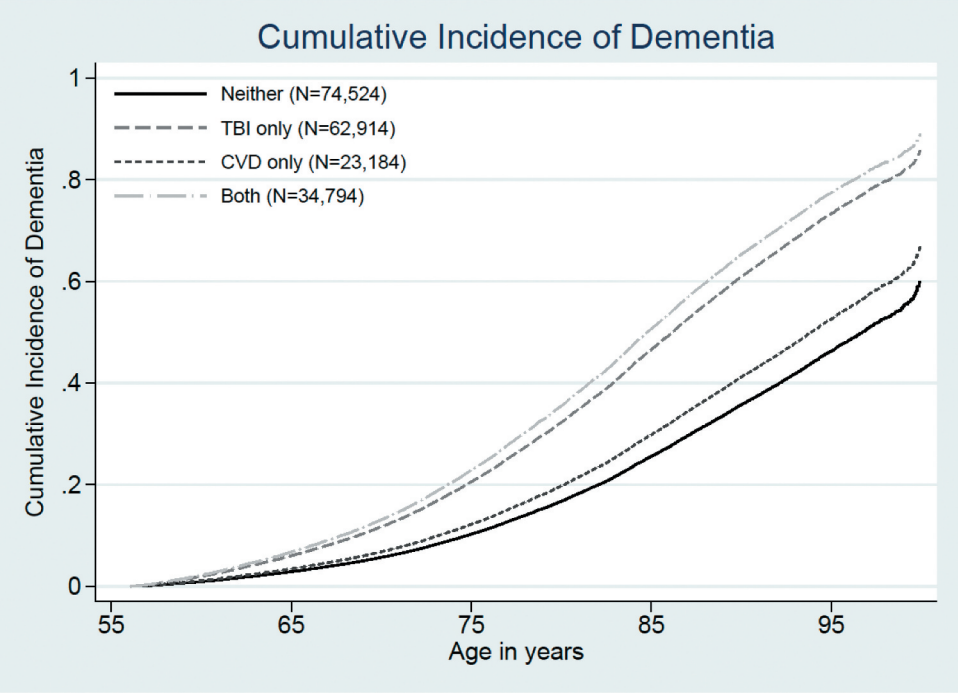

Figure 1. The additive association between traumatic brain injury (TBI) and cardiovascular disease (CVD) is illustrated by showing the cumulative incidence of dementia with age as the timescale for veterans with TBI only (dark gray), CVD only (dashed black), both TBI and CVD (light gray), or neither (solid black).

dementia and Parkinson's disease neuropathology, rather than the neurofibrillary plaques and tangles that define Alzheimer's disease (27). Dementia diagnoses after TBI may also reflect cognitive impairment associated with the TBI-related structural damage rather than from the presence of a secondary neurodegenerative process (28). This is supported by the accumulating evidence that greater severity of TBI is linked to higher risk of dementia (21). Finally, repeated TBIs are associated with chronic traumatic encephalopathy (CTE), a condition characterized by a unique pattern of neuropathology detectable only by autopsy (29) and a loosely defined clinical syndrome that may include aggression, personality change, and cognitive impairment (30). It is possible that CTE pathology alone or in combination with other aging processes could result in a clinical dementia presentation in some cases.

There are limitations to our study that impact the interpretation and generalizability of our results. While we carefully matched on the key variables of age, sex and race and adjusted for important confounders, all observational studies retain the risk of unmeasured confounding. We used ICD-9 and 10 codes as well as dementia medications in existing medical records for dementia diagnoses, which may result in less sensitive categorization of participants compared to studies in which participants were given a comprehensive dementia examination. Finally, the results may not generalize to veterans who do not receive VA health care or to non-Veterans.

This is one of the first studies to examine the impact of CVD and CVD risk factors on risk for dementia diagnosis after TBI. Our primary finding was that, in a large, diverse, nationally representative sample of older veterans, TBI was associated with a higher prevalence of CVD and risk factors. Yet, the statistical association between TBI and dementia diagnosis was not attenuated by adjustment for CVD risk factors or CVD, indicating that CVD does not seem to account for much of the risk for dementia after TBI. Our results also revealed an additive statistical association between TBI and CVD. Given the high prevalence of CVD in veterans with a history of TBI, as well as their increased risk of dementia, these findings suggest that more research is needed to determine causal links among CVD, TBI, and dementia and to inform clinical guidelines for older veterans post-TBI in order to optimize healthy cognitive aging.

Disclosure statement

Erica Kornblith: Reports no disclosures relevant to the manuscript.Amber Bahorik: Reports no disclosures relevant to the manuscript.Yixia Li: Reports no disclosures relevant to the manuscript.Carrie B. Peltz: Reports no disclosures relevant to the manuscript.Deborah E. Barnes: Reports no disclosures relevant to the manuscript.Kristine Yaffe: Dr. Yaffe serves on Data Safety Monitoring Boards for Eli Lilly and several National Institute on Aging-sponsored studies, and serves on the board of directors for Alector, Inc.

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Statistical analysis

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References

1. Whiteneck GG, Cuthbert JP, Corrigan JD, Bogner JA. 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.
2. Selassie AW, Zaloshnja E, Langlois JA, Miller T, Jones P, Steiner C. Incidence of long-term disability following traumatic brain injury hospitalization, United States, 2003. J Head Trauma Rehabil. 2008;23(2):123–31. doi:10.1097/01.HTR.0000314531.30401.39.
3. Thompson HJ, McCormick WC, Kagan SH. Traumatic brain injury in older adults: epidemiology, outcomes, and future implications. J Am Geriatr Soc. 2006;54(10):1590–95. doi:10.1111/j.1532-5415.2006.00894.x.
4. Gardner RC, Dams-O'Connor K, Morrissey MR, Manley GT. Geriatric traumatic brain injury: epidemiology, outcomes, knowledge gaps, and future directions. J Neurotrauma. 2018;35(7):889–906. doi:10.1089/neu.2017.5371.
5. Barnes DE, Byers AL, Gardner RC, Seal KH, Boscardin WJ, Yaffe K. Association of mild traumatic brain injury with and without loss of consciousness with dementia in US military veterans. JAMA Neurol. 2018;75(9):1055–61. doi:10.1001/jamaneurol.2018.0815.
6. Mortimer JA, Van Duijn CM, Fratiglioni L, Graves AB, Heyman A, Jorm AF, et al. Head trauma as a risk factor for Alzheimer's disease: a collaborative re-analysis of case-control studies. Int J Epidemiol. 1991;20(Supplement_2):S28–S35. doi:10.1093/ije/20.Supplement_2.S28.
7. Plassman BL, Havlik RJ, Steffens DC, Helms MJ, Newman TN, Drosdick D, Phillips C, Gau BA, Welsh-Bohmer KA, Burke JR, et al. Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology. 2000;55(8):1158–66. doi:10.1212/WNL.55.8.1158.
8. Guo Z, Cupples LA, Kurz A, Auerbach SH, Volicer L, Chui H, Green RC, Sadovnick AD, Duara R, DeCarli C, et al. Head injury and the risk of AD in the MIRAGE study. Neurology. 2000;54(6):1316–23. doi:10.1212/WNL.54.6.1316.
9. Wang HK, Lin SH, Sung PS, Wu MH, Hung KW, Wang LC, et al. Population based study on patients with traumatic brain injury suggests increased risk of dementia. J Neurol Neurosurg Psychiatry. 2012;83(11):1080–85. doi:10.1136/jnnp-2012-302633.
10. Gardner RC, Burke JF, Nettiksimmons J, Kaup A, Barnes DE, Yaffe K. Dementia risk after traumatic brain injury vs nonbrain trauma: the role of age and severity. JAMA Neurol. 2014;71(12):1490–97. doi:10.1001/jamaneurol.2014.2668.
11. Lee Y-K, Hou S-W, Lee -C-C, Hsu C-Y, Huang Y-S, Su Y-C. 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.
12. Nordström P, Michaëlsson K, Gustafson Y, Nordström A. Traumatic brain injury and young onset dementia: a nationwide cohort study. Ann Neurol. 2014;75(3):374–81. doi:10.1002/ana.24101.
13. Hammond FM, Corrigan JD, Ketchum JM, Malec JF, Dams-O'Connor K, Hart T, Novack TA, Bogner J, Dahdah MN, Whiteneck GG, et al. Prevalence of medical and psychiatric comorbidities following traumatic brain injury. J Head Trauma Rehabil. 2019;34(4):E1. doi:10.1097/HTR.0000000000000465.
14. Nyam -T-TE, Ho C-H, Chio -C-C, Lim S-W, Wang -J-J, Chang C-H, Kuo J-R, Wang -C-C. Traumatic brain injury increases the risk of major adverse cardiovascular and cerebrovascular events: a 13-year, population-based study. World Neurosurg. 2019;122:e740–e753.
15. Kumar, RG, Juengst, SB, Wang, Z, Dams-O'Connor, K, Dikmen, SS, O'Neil-Pirozzi, TM, Dahdah, MN, Hammond, FM, Felix, ER, Arenth, PM, et al.Epidemiology of comorbid conditions among adults 50 years and older with traumatic brain injury. Journal of head trauma rehabilitation, 2018;33(1):p. 15–24. doi:10.1097/HTR.0000000000000273.
16. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology. 2005;64(2):277–81. doi:10.1212/01.WNL.0000149519.47454.F2.
17. Stampfer M. Cardiovascular disease and Alzheimer's disease: common links. J Intern Med. 2006;260(3):211–23. doi:10.1111/j.1365-2796.2006.01687.x.
18. Eriksson UK, Bennet AM, Gatz M, Dickman PW, Pedersen NL. Non-stroke cardiovascular disease and risk of Alzheimer's disease and dementia. Alzheimer Dis Assoc Disord. 2010;24(3):213. doi:10.1097/WAD.0b013e3181d1b99b.
19. Coronado VG, Thomas KE, Sattin RW, Johnson RL. The CDC traumatic brain injury surveillance system: characteristics of persons aged 65 years and older hospitalized with a TBI. J Head Trauma Rehabil. 2005;20(3):215–28. doi:10.1097/00001199-200505000-00005.
20. Caplan B, Bogner J, Brenner L, Malec J, Kumar RG, Juengst SB, et al. Epidemiology of comorbid conditions among adults 50 years and older with traumatic brain injury. J Head Trauma Rehabil. 2018;33(1):15–24. doi:10.1097/HTR.0000000000000273.
21. Barnes DE, Kaup A, Kirby KA, Byers AL, Diaz-Arrastia R, Yaffe K. Traumatic brain injury and risk of dementia in older veterans. Neurology. 2014;83(4):312–19. doi:10.1212/WNL.0000000000000616.
22. *US Department of Veterans Affiars (VA) Veterans Health Administration (VHA) Dementia Steering Committee (DSC)*. VHA dementia steering committee recommendations for dementia care in the VHA healthcare system 2016; 2016 [cited 2019 Sep 3]. https://www.va.gov/GERIATRICS/docs/VHA_DSC_RECOMMENDATIONS_SEPT_2016_9-12-16.pdf .
23. Salehi A, Zhang JH, Obenaus A. Response of the cerebral vasculature following traumatic brain injury. J Cereb Blood Flow. 2017;37(7):2320–39. doi:10.1177/0271678X17701460.
24. Fletcher-Sandersjöö A, Maegele M, Bellander B-M. Does complement-mediated hemostatic disturbance occur in traumatic brain injury? A literature review and observational study protocol. Int J Mol Sci. 2020;21(5):1596. doi:10.3390/ijms21051596.
25. Ramos-Cejudo J, Wisniewski T, Marmar C, Zetterberg H, Blennow K, de Leon MJ, Fossati S. Traumatic brain injury and Alzheimer's disease: the cerebrovascular link. EBioMedicine. 2018;28:21–30.
26. Peltz CB, Kenney K, Gill J, Diaz-Arrastia R, Gardner RC, Yaffe K. Blood biomarkers of traumatic brain injury and cognitive impairment in older veterans. Neurology. 2020;95(9):e1126–e1133. doi:10.1212/WNL.0000000000010087.
27. Crane PK, Gibbons LE, Dams-O'Connor K, Trittschuh E, Leverenz, JB, Keene CD, et al. Association of traumatic brain injury with late-life neurodegenerative conditions and neuropathologic findings. JAMA Neurol. 2016;73(9):1062–69. doi:10.1001/jamaneurol.2016.1948.
28. Peterson K, Veazie, S, Bourne, D, Anderson, J. *Evidence brief: Traumatic brain injury and dementia*; 2019.
29. McKee AC, Stein TD, Kiernan PT, Alvarez VE. The neuropathology of chronic traumatic encephalopathy. Brain Pathol. 2015;25(3):350–64. doi:10.1111/bpa.12248.
30. McAllister T, McCrea M. Long-term cognitive and neuropsychiatric consequences of repetitive concussion and head-impact exposure. J Athl Train. 2017;52(3):309–17. doi:10.4085/1062-6050-52.1.14.

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Comparison Groups Matter in Traumatic Brain Injury Research: An Example with Dementia

Jennifer S. Albrecht,[1,*] Raquel C. Gardner,[2,3] Douglas Wiebe,[4] Amber Bahorik,[2,5] Feng Xia,[2,6] and Kristine Yaffe[2,3,5,7]

Abstract

The association between traumatic brain injury (TBI) and risk for Alzheimer disease and related dementias (ADRD) has been investigated in multiple studies, yet reported effect sizes have varied widely. Large differences in comorbid and demographic characteristics between individuals with and without TBI could result in spurious associations between TBI and poor outcomes, even when control for confounding is attempted. Yet, inadvertent control for post-TBI exposures (e.g., psychological and physical trauma) could result in an underestimate of the effect of TBI. Choice of the unexposed or comparison group is critical to estimating total associated risk. The objective of this study was to highlight how selection of the comparison group impacts estimates of the effect of TBI on risk for ADRD. Using data on Veterans aged ≥55 years obtained from the Veterans Health Administration (VA) for years 1999–2019, we compared risk of ADRD between Veterans with incident TBI ($n = 9440$) and (1) the general population of Veterans who receive care at the VA (All VA) ($n = 119{,}003$); (2) Veterans who received care at a VA emergency department (VA ED) ($n = 111{,}342$); and (3) Veterans who received care at a VA ED for non-TBI trauma (VA ED NTT) ($n = 65{,}710$). In inverse probability of treatment weighted models, TBI was associated with increased risk of ADRD compared with All VA (hazard ratio [HR] 1.94; 95% confidence interval [CI] 1.84, 2.04), VA ED (HR 1.42; 95% CI 1.35, 1.50), and VA ED NTT (HR 1.12; 95% CI 1.06, 1.18). The estimated effect of TBI on incident ADRD was strongly impacted by choice of the comparison group.

Keywords: Alzheimer disease; epidemiologic methods; traumatic brain injury; veterans

Introduction

The association between traumatic brain injury (TBI) and risk for Alzheimer disease and related dementias (ADRD) has been investigated in multiple studies, with most,[1–8] but not all,[9,10] reporting that TBI increases risk for ADRD. Nonetheless, reported effect sizes have varied widely, ranging from relatively small (hazard ratio [HR] 1.24)[7] to very large (odds ratio 4.6).[8] This observed heterogeneity across studies suggests that bias may have been introduced at the design or analysis stage. One route for the introduction of such bias lies in the selection of the unexposed or comparison group.

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This is particularly important in research on outcomes after TBI because both younger and older individuals who sustain TBI differ significantly across most demographic, clinical, and even socioeconomic characteristics from individuals without TBI.[2,11,12] The same is true of Veterans who sustain TBI post-deployment. For example, among a large cohort of US Veterans aged 55 and older, those recently with a diagnosis of TBI had significantly higher prevalence of almost all comorbid conditions, including those associated with increased risk of ADRD such as hypertension and cerebrovascular disease, compared with older Veterans without TBI.[2] Further, Veterans with TBI also had more than double the prevalence of psychological conditions such as depression, and substance and alcohol dependence, also risk factors for ADRD.[2]

These large differences in comorbid burden between individuals with and without TBI could result in spurious associations between TBI and poor outcomes, even when control for confounding is attempted. In fact, most methods of confounding control require both the strong assumption of no unmeasured confounding and adequate overlap of covariate distribution between exposure (comparison) groups. Failure to meet either of these requirements can result in residual confounding, leading in this case to an overestimate of the association between TBI and ADRD.

On the other hand, many factors that occur as a direct result of TBI (e.g., psychological trauma, body trauma, inflammation, pain, hospitalization, surgery) may also contribute to long-term outcomes and dementia risk. Comparison with non-TBI trauma (NTT) groups may inadvertently control for these post-TBI factors, resulting in an underestimate of the population-level risk of ADRD or other outcomes associated with TBI.

Clearly, the choice of the comparison group in TBI research has significant implications for the validity and interpretability of results, particularly when the research interest is in predicting relative risk of sequelae of TBI such as ADRD. An important consideration in selection of the comparison group is the intended audience and the inference to be drawn from the analysis. In this study, our objective was to highlight how the choice of the comparison group can influence results by estimating the risk of ADRD associated with TBI using three different comparison groups. Results from these analyses may inform comparison group selection in future studies.

Methods

Data source

We obtained a random sample of all Veterans aged 55 and older who received care from the Veterans Health Administration (VHA) between 10/1/1999–9/30/2019. Data were from the National Patient Care Database, an electronic database that captures information on all inpatient and outpatient encounters that occur at VHA health care facilities nationwide, and the Vital Status File.

For each fiscal year from 2000 through 2019, we selected a 5% random sample from a total sample of 9,499,881 unique Veterans, and then merged these samples for all years ($n = 2{,}806{,}407$), removing duplicates ($n = 628{,}079$). This resulted in a random sample of 2,178,328 Veterans, more than 20% of all Veterans receiving care in that time period.

Institutional Review Boards at the University of California, San Francisco, the San Francisco Veterans Affairs Medical Center, and the US Army Medical Research and Material Command approved all study procedures. Informed consent was waived because it was deidentified archival data.

Incident TBI

We defined TBI using the standard surveillance case diagnostic codes used by the Armed Forces Health Surveillance Branch for routine surveillance and reporting.[13] Incident TBI was defined as the first emergency department (ED) visit containing one or more International Classification of Disease (ICD) codes for TBI after a 12-month TBI-free period. To be included in the analytic cohort, a computed tomography (CT) or magnetic resonance imaging (MRI) scan was also required within one day before or after the ED visit to increase the likelihood that these were indeed incident acute TBIs of sufficient severity to warrant urgent neuroimaging. After excluding those with no follow-up visit after the date of TBI (N = 301) or pre-existing diagnosis of mild cognitive impairment (MCI) or ADRD during the 12-months pre-TBI (see definitions below ($n = 3968$), our final incident TBI cohort contained 9440 older Veterans.

Comparison groups

We selected three plausible comparison groups that might control for different characteristics associated with TBI. All groups were required to have evidence of VHA utilization at least 12 months before the index date. First, we took a random sample of all Veterans from the 5% sample equal to ten times the number in the TBI cohort, matching the first visit year to the year of TBI, then excluded those with prevalent TBI, no follow-up visit after the randomly selected index date, and those with pre-existing MCI or ADRD (i.e., diagnosis within the last 12 months). This group (All VA) represents the general population of unexposed (i.e., non-TBI) older Veterans who receive care from VHA facilities ($n = 119{,}003$). The general population without TBI is the most common comparison group in studies of TBI sequelae and of ADRD specifically.[2,4–6]

Next, from the 5% random sample, we selected a random sample of ED visits at a 10:1 ratio with the TBI cohort, again excluding those with TBI, those with no

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follow-up visit after the index date (ED visit), and those with pre-existing MCI or ADRD. This group (VA ED) represents unexposed older Veterans who experienced an acute event that required care in the VA ED ($n=$ 111,342). Not only does this group share the experience of an acute event, but also individuals who regularly receive care in the ED differ from the general population in ways that are associated with increased risk of TBI.[11,14,15]

Finally, for the last comparison group, we selected Veterans with an ED visit for non-TBI related fractures, excluding those with TBI, those with no follow-up visit after the index date (ED visit), and those with pre-existing MCI or ADRD. Non-TBI fractures have been previously defined[3] and were updated to include ICD-10 codes for this study. This group did not contain more than ten times the TBI cohort; thus, we included all Veterans who met criteria. This group (VA ED NTT) represents unexposed older Veterans more likely to be injured and receive care in the ED ($n=65,710$). The VA ED NTT group has been used previously as a comparison group in TBI research.[3] In addition to increased similarity to the TBI group, this group also shares the experience of a traumatic event treated at the VA ED, including subsequent inflammation, pain, hospitalization, and possibly surgery.

ADRD

The primary outcome of ADRD was defined using ICD codes and prescription fills (Supplementary Appendix) for antidementia medications. We excluded from analysis individuals with a diagnosis of ADRD, MCI, or a prescription fill for antidementia medication during the 12 months before the index date. Individuals were followed until the first of either ADRD diagnosis, death, or administrative censoring (end of observed follow-up).

Statistical analysis

We examined distributions of demographic and clinical variables and tested comparisons across all groups using analysis of variance (ANOVA) or Chi-square Goodness of Fit as appropriate.

We estimated the unadjusted association between TBI and ADRD with death as a competing risk using the Fine and Gray subdistribution hazard model for each comparison cohort, with censoring at death or end of observed follow-up.[16] Next, we created stabilized inverse probability of treatment weights (IPTW) to balance covariates between the TBI cohort and each of the three comparison groups and checked the balance of each covariate in the weighted sample using the standardized mean difference. Finally, we estimated the adjusted associations in the IPT weighted sample. We also plotted the unadjusted and adjusted cumulative incidence of ADRD against follow-up time for the TBI cohort and each of the comparison groups.

Results

Demographic and clinical characteristics of the TBI cohort and the three comparison groups are presented in Table 1. All differences across groups were significant at $p<0.001$. Veterans with TBI were older with a heavier medical and psychiatric comorbidity burden compared with the comparison groups. For example, prevalence of stroke history was 38.1% in the TBI cohort, compared with 13.7% in All VA, 16.9% in VA ED, and 18.1% in VA ED NTT ($p<0.001$). Burden of psychiatric comorbidities was high in the TBI cohort, especially depression (37.9%), post-traumatic stress disorder (PTSD) (16.3%), and alcohol use disorder (17.8%). Finally, death was elevated in the TBI cohort (35.9%), compared with All VA (27.4%), VA ED (26.7%), and VA ED NTT (28.1%) ($p<0.001$).

The average age in each group decreased from 76.1 (standard deviation [SD] 9.0) years in the TBI cohort to All VA (73.6 [SD 8.5] years) to VA ED (72.1 [SD 8.3] to VA ED NTT (70.9 [SD 8.3] ($p<0.001$). Interestingly, prevalence of psychiatric comorbidities increased across the groups. For example, prevalence of depression increased from All VA (20.0%) to VA ED (26.0%) to VA ED NTT (31.0%) to 37.9% in TBI ($p<0.001$).

Over an average follow-up of 4.4 (SD 3.6) years, ADRD developed in 22.4% of the TBI cohort compared with 9.5% in All VA (average follow-up 6.0 [SD 3.7] years), 12.9% in VA ED (average follow-up 6.3 [SD 3.8] years), and 17.8% in VA ED NTT (average follow-up 7.3 [SD 4.0] years) ($p<0.001$ for all comparisons with the TBI cohort) (Table 1). The unadjusted cumulative incidence of ADRD by cohort is presented in Figure 1.

Both before and after adjustment, risk of ADRD associated with TBI varied widely by comparison group, with the lowest risk estimate for VA ED NTT and highest estimate for All VA. For example, the unadjusted association between TBI and incident ADRD was significantly elevated compared with All VA (HR 2.63; 95% confidence interval [CI] 2.51, 2.76), VA ED (HR 2.00; 95% CI 1.91, 2.10), and VA ED NTT (HR 1.59; 95% CI 1.51, 1.66) (Table 2). The IPTW were well balanced between the TBI cohort and each of the comparison groups.

In weighted models, the risk of ADRD associated with TBI remained significantly elevated but attenuated compared with All VA (HR 1.94; 95% CI 1.84, 2.04), VA ED (HR 1.42; 95% CI 1.35, 1.50), and VA ED NTT (HR 1.12; 95% CI 1.06, 1.18). Adjusted cumulative incidence of ADRD over follow-up by group is displayed in Figure 1.

Discussion

In this large, nationally representative study of older Veterans receiving care from VA health care facilities, TBI was associated with elevated incidence of ADRD, but the estimated effect was strongly impacted by choice of

Table 1. Characteristics of Veterans Aged 55 and Older with Traumatic Brain Injury and Three Comparison Cohorts, Excluding Those with Pre-Existing Alzheimer Disease and Related Dementias, 2001–2019[1]

	TBI n = *9,440*	*All VA*[2] n = *119,003*	*VA ED*[3] n = *111,342*	*VA ED NTT*[4] n = *65,710*	p
Age, y, mean (SD)	76.1 (9.0)	73.6 (8.5)	72.1 (8.3)	70.9 (8.3)	< 0.001
Age group, n (%)					< 0.001
55–64	1152 (12.2)	20,237 (17.0)	24,115 (21.7)	17,944 (27.3)	
65–74	3326 (35.2)	48,650 (40.9)	49,334 (44.3)	28,064 (42.7)	
75–84	3147 (33.3)	37,105 (31.2)	28,990 (26.0)	15,448 (23.5)	
85+	1815 (19.2)	13,011 (10.9)	8903 (8.0)	4254 (6.5)	
Female sex, n(%)	355 (3.8)	2780 (2.3)	2775 (2.5)	2803 (4.3)	< 0.001
Race, n(%)					< 0.001
Non-Hispanic White	7672 (81.3)	101,590 (85.4)	90,510 (81.3)	55,495 (84.4)	
Non-Hispanic Black	1208 (12.8)	10,706 (9.0)	15,568 (14.0)	7305 (11.1)	
Hispanic	264 (2.8)	1099 (0.9)	1383 (1.2)	905 (1.4)	
Asian	62 (0.7)	516 (0.4)	485 (0.4)	244 (0.4)	
Others/unknown	234 (2.5)	5092 (4.3)	3396 (3.1)	1761 (2.7)	
>25% college-educated in zip code, n(%)	4239 (46.1)	50,030 (43.0)	45,006 (41.5)	26,892 (42.1)	< 0.001
% income <$43,700 in zip code, n(%)	3537 (38.6)	37,730 (32.5)	39,994 (37.0)	23,611 (37.1)	< 0.001
Medical comorbidities					< 0.001
Stroke	3599 (38.1)	16,294 (13.7)	18,857 (16.9)	11,876 (18.1)	< 0.001
Parkinson disease	324 (3.4)	1418 (1.2)	1289 (1.2)	937 (1.4)	< 0.001
Diabetes	4307 (45.6)	40,908 (34.4)	42,503 (38.2)	25,448 (38.7)	< 0.001
Hypertension	8342 (88.4)	93,590 (78.6)	90,132 (81.0)	52,265 (79.5)	< 0.001
Myocardial infarction	1650 (17.5)	9241 (7.8)	11,207 (10.1)	6951 (10.6)	< 0.001
Obesity	3,197 (33.9)	33,212 (27.9)	35,729 (32.1)	20,752 (31.6)	< 0.001
Congestive heart failure	2892 (30.6)	14,395 (12.1)	18,054 (16.2)	11,280 (17.2)	
Psychiatric comorbidities					< 0.001
Depression	3579 (37.9)	23,797 (20.0)	28,993 (26.0)	20,348 (31.0)	< 0.001
PTSD[6]	1541 (16.3)	11,173 (9.4)	13,767 (12.4)	9183 (14.0)	<0.001
Anxiety	2017 (21.4)	14,053 (11.8)	17,414 (15.6)	11,682 (17.8)	<0.001
Alcohol use disorder	1680 (17.8)	10.040 (8.4)	13,657 (12.3)	10,017 (15.2)	<0.001
Substance use disorder	727 (7.7)	3242 (2.7)	5073 (4.6)	4043 (6.2)	
Follow-up in years, mean (SD)	4.4 (3.6)	6.0 (3.7)	6.3 (3.8)	7.3 (4.0)	<0.001
Mortality over follow-up, n (%)	3387 (35.9)	32,658 (27.4)	29,671 (26.7)	18,485 (28.1)	<0.001

TBI, traumatic brain injury; VA, Veterans Health Administration; VA ED, Veterans Health Administration Emergency Department; VA ED NTT, Veterans Health Administration Emergency Department non-TBI trauma; SD, standard deviation; PTSD, post-traumatic stress disorder.

[1]All differences between the TBI cohort and each comparison cohort are significant at $p < 0.001$ unless otherwise noted.

[2]Random sample of older Veterans receiving care at VA facilities.

[3]Random sample of older Veterans who had an ED visit at a VA facility.

[4]Random sample of older Veterans with an ED visit for non-TBI fracture at a VA facility.

[5]Analysis of variance for continuous variables and chi-square tests for categorical variables.

[6]PTSD.

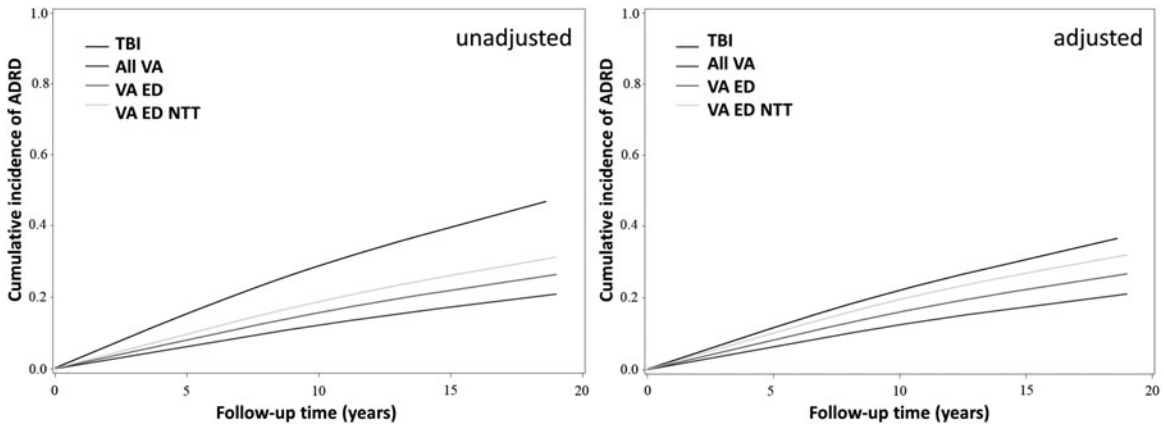

FIG. 1. Unadjusted and adjusted cumulative incidence of Alzheimer disease and related dementias over follow-up in the traumatic brain injury (TBI) and each comparison cohort.

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Table 2. Unadjusted and Inverse Probability of Treatment Weighted (IPTW) Hazard Ratios and 95% Confidence Intervals of the Association between Traumatic Brain Injury and Incident Alzheimer Disease and Related Dementias among Veterans Aged 55 and Older Using Three Comparison Cohorts, 2001–2019

	All VA[1] n = *119,003*	*VA ED*[2] n = *111,342*	*VA ED NTT*[3] n = *65,710*
Unadjusted	2.63 (2.51, 2.76)	2.00 (1.91, 2.10)	1.59 (1.51, 1.66)
IPTW	1.94 (1.84, 2.04)	1.42 (1.35, 1.50)	1.12 (1.06, 1.18)

VA, Veterans Health Administration; VA ED, Veterans Health Administration Emergency Department; VA ED NTT, Veterans Health Administration Emergency Department non-traumatic brain injury (TBI) trauma; IPTW, inverse probability of treatment weighted.

[1]Random sample of older Veterans receiving care at VA facilities.

[2]Random sample of older Veterans who had an ED visit at a VA facility.

[3]Random sample of older Veterans with an ED visit for non-TBI fracture at a VA facility.

the comparison group. Compared with the VA ED NTT group, the adjusted effect estimate for TBI was consistent with a 12% increase in risk of ADRD (95% CI 1.06, 1.18). This is much lower than previous estimates and lower even than our estimates using the different comparison groups.[1,2,4,6,7,17] Two previous studies that compared older adults with TBI with a non-TBI trauma group reported risk of ADRD that was closer to, but still larger than, our adjusted estimate (HR 1.26 and HR 1.29).[3,7] Differences in study population (Veterans vs. civilians), exposure definition, and analysis methods may have contributed to our smaller effect estimate.

Previous studies conducted in Veterans have reported that TBI increased risk of ADRD, with effect estimates ranging from 1.57–2.71[1,2,6,17] while those in civilians have reported estimates ranging from 1.24–4.6.[3,4,7,8] Our estimates from the All VA and VA ED comparisons fell within the lower end of these ranges, while our estimate from the VA ED NTT comparison did not.

There are several possible explanations for our results. Clearly, choice of the comparison group plays an important role in the estimated effect size as evidenced by increasing effect estimates as we moved from VA ED NTT (HR 1.12) to VA ED (HR 1.42; 95% CI 1.35, 1.50) to All VA (HR 1.94). Given the large differences in distribution of comorbid and demographic characteristics between comparison groups (see Table 1), it is likely that residual confounding[18] contributed to some of these differences. As well, our use of IPTW to estimate the causal effect of TBI on ADRD may have helped to minimize more of this confounding bias compared with adjusting for covariates in a regression model as has been done in previous studies.[1–3,19,20]

Study populations may also have differed in characteristics that are unmeasured, potentially leading to differences in risk for ADRD. Importantly, this study is the first to model risk of ADRD in the presence of death as a competing risk. Given that individuals with TBI were much more likely to die (and thus had less time to experience the ADRD outcome), this may have resulted in increased risk estimates for TBI. Finally, although we excluded individuals with a diagnosis of TBI from the comparison groups, it is possible that undiagnosed TBI was present. This possibility could be higher in the VA ED NTT group, which would bias results toward the null.

Consideration of the objective of an analysis is critical to selecting the proper comparison group. Results from this study suggest that interpretation of results should be measured as well. Studies that compare individuals with TBI to a general population of individuals without TBI may be estimating the effect that being a person at high risk for TBI has on outcomes, rather than the effect of the TBI itself. This comparison could be important when considering TBI risk reduction. On the other hand, studies that compare individuals with TBI with those with NTT (e.g., the ED VA NTT group) may inadvertently control for the psychological and physiological effects of trauma, which may lead to an underestimate of the total burden of TBI-associated ADRD.

Importantly, the control groups selected in this study do not represent all possible control groups. Researchers must compromise between balancing important covariates that contribute to risk of the outcome against ''over adjustment'' for these post-injury factors that also contribute to poor outcomes.

Conclusion

Results from this study highlight the importance of comparison group selection in TBI research. Understanding the impact of comparison group selection on estimates of the causal effect of TBI on outcomes will inform carefully considered study designs. Future work should focus on identification of the optimal comparison group for different types of TBI research.

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Author Disclosure Statement

No competing financial interests exist.

Supplementary Material

Supplementary Appendix

References

1. 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
2. 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
3. Gardner RC, Burke JF, Nettiksimmons 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
4. Nordström A, Nordström P. Traumatic brain injury and the risk of dementia diagnosis: a nationwide cohort study. PLoS Med 2018;15(1):e1002496; doi: 10.1371/journal.pmed.1002496
5. Nordstrom P, Michaelsson K, Gustafson Y, et al. Traumatic brain injury and young onset dementia: a nationwide cohort study. Ann Neurol 2014;75(3):374-381; doi: 10.1002/ana.24101
6. 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
7. 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
8. 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
9. Dams-O'Connor K, Gibbons LE, Bowen JD, et al. Risk for late-life re-injury, dementia and death among individuals with traumatic brain injury: a population-based study. J Neurol Neurosurg Psychiatry 2013;84(2):177-182; doi: 10.1136/jnnp-2012-303938
10. 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
11. Albrecht JS, Barbour L, Abariga SA, et al. Risk of depression after traumatic brain injury in a large national sample. J Neurotrauma 2019;36(2):300-307; doi: 10.1089/neu.2017.5608
12. Albrecht JS, Kiptanui Z, Tsang Y, et al. Depression among older adults after traumatic brain injury: a national analysis. Am J Geriatr Psychiatry 2015;23(6):607-614; doi: 10.1016/j.jagp.2014.07.006
13. Branch AFHS. Surveillance case definition for traumatic brain injury. Available from: https://health.mil. [Last accessed: June 2, 2002].
14. Byrne M, Murphy AW, Plunkett PK, et al. Frequent attenders to an emergency department: a study of primary health care use, medical profile, and psychosocial characteristics. Ann Emerg Med 2003;41(3):309-318; doi: 10.1067/mem.2003.68
15. Hunt KA, Weber EJ, Showstack JA, et al. Characteristics of frequent users of emergency departments. Ann Emerg Med 2006;48(1):1-8; doi: 10.1016/j.annemergmed.2005.12.030
16. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94(446):496-509.
17. Kornblith E, Peltz CB, Xia F, et al. Sex, race, and risk of dementia diagnosis after traumatic brain injury among older veterans. Neurology 2020;95(13):e1768-e1775; doi: 10.1212/WNL.0000000000010617
18. Hernán MA. Beyond exchangeability: the other conditions for causal inference in medical research. Stat Methods Med Res 2012;21(1):3-5; doi: 10.1177/0962280211398037
19. Hernan MA, Robins JM. Estimating causal effects from epidemiological data. J Epidemiol Community Health 2006;60(7):578-586; doi: 10.1136/jech.2004.029496
20. Austin PC, Stuart EA Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med 2015;34(28):3661-3679; doi: 10.1002/sim.6607

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REVIEW

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

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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

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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

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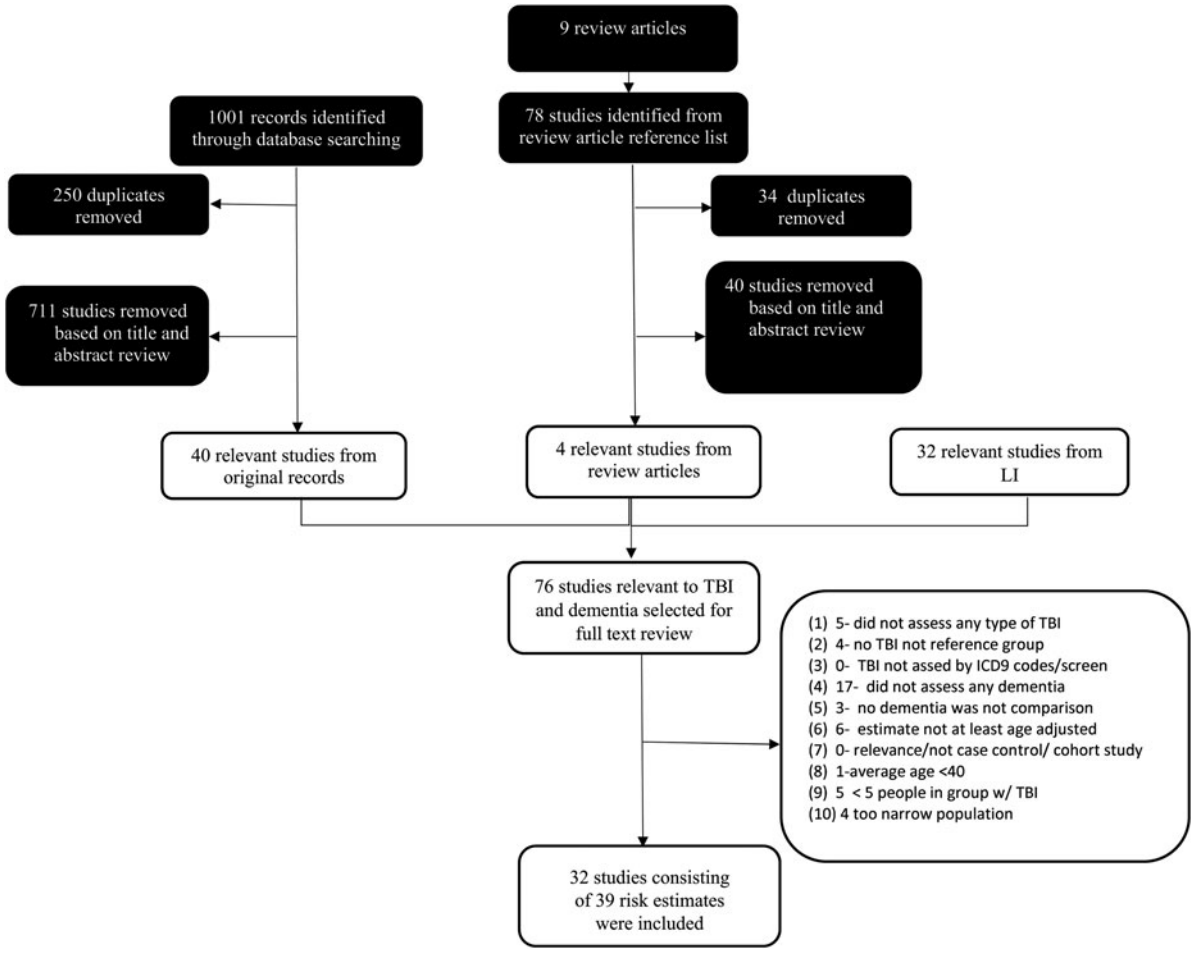

FIG. 1. Study screening and selection flowchart. The search window spanned January 1990 to January 2019 and included searches in PubMed, Embase, and Web of Science databases.

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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.

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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*)

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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*)

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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*)

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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*)

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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.

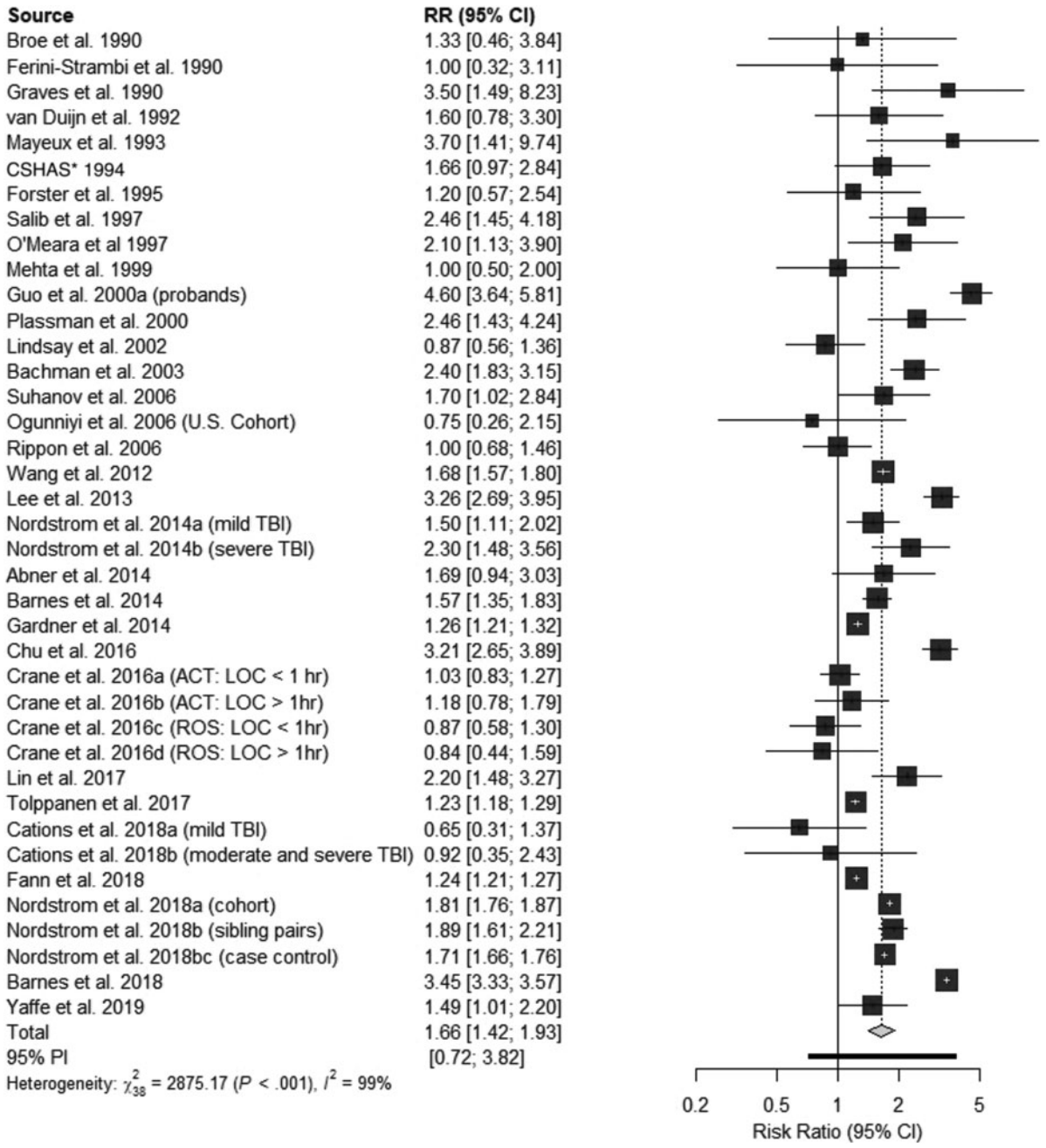

FIG. 2. Pooled risk ratios (RRs) for dementia risk associated with traumatic brain injury (TBI). Studies are listed in chronological order. Individual study RRs are depicted as squares; the pooled RR is depicted as a diamond. CI, confidence interval; *CSHAS, Canadian Study of Health and Aging Study group.

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

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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.

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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]

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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

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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

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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.

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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

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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

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RESEARCH ARTICLE

Associations Between Traumatic Brain Injury and Cognitive Decline Among Older Male Veterans

A Twin Study

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Abstract

Background and Objectives

Traumatic brain injuries (TBIs) are associated with increased risk of dementia, but whether lifetime TBI influences cognitive trajectories in later life is less clear. Cognitive interventions after TBI may improve cognitive trajectories and delay dementia. Because twins share many genes and environmental factors, we capitalize on the twin study design to examine the association between lifetime TBI and cognitive decline.

Methods

Participants were members of the National Academy of Sciences-National Research Council's Twin Registry of male veterans of World War II with self or proxy-reported history of TBI and with up to 4 observations over 12 years of the modified Telephone Interview for Cognitive Status (TICS-m). We used linear random-effects mixed models to analyze the association between TBI and TICS-m in the full sample and among co-twins discordant for TBI. Additional TBI predictor variables included number of TBIs, severity (loss of consciousness [LOC]), and age of first TBI (age <25 vs 25+ years [older age TBI]). Models were adjusted for age (centered at 70 years), age-squared, education, wave, twin pair, lifestyle behaviors, and medical conditions.

Results

Of 8,662 participants, 25% reported TBI. History of any TBI (β = −0.56, 95% CI −0.73 to −0.39), TBI with LOC (β = −0.51, 95% CI −0.71 to −0.31), and older age TBI (β = −0.66, 95% CI −0.90 to −0.42) were associated with lower TICS-m scores at 70 years. TBI with LOC (β = −0.03, 95% CI −0.05 to −0.001), more than one TBI (β = −0.05, 95% CI −0.09 to −0.002,), and older age TBI (β = −0.06, 95% CI −0.09 to −0.03) were associated with faster cognitive decline. Among monozygotic pairs discordant for TBI (589 pairs), history of any TBI (β = −0.55, 95% CI −0.91 to −0.19) and older age TBI (β = −0.74, 95% CI −1.22 to −0.26) were associated with lower TICS-m scores at 70 years. Those with more than one TBI (β = −0.13, 95% CI −0.23 to −0.03) and older age TBI (β = −0.07, 95% CI −0.13 to −0.002) showed greater cognitive decline compared with their co-twin without TBI.

Discussion

These findings support an association of the effect of TBI on cognitive score and the rapidity of cognitive decline in later life. The results in monozygotic pairs, who share all genes and many exposures, particularly in early life, provide additional evidence of a causal relationship between TBI and poorer late-life cognitive outcomes.

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Glossary

ApoE = Apolipoprotein epsilon; **LOC** = loss of consciousness; **MMSE** = Mini-Mental State Examination; **TBI** = traumatic brain injury; **TICS-m** = modified Telephone Interview for Cognitive Status.

Introduction

Approximately 64–74 million people worldwide are affected by traumatic brain injuries (TBIs) each year,[1,2] with the highest prevalence of TBIs occurring before 30 years[3] and again in those aged 70 years and older.[3,4] Substantial evidence supports an association between TBI across the life span and higher rates of Alzheimer disease and other dementias in later life.[3,5-12] This finding indicates that individuals with TBIs in earlier life who seem to have fully recovered from them may still be at increased risk of cognitive deficits and dementia later in life. Despite the extensive research on TBI and dementia, there is relatively little evidence on poorer cognitive outcomes in later life, especially cognitive decline, that do not meet the threshold for dementia.[13-15] Cognitive decline is common and often reflects the prodromal stages of a dementing process. Understanding the effect of lifetime TBI on the rate of cognitive decline in later life may help identify individuals who may benefit from early interventions that may slow cognitive decline and potentially delay or prevent the onset of dementia. Yet, the numerous prior studies evaluating TBI and cognition have been mostly cross-sectional or had short duration of follow-up after TBI, focused only on early or late-life TBIs, or did not examine cognition in later life when cognitive decline is most common.[16,17] To date, only one study has explored the association between lifetime history of TBI and 4-year cognitive trajectory among adults older than 50 years. The authors found lower baseline cognitive function among those with TBI compared with those without TBI, but no differences in slope of decline over the 4 years of follow-up.[18] A strength of our study is cognitive assessment follow-ups for more than a decade in later life.

Other factors across the life span have been reported to affect the risk of dementia and poor cognition later in life. Among these are social isolation, hearing loss, and physical inactivity.[19] Others, such as chronic cardiovascular and cerebrovascular conditions, are among the most researched and are consistently reported to have a detrimental influence on cognition in later life.[20,21] Yet, there are numerous other factors that are often unmeasurable but have a cumulative effect on the rate of cognitive decline in later life. These factors include both genetic and nongenetic factors, such as early-life socioeconomic status, quality of education, nutrition, and medical care.[22] Twin studies provide an ideal design to account for many of these factors because twins share many genetic and early-life exposures that cannot be reliably measured in the general population. Members of twin pairs typically share early-life experiences such as home environment and socioeconomic status. In addition, monozygotic (MZ) twins share 100% of their genes while dizygotic (DZ) twins share approximately half of their genes. Given this, twin studies allow for support of the causal nature of the relationship between TBI and cognition by accounting for within-pair differences in TBI exposure to evaluate its effect on cognitive function. Observed differences in genetically identical twin pairs (MZ twins) indicate environmental exposure differences vs if shared genetic factors are implicated, differences would be observed only among DZ twins.

We investigated the association between TBI and subsequent rate of cognitive decline in members of the National Academy of Sciences-National Research Center (NAS-NRC) Twin Registry of male World War II veterans. We examined the influence of a number of TBI-associated characteristics that have been reported to affect late-life cognitive outcomes, such as the number of TBIs, severity of the TBI (with or without loss of consciousness [LOC]), and age at the time of first TBI. We also controlled for several medical conditions that may also influence late-life cognition. Using the twin study design, we aimed to gain a better understanding of the association between TBI and rate of cognitive decline in later life.

Methods

Sample

Data were obtained from participants in the Duke Twins Study of Memory in Aging who were also members of the NAS-NRC Registry of World War II veteran male twins born between 1917 and 1927. The NAS-NRC Twin Registry was constructed in the mid-1950s using information from vital statistics offices in 42 states to identify White male twin pairs born in 1917–1927. The 54,000 pairs identified were estimated to represent 93% of the White male twin pairs born during this period in the United States. Birth certificates from these individuals were then matched to Department of Veterans Affairs files to determine veteran status, resulting in 15,924 pairs, which made up the original NAS-NRC Twin Registry.[23] Eligibility criteria for this study included cohort members with data on TBI and education and at least one modified Telephone Interview for Cognitive Status (TICS-m) score.

Standard Protocol Approvals, Registrations, and Patient Consents

All procedures were approved by the Duke University Medical Center Institutional Review Board, and verbal or written consent was obtained from participants or their legal representatives for data collected from 1990 onward.

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Modified Telephone Interview for Cognitive Status

The original TICS instrument[24] and its modified[25] form provide a brief assessment of cognitive function that can be administered through telephone. The modified Telephone Interview for Cognitive Status (TICS-m) is modeled after the Mini-Mental State Examination (MMSE), but enhances its content with the inclusion of immediate and delayed recall of a 10-item word list and avoids the ceiling effect often seen with the MMSE.[26] It produces scores ranging from 0 to 50, is highly correlated with the MMSE,[25,27] and has high test-retest reliability.[27] The TICS-m has been shown to be sensitive to detecting change over time in studies evaluating cognitive performance in older adults.[27-31] Education-adjusted scores below 28 indicate suspect dementia.[28] In this study, the TICS-m was administered every 3–4 years beginning in 1990 as part of a screening and assessment protocol for dementia, as part of the Duke Twins Study. Participants completed up to 4 waves of cognitive screening, which represent a period of up to 12 years of cognitive follow-up.

Traumatic Brain Injury

For most of the participants, TBI data were collected directly from participants during telephone interviews at either Wave 3 (1996–1998) or Wave 4 (2000–2001) of the Duke Twins Study. For a subset of participants, information on TBI was collected during in-person or telephone interviews before the Wave 3 interviews, and for those who were unable to complete an interview, this information was obtained from a proxy informant. TBI data included (1) history of occurrence of TBI severe enough to require medical attention or cause LOC, (2) presence and duration of LOC, (3) number of TBIs, and (4) age(s) of TBI. We dichotomized TBI and LOC as yes/no.

Covariates/Demographics

Baseline age was defined as the age at their first TICS-m. For statistical modeling, we considered centered TICS-m age at 70 years for an individual; thus, TBI differences reflect TICS-m differences at 70 years. A squared-age term $(age\text{-}70)^2$ was added to allow for the accelerated-progression cognitive decline with older ages and to improve the model fit and reduce colinearity.[32] Years of education was collected at baseline TICS-m. Study wave was added to control for time in the study and TICS-m practice effects. A variable for twin pairs was included in the model to account for twins with a co-twin or singletons (without a co-twin). For a subset of twin pairs, zygosity was determined by DNA. For 87% of twins, it was determined from physical characteristics reported in military records, fingerprint records, by questionnaire, and (for a small sample) blood group testing.[33-35] This method of establishing zygosity has been estimated by cross-validation with DNA to be 97% accurate.[35] Apolipoprotein epsilon (*ApoE*) genotyping was determined from blood or buccal DNA using PCR amplification and a restriction isotyping method.[36] Because MZ twin pairs share the same genes, for 87 MZ twin pairs where DNA was not available for one twin, we assigned the *ApoE* genotype for the twin with DNA to the twin with no DNA. *ApoE* genotype was dichotomized into e4 allele carriers (*ApoE* 2/4, 3/4, 4/4) vs non–e4 carriers (*ApoE* 2/2, 2/3, 3/3).

Other covariates collected by questionnaire during the same interviews that the TBI information was collected include alcohol overuse (yes/no: defined as reporting a problem drinking more alcohol than he should or drinking 12 or more drinks per day at some time); smoking (current, past, or never smokers); and medical conditions categorized as follows: (a) cardiovascular and/or cerebrovascular disease (myocardial infarction or coronary thrombosis, coronary artery bypass graft, congestive heart failure, and/or stroke or transient ischemic attack); (b) cardiovascular risk (diabetes mellitus, hypertension, and/or hyperlipidemia); (c) neurologic conditions (Parkinson disease and/or seizure disorder); and (d) depression ("ever had a period of two weeks or more when, nearly every day you felt sad, blue or depressed, or unusually cross or irritable, or lost all interest and pleasure in things that you usually cared about or enjoyed?").

Statistical Analyses

Baseline descriptive statistics were calculated to characterize the overall study population and were stratified by TBI. We tested the longitudinal relationship between TBI (history of TBI, number of TBIs, LOC, and age of TBI) and cognitive score and change in score using random-effects linear mixed models. As implemented in this analysis, the model assumes a normal distribution of the residuals (error) of the outcome, linearity of response for the continuous predictors, homogeneity of variance of error across the predictor space, and that the variables randomly specified are not correlated. In the model we present, only 3 effects were considered random: (1) the intercept for the pair (allowing a different intercept for the pair when all continuous covariates are zero and all discrete variables are at the reference), (2) the intercept for the person within the pair (to distinguish difference that zero point between individuals within the pair), and (3) error of the residual. The 2 intercept estimates are typically ignored while the third term speaks of the precision of the model, that is, how well the model fits the prediction of the outcome. TBI was added in the models as a time-varying variable, which means that if a participant had a TBI during the assessment period, their status would change to reflect going from 'no TBI' to 'TBI'; this information was provided at the TICS-m assessment. We analyzed 2 models. Model 1 adjusts for age, age-squared, education, wave, and pair plus the interaction between age by TBI to measure difference in change in cognitive slope over time. Trajectory in all models was measured as interaction between main effect and time, calculated as age in years. Based on goodness-of-fit measures (model 1 AIC = 150,935.6 and BIC = 151,084.0 while model 2 AIC = 149,508.0 and BIC = 149,656.4), model 2 was determined to be the better fit model and included Model 1 variables plus alcohol abuse, smoking status, and medical conditions. A missing category was coded for all covariates with the purpose of not losing observations for a missing condition. We tested both models examining the association between TBI and TICS-m, followed by assessing the specificity of the TBI

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Table 1 Sample Baseline Characteristics

	All (n = 8,662)	No TBI (n = 6,494)	TBI (n = 2,168)
Baseline TICS-m Score, mean ± SD	32.5 ± 5.0	32.5 ± 5.0	32.5 ± 4.9
Baseline TICS-m Age, mean ± SD	67.0 ± 3.0	66.9 ± 3.0	67.0 ± 2.9
Education, mean ± SD	13.2 ± 3.2	13.1 ± 3.2	13.4 ± 3.3
Age of first TBI (n = 2,120), mean ± SD			33.0 ± 23.3
Years between age of first TBI and baseline TICS (n = 2,120), mean ± SD			34.0 ± 23.1
Number of Head Injuries, % (n)			
One			78.9 (1710)
Two or More			18.7 (405)
Missing/DK			2.4 (53)
TBI with LOC, % (n)			
No			22.3 (484)
Yes			69.7 (1,510)
Missing/DK			8.0 (174)
TBI before 25 years, % (n)			
No			46.3 (1,003)
Yes			51.5 (1,117)
Missing			2.2 (48)
Alcohol Abuse, % (n)			
Yes	23.7 (2049)	21.6 (1,402)	29.8 (647)
No	75.0 (6,500)	77.1 (5,004)	69.0 (1,496)
Missing/DK	1.3 (113)	1.4 (88)	1.2 (25)
Smoking Status, % (n)			
Current smoker	8.0 (688)	7.8 (508)	8.3 (180)
Never smoked	28.0 (2,428)	27.7 (1798)	29.0 (630)
Past smoker	50.3 (4,357)	49.1 (3,187)	54.0 (1,170)
Missing/DK	13.7 (1,189)	15.4 (1,001)	8.7 (188)
All cardiovascular conditions			
Yes	32.1 (2,783)	30.6 (1986)	36.8 (797)
No	53.7 (4,646)	53.6 (3,482)	53.7 (1,164)
Missing	14.2 (1,233)	15.8 (1,026)	16.8 (207)
Cardiovascular risk			
Yes	61.4 (5,314)	60.1 (3,902)	65.1 (1,412)
No	24.8 (2,150)	24.5 (1,590)	25.8 (560)
Missing	13.8 (1,198)	15.4 (1,002)	9.0 (196)
Neurologic conditions			
Yes	3.4 (294)	2.7 (178)	5.4 (116)
No	83.6 (7,238)	82.6 (5,364)	86.4 (1874)
Missing	13.0 (1,130)	14.7 (952)	8.2 (178)
Depression			
Yes	20.5 (1777)	18.0 (1,168)	28.1 (609)
No	64.1 (555)	64.9 (4,214)	61.7 (1,338)
Missing	15.4 (1,333)	17.1(1,112)	10.2 (221)

Abbreviations: DK = do not know; LOC = loss of consciousness; TBI = traumatic brain injury; TICS-m = modified Telephone Interview for Cognitive Status. Cardiovascular and/or cerebrovascular conditions included myocardial infarction or coronary thrombosis, coronary artery bypass graft, congestive heart failure, and/or stroke or transient ischemic attack. Cardiovascular risk included diabetes mellitus, hypertension, and/or hyperlipidemia. Neurologic conditions included Parkinson disease and/or seizure disorder.

including severity of the TBI (with or without LOC), number of TBIs, and age at the time of first TBI as young (age younger than 25 years) vs not young (25 years and older).

We analyzed the full sample, which included singletons, because these individuals contribute to the estimation of the parameters of the cognitive function and thus increase the precision of the parameter estimates of the model and statistical power of the analyses. A sensitivity analysis was performed with complete pairs only to assess bias. We then conducted co-twin controlled analyses, which included just the complete pairs of twins with known zygosity (MZ vs DZ) who were discordant for TBI; thus, one twin is used as the matched control for the other twin. This approach allows the most control of confounding from genetics and early-life shared environmental factors. We first analyzed all the twin pairs and then repeated the analysis, stratified by zygosity. As a final step, for a subsample of twins with *ApoE* genotype, we ran both models stratified by *ApoE*-e4 carriers vs non–e4 carriers. All data analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, NC).

Data Availability

Deidentified individual-level data not provided in this article may be requested by any qualified investigator for purposes of replicating procedures and results.

Results

Our sample included 8,662 participants, of which 25% of twins endorsed having ever had a TBI. Detailed sample characteristics for the entire cohort are summarized in Table 1. Twins with and without TBI did not differ by age at baseline TICS-m (mean 67 years) or by baseline TICS-m

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Table 2 Linear Mixed-Effect Regression Models Examining the Association Between Cognitive Function Measure by the Modified Telephone Interview for Cognitive Status and Traumatic Brain Injury Variables

	Model 1[a]		Model 2[b]	
	Estimated coefficient	95% CI	Estimated coefficient	95% CI
TICS-m level				
TBI (reference = no TBI), n = 8,662	−0.48	−0.66 to −0.30	−0.56	−0.73 to −0.39
Number of TBIs (reference = no TBI), n = 8,609				
One TBI	−0.28	−0.48 to −0.08	−0.39	−0.58 to −0.20
More than one TBI	0.05	−0.32 to 0.43	−0.21	−0.56 to 0.14
TBI with LOC (Reference = no TBI), n = 8,488	−0.44	−0.65 to −0.23	−0.51	−0.71 to −0.31
Age of First TBI (reference = no TBI), n = 8,614				
TBI at age <25	0.07	−0.17 to 0.31	−0.12	−0.34 to 0.11
TBI at age ≥25	−0.59	−0.84 to −0.34	−0.66	−0.90 to −0.42
TICS-m trajectory (per year)				
TBI (reference = no TBI), n = 8,662	−0.02	−0.05 to −0.001	−0.02	−0.05 to 0.001
Number of TBIs (reference = no TBI), n = 8,609				
One TBI	−0.02	−0.04 to 0.01	−0.02	−0.04 to 0.01
More than one TBI	−0.06	−0.10 to −0.01	−0.05	−0.09 to −0.002
TBI with LOC (Reference = no TBI), n = 8,488	−0.03	−0.05 to −0.002	−0.03	−0.05 to −0.001
Age of First TBI (reference = no TBI), n = 8,614				
TBI at age <25	0.001	−0.03 to 0.03	0.002	−0.03 to 0.03
TBI at age ≥25	−0.06	−0.09 to −0.03	−0.06	−0.09 to −0.03

Abbreviations: LOC = loss of consciousness; TBI = traumatic brain injury; TICS-m = modified Telephone Interview for Cognitive Status.
[a] Model 1 adjusts for age (centered at 70 years), age^2 (centered at 70 years), education, wave, singleton/twin pair, and TBI by time.
[b] Model 2 adjusts for age (centered at 70 years); age^2 (centered at 70 years); education; wave; singleton/twin pair; alcohol abuse; smoking status; and medical conditions (hypertension, cholesterolemia, myocardial infarction, coronary artery bypass graft, congestive heart failure, stroke/transient ischemic attack, diabetes, depression, Parkinson disease, and seizures at baseline) grouped as: cardiovascular disease risk factors, cardiovascular disease, neurologic conditions, depression, and TBI by time.

score (mean 32.5), but those with a TBI had slightly more education (3.6 more months) and reported more medical conditions than those without a TBI. There were no significant differences in education, alcohol, smoking, or any of the medical conditions within twin pairs. There were 1,474 singletons and 7,188 members of complete twin pairs (3,594 pairs). A total of 1,195 twin pairs were discordant for TBI and had known zygosity. A total of 1,392 twins had *ApoE* genotype: 425 e4 allele carriers (*ApoE* 2/4, 3/4, 4/4) vs 967 non–e4 carriers (*ApoE* 2/2, 2/3, 3/3). By zygosity, 248 MZ twins were *ApoE*-e4 carriers and 532 were non–e4 carriers while 177 DZ twins were carriers and 435 were non–e4 carriers.

Classical Cohort Study Design Results

Several modest but significant associations were observed between TBI and worse performance on the TICS-m (Table 2). After adjustment for age centered at 70 years, age-squared ((age-70)^2), education, wave, and twin pair, TBI was associated with lower TICS-m score and faster decline on the TICS-m across the study in Model 1 (TICS-m-$\beta_{(TBI)}$-0.48 [95% CI −0.66 to −0.30], slope $\beta_{(TBI*age)}$-0.02 [95% CI −0.05 to −0.001]). These results indicate that at 70 years, the twin who experienced a prior TBI scored 0.48 TICS-m points lower relative to his co-twin without TBI and his cognition declined faster (0.02 TICS-m points faster decline per year). Thus, over a 10-year period, the twin with a TBI would have declined 0.20 TICS-m points more than the co-twin without TBI. In Model 2, the effect sizes were similar but the slope did not reach statistical significance (TICS-m-$\beta_{(TBI)}$-0.56 [95% CI −0.73 to −0.39], slope $\beta_{(TBI*age)}$-0.02 [95% CI −0.05 to 0.001]).

Analyses of the number of TBIs showed that one TBI was associated with lower TICS-m scores in both models (model 1 TICS-m-$\beta_{(TBI)}$-0.28 [95% CI −0.48 to −0.08] model 2 TICS-m-$\beta_{(TBI)}$-0.39 [95% CI −0.58 to −0.20]), but the effect of additional TBIs was not associated with TICS-m level in either model (model 1 TICS-m-$\beta_{(TBI)}$0.05 [95% CI −0.32 to 0.43] model 2 TICS-m-$\beta_{(TBI)}$-0.21 [95% CI −0.56 to 0.14]).

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Table 3 Linear Mixed-Effect Regression Models Examining the Association Between TBI and Cognitive Status Measured by the Modified Telephone Interview for Cognitive Status in Co-twin Control Sample Discordant for TBI

	Full sample		Monozygotic		Dizygotic	
	Estimated coefficient	95% CI	Estimated coefficient	95% CI	Estimated coefficient	95% CI
	Model 1[a]					
TICS-m level	n = 2,390		n = 1,178		n = 1,212	
TBI (reference = no TBI)	−0.64	−0.91 to −0.37	−0.61	−0.98 to −0.24	−0.67	−1.06 to −0.28
Number of TBIs (reference = no TBI)	n = 2,370		n = 1,170		n = 1,200	
One TBI	−0.34	−0.65 to −0.03	−0.44	−0.85 to −0.02	−0.24	−0.69 to 0.21
More than one TBI	−0.08	−0.61 to 0.44	−0.28	−1.02 to 0.46	0.06	−0.65 to 0.85
Age of First TBI (reference = no TBI)	n = 2,363		n = 1,162		n = 1,201	
TBI at age <25	0.02	−0.33 to 0.38	0.02	−0.47 to 0.50	0.05	−0.47 to 0.56
TBI at age ≥25	−0.66	−1.02 to −0.29	−0.82	−1.32 to −0.32	−0.51	−1.04 to 0.02
TICS-m trajectory (per year)						
TBI	−0.01	−0.05 to 0.03	−0.03	−0.08 to 0.02	0.01	−0.04 to 0.06
Number of TBIs (reference = no TBI)						
One TBI	−0.001	−0.04 to 0.04	−0.001	−0.06 to 0.05	−0.002	−0.06 to 0.05
More than one TBI	−0.04	−0.11 to 0.02	−0.14	−0.24 to −0.04	0.04	−0.05 to 0.13
Age of First TBI (reference = no TBI)						
TBI at age <25	0.03	−0.01 to 0.08	0.02	−0.04 to 0.09	0.04	−0.02 to 0.11
TBI at age ≥25	−0.05	−0.10 to −0.01	−0.07	−0.14 to −0.01	−0.03	−0.10 to 0.03
	Model 2[b]					
TICS-m level	n = 2,390		n = 1,178		n = 1,212	
TBI (reference = no TBI)	−0.59	−0.85 to −0.33	−0.55	−0.91 to −0.19	−0.65	−1.02 to −0.28
Number of TBIs (reference = no TBI)	n = 2,370		n = 1,170		n = 1,200	
One TBI	−0.31	−0.60 to −0.02	−0.37	−0.77 to 0.03	−0.27	−0.69 to 0.16
More than one	−0.23	−0.73 to 0.27	−0.49	−1.20 to 0.22	−0.03	−0.74 to 0.67
Age of First TBI (reference = no TBI)	n = 2,363		n = 1,162		n = 1,201	
TBI at age <25	−0.04	−0.37 to 0.30	−0.02	−0.49 to 0.44	−0.09	−0.58 to 0.39
TBI at age ≥25	−0.59	−0.94 to −0.24	−0.74	−1.22 to −0.26	−0.44	−0.98 to 0.05
TICS-m trajectory (per year)						
TBI	−0.01	−0.05 to 0.03	−0.03	−0.08 to 0.02	0.01	−0.04 to 0.06
Number of TBIs (reference = no TBI)						
One TBI	−0.002	−0.04 to 0.04	−0.003	−0.06 to 0.05	−0.005	−0.06 to 0.05
More than one TBI	−0.04	−0.10 to 0.03	−0.13	−0.23 to −0.03	0.04	−0.04 to 0.14

Continued

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Table 3 Linear Mixed-Effect Regression Models Examining the Association Between TBI and Cognitive Status Measured by the Modified Telephone Interview for Cognitive Status in Co-twin Control Sample Discordant for TBI *(continued)*

	Full sample		Monozygotic		Dizygotic	
	Estimated coefficient	95% CI	Estimated coefficient	95% CI	Estimated coefficient	95% CI
Age of First TBI (reference = no TBI)						
TBI at age <25	0.03	−0.01 to 0.07	0.02	−0.05 to 0.08	0.04	−0.02 to 0.10
TBI at age ≥25	−0.05	−0.10 to −0.01	−0.07	−0.13 to −0.002	−0.03	−0.10 to 0.03

Abbreviations: LOC = loss of consciousness; TBI = traumatic brain injury; TICS-m = modified Telephone Interview for Cognitive Status.
[a] Model 1 adjusts for age (centered at 70 years), age^2 (centered at 70 years), education, wave, singleton/twin pair, and TBI by time.
[b] Model 2 adjusts for age (centered at 70 years); age^2 (centered at 70 years), education; wave; singleton/twin pair; alcohol abuse; smoking status; and medical conditions (hypertension, cholesterolemia, myocardial infarction, coronary artery bypass graft, congestive heart failure, stroke/transient ischemic attack, diabetes, depression, Parkinson disease, and seizures at baseline) grouped as: cardiovascular disease risk factors, cardiovascular disease, neurologic conditions, depression, and TBI by time.

However, having more than one TBI led to faster TICS-m decline in both models (model 1 TICS-m-$\beta_{(TBI*age)}$-0.06 [95% CI −0.10 to −0.01] model 2 TICS-m-$\beta_{(TBI\ TBI*age)}$-0.05 [95% CI −0.09 to −0.002]). Model 2 indicates that at 70 years, the twin who experienced more than one TBI declined 0.05 TICS-m points faster per year than his co-twin without TBI. Thus, over a 10-year period, the twin with more than one TBI would have declined half a TICS-m point more than the co-twin without TBI.

We assessed severity of TBI based on the presence vs absence of LOC. Both models showed TBI with LOC to be associated with lower TICS-m scores at 70 years and faster rate of TICS-m decline compared with no TBI (Table 2). Finally, in models assessing the association of cognition with age of TBI, those with TBI after 24 years had lower TICS-m scores at 70 years and faster rates of cognitive decline in both models (Table 2).

We conducted a post hoc sensitivity analysis to look at the effect of TBI excluding singletons from the full sample to assess for any possible bias (n = 7,188), and the results (Model 1 TICS-m-$\beta_{(TBI)}$-0.53 [95% CI −0.72 to −0.34], slope TICS-m-$\beta_{(TBI*age)}$-0.02 [95% CI −0.05 to 0.002]) differed a little from those reported on the full sample in Table 2 (model 1 TICS-m-$\beta_{(TBI)}$-0.48 [95% CI −0.66 to −0.30], slope TICS-m-$\beta_{(TBI*age)}$-0.02 [95% CI −0.05 to 0.001]).

Matched Co-Twin Control Sample

Among twin pairs discordant for TBI (Table 3), both models showed lower TICS-m scores at 70 years associated with (1) TBI (model 1 TICS-m-$\beta_{(TBI)}$-0.64 [95% CI −0.91 to −0.37], model 2 TICS-m-$\beta_{(TBI)}$-0.59 [95% CI −0.85 to −0.33]), (2) having only one reported TBI (model 1 TICS-m-$\beta_{(TBI)}$-0.34 [95% CI −0.65 to −0.03], model 2 TICS-m-$\beta_{(TBI)}$-0.31 [95% CI −0.60 to −0.02]), and (3) TBI at older age (model 1 TICS-m-$\beta_{(TBI\ age\ \geq 25)}$-0.66 [95% CI −1.02 to −0.29], model 2 TICS-m-$\beta_{(TBI\ age\ \geq 25)}$-0.59 [95% CI −0.94 to −0.24]). In addition, having a TBI at an older age vs younger age was associated with faster rate of TICS-m decline (both model 1 and model 2 TICS-m-$\beta_{(TBI\ age\ \geq 25)}$-0.05 [95% CI −0.10 to −0.01]). Thus, for example, in Model 2, in a twin pair, the twin who experienced a TBI after 24 years scored 0.59 TICS-m points lower at 70 years and his cognition declined faster (0.05 TICS-m points faster decline per year) relative to his non-TBI co-twin. Over a 10-year period, the co-twin with a TBI after 24 years would have declined half a point more on the TICS-m than the co-twin without TBI after accounting for covariates.

Stratification of these models by zygosity showed that most associations observed among the full group of TBI-discordant twins were strengthened for the MZ pairs. Notably, within MZ twin pairs discordant for TBI, twins with a TBI which occurred after 24 years scored lower relative to their co-twin at 70 years without TBI and their cognition declined faster (model 1 TICS-m-$\beta_{(TBI\ age\ \geq 25)}$-0.82 [95% CI −1.32 to −0.32], model 2 TICS-m-$\beta_{(TBI\ age\ \geq 25)}$-0.74 [95% CI −1.22 to −0.26]). In addition, among MZ pairs, twins with more than one TBI declined more rapidly than their co-twins without a TBI (model 1 TICS-m-$\beta_{(more\ than\ one\ TBI)}$-0.14 [95% CI −0.24 to −0.04], model 2 TICS-m-$\beta_{(more\ than\ one\ TBI)}$-0.13 [95% CI −0.23 to −0.03]). We further tested this last association in both models with a 3-way interaction (more than one TBI by age by zygosity), and in both models, the interactions were statistically significant (model 1 TICS-m-$\beta_{(more\ than\ one\ TBI*age*zyg\ =\ MZ)}$-0.003 [95% CI −0.08 to 0.07] and TICS-m-$\beta_{(more\ than\ one\ TBI*age*zyg\ =\ DZ)}$0.18 [95% CI 0.05–0.32] and model 2 TICS-m-$\beta_{(more\ than\ one\ TBI*age*zyg\ =\ MZ)}$0.004 [95% CI −0.07 to 0.08] and TICS-m-$\beta_{(more\ than\ one\ TBI*age*zyg\ =\ DZ)}$-0.18 [95% CI −0.31 to −0.05]). Among DZ discordant twin pairs, TBI was only associated with lower TICS-m levels at 70 years (model 1 TICS-m-$\beta_{(TBI)}$-0.67 [95% CI −1.06 to −0.28], model 2 TICS-m-$\beta_{(TBI)}$-0.65 [95% CI −1.02 to −0.28]).

Exploratory Analyses With *ApoE* e4 Allele

Sixteen percent of the study sample had *ApoE* genotype (n = 1,392). TICS-m scores in this sample were lower among *ApoE*-e4 carriers (mean TICS-m 31.6 [SD 5.4]) than non–e4 carriers (mean TICS-m 32.8 [SD 5.3]). The three-way

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interaction (age by *ApoE*-e4 by TBI) in model 1 did not reach statistical significance (model 1 TICS-m $\beta_{(TBI*age*ApoE\text{-}e4)}$0.01 [95% CI −0.11 to 0.12]), but all lower level terms (2-way interactions) in the same model were statistically significant (model 1 TICS-m $\beta_{(age*ApoE\text{-}e4)}$-0.07 [95% CI −0.14 to −0.004] and TICS-m $\beta_{(TBI*ApoE\text{-}e4)}$1.52 [95% CI 0.58–2.46]). We then dropped the three-way interaction and kept the two-way interactions to determine whether the TBI effect was modified by age or *ApoE* status. Age by TBI (model 1 TICS-m $\beta_{(TBI*age)}$ −0.06 [95% CI −0.12 to −0.01]) and age by *ApoE*-e4 (model 1 $\beta_{(TBI*ApoE\text{-}e4)}$-0.07 [95% CI −0.12 to −0.004]) remained statistically significant. However, TBI by *ApoE*-e4 was not significant (model 1 TICS-m $\beta_{(TBI*ApoE\text{-}e4\ carriers)}$0.18 [95% CI −0.78 to 1.15] and TICS-m $\beta_{(TBI*ApoE\text{-}e4\ non\text{-}carriers)}$-0.26 [95% CI −1.10 to 0.58]). Overall, these interactions indicate that as male veterans age, those with TBI had lower TICS-m scores and declined faster if they were *ApoE*-e4 carriers relative to *ApoE*-e4 non-carriers.

Discussion

In this nationwide study of twins, we found that veterans who experienced at least one TBI in their lifetime generally had lower cognitive scores and faster rates of cognitive decline in later life, particularly among those with more severe TBI indicated by LOC and those who experienced TBI after 24 years. Although our results show modest effect sizes for TBI on cognition in later life, we note that the effect sizes reflect the contribution TBI has on cognitive function as compared with the co-twin without TBI (for pairs in which both twins were included in the analyses). This is the effect of TBI on cognition after accounting for sociodemographic and medical condition covariates and unidentified factors throughout the life span that are shared by the co-twins that may influence cognition. For instance, for a monozygotic twin pair, the co-twin who had a TBI after 24 years scored approximately 3 quarters of a TICS-m point (0.74 TICS-m points) lower than the twin without TBI at 70 years. In the example above, the twin with TBI is declining 0.07 points faster per year than his co-twin without TBI. Therefore, in 12 years of follow-up of this study, the co-twin with TBI would have steeper cognitive decline (0.84 TICS-m points) than his co-twin without TBI. Thus, the contribution of TBI on late-life cognition, in addition to the numerous other factors with a detrimental effect on cognition, may be sufficient to trigger an evaluation for cognitive impairment. These findings extend the results from prior research. One recent epidemiologic study of community adults older than 50 years measured cognition longitudinally in late life with a 4-year follow-up period and did not observe significant cognitive decline differences between those with and without TBI, regardless of TBI severity.[18] Our observed differences in rates of cognitive decline from the previous study may, in part, be because of adjustment of covariates and medical conditions known to influence cognitive trajectories (i.e., Parkinson disease, seizures, and depression). No other studies have repeatedly measured cognition in association with TBI for a period extending over a decade in later life.[16,17,22,37,38] We examined cognitive function longitudinally for up to 12 years, beginning an average of 34 years after TBI. This longer follow-up period and added control provided by the twin study design may have allowed us to detect differences in rates of decline.

The effect of specific risk factors of dementia varies by age.[19] Our finding that individuals with TBI at older ages had lower cognitive function and more rapid decline than those who had a TBI before 25 years suggests that age of exposure may also matter for cognitive decline in later life. Among the few studies exploring age effects of TBI, one reported a more rapid decline in processing speed but not in episodic memory for those 60 years and older who had a TBI during adulthood, compared with individuals who had a TBI during childhood.[39] This contrasts somewhat with our finding that global cognitive status, which included episodic memory, declined more rapidly after 60 years. One explanation for TBIs after early adulthood having a greater negative effect on late-life cognition is that the remyelination process is likely to be affected by TBI and becomes less efficient and occurs at a slower rate with age.[40]

Twin studies contribute uniquely to investigating associations between exposures and outcomes and add key information in building evidence for an association being due to causation.[41,42] Heterogeneity in cognitive reserve, genetic risk of neurodegenerative conditions, and underlying comorbidities complicate the degree to which we can predict risk of cognitive decline in late life attributable to a single factor such as TBI. However, the twin study design controls for many genes and shared early-life exposures, many of which have not been identified and cannot be reliably measured in other non-twin studies of late-life cognitive decline. Our study also controlled for many health conditions, alcohol overuse, and smoking, factors that negatively affect late-life cognition and could differ within twin pairs.[2,43] Most of our observed associations between TBI and worse cognition remained statistically significant after accounting for these additional factors, indicating the robustness of the results.

In the co-twin control analyses that used only twin pairs discordant for TBI, with each twin within the pair serving as his co-twin's matched control, TBI was most frequently associated with poorer cognitive outcomes in the MZ pairs. Notably, MZ twins with TBI after 25 years had a lower cognitive level and faster rate of decline than their co-twins without TBI. This finding suggests that in genetically identical individuals, TBI both lowers cognitive reserve (i.e., cognitive level) and quickens the pace of cognitive decline. Because MZ pairs share all of their genes and typically also share many early-life exposures, this finding suggests that the association between TBI and cognitive decline is likely not because of genetic confounding or the many early-life environmental exposures shared by co-twins. Thus, these findings strengthen the case for concluding that TBI contributes uniquely to late-life poorer cognitive outcomes beyond those observed in normal aging.

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In a subsample with *ApoE* genotype, we found that *ApoE*-e4 carriers with TBI had lower cognitive scores and declined faster than non–e4 carriers, but we did not observe significant modification of the TBI effect by *ApoE* status. Evidence from other studies on the role of *ApoE*-e4 on cognitive outcomes has been mixed,[44,45] likely because of the study design differences, the small sample sizes of studies included, and the timing of cognitive assessments after TBI.

Our study has limitations. We relied on self or proxy report for the history of TBI, which may have resulted in some exposure misclassification, particularly for those with TBIs in early life. Our prior work[9] compared medical record documentation of TBI with self or proxy report decades later and showed that both individuals and their proxies tend to under-report lifetime history of TBI, with the less severe TBIs under-reported at a higher rate. However, this prior work did not indicate that under-reporting was more common among twins who later eventually developed dementia; thus, such under-reporting was unlikely to bias our results.[9] We note also that even studies using medical records to identify TBI may misclassify exposure to TBI because they are typically limited to relatively few years of the individual's total life span. Finally, the cohort consists exclusively of male veterans, primarily of White race born between 1917 and 1927, which means that the results may not be generalizable to female patients, other race and ethnic groups, or non-veteran populations, and our findings may be affected by secular trends in diagnosis and treatment of TBI and cognitive disorders.

Little is known about the interface between cognitive aging and the long-term effects of TBIs. Our twin study shows that TBIs, even decades before cognitive testing, led to lower cognitive levels and faster rates of cognitive decline in late life, regardless of shared genetics and early-life exposures and medical conditions. This association was stronger for those having a TBI at 25 years or later, suggesting that TBI both lowers cognitive reserve (level of cognition) and accelerates cognitive aging. Although many TBIs go unreported, there is a trend toward increased emergency department visits because of sports or recreational activities,[46,47] particularly among male patients aged 10–24 years or those 45 years or older.[47] These numbers combined with the estimated half million members of the military who suffered a TBI between 2000 and 2020[48,49] emphasize the potential long-term effect of TBIs in this population that cannot be overlooked.

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Appendix Authors

Name	Location	Contribution
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References

1. Dewan MC, Rattani A, Gupta S, et al. Estimating the global incidence of traumatic brain injury. *J Neurosurg*. 2019;130(4):1080-1097. doi:10.3171/2017.10.jns17352
2. Moretti L, Cristofori I, Weaver SM, Chau A, Portelli JN, Grafman J. Cognitive decline in older adults with a history of traumatic brain injury. *Lancet Neurol*. 2012;11(12):1103-1112. doi:10.1016/s1474-4422(12)70226-0
3. 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;5:424-431. doi:10.1016/s2215-0366(18)30065-8
4. Taylor CA, Bell JM, Breiding MJ, Xu L. Traumatic brain injury-related emergency department visits, hospitalizations, and deaths - United States, 2007 and 2013. *MMWR Surveill Summ*. 2017;66(9):1-16. doi:10.15585/mmwr.ss6609a1
5. Perry DC, Sturm VE, Peterson MJ, 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
6. Plassman BL, Grafman J. Chapter 44 - traumatic brain injury and late-life dementia. In: Grafman J, Salazar AM, eds. *Handbook of Clinical Neurology*. Elsevier; 2015:711-722.
7. Zhang L, Yang W, Li X, et al. *Association of Life-course Traumatic Brain Injury with Dementia Risk: A Nationwide Twin Study*. Alzheimer's & Dementia; 2022.
8. Kornblith E, Peltz CB, Xia F, Plassman B, Novakovic-Apopain T, Yaffe K. Sex, race, and risk of dementia diagnosis after traumatic brain injury among older veterans. *Neurology*. 2020;95(13):e1768-e1775. doi:10.1212/wnl.0000000000010617
9. 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
10. Barnes DE, Byers AL, Gardner RC, Seal KH, Boscardin WJ, Yaffe K. Association of mild traumatic brain injury with and without loss of consciousness with dementia in US Military Veterans. *JAMA Neurol*. 2018;75(9):1055-1061. doi:10.1001/jamaneurol.2018.0815
11. Gardner RC, Yaffe K. Epidemiology of mild traumatic brain injury and neurodegenerative disease. *Mol Cell Neurosci*. 2015;66:75-80. doi:10.1016/j.mcn.2015.03.001

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12. Gardner RC, Burke JF, Nettiksimmons J, Kaup A, Barnes DE, Yaffe K. 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
13. Godbolt AK, Cancelliere C, Hincapié CA, et al. Systematic review of the risk of dementia and chronic cognitive impairment after mild traumatic brain injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch Phys Med Rehabil.* 2014;95(3):S245-S256. doi:10.1016/j.apmr.2013.06.036
14. Almeida OP, Hankey GJ, Yeap BB, Golledge J, Flicker L. Prevalence, associated factors, mood and cognitive outcomes of traumatic brain injury in later life: the health in men study (HIMS). *Int J Geriatr Psychiatry*. 2015;30(12):1215-1223. doi:10.1002/gps.4276
15. Gardner RC, Langa KM, Yaffe K. Subjective and objective cognitive function among older adults with a history of traumatic brain injury: a population-based cohort study. *PLoS Med.* 2017;14(3):e1002246. doi:10.1371/journal.pmed.1002246
16. Mollayeva T, Mollayeva S, Pacheco N, D'Souza A, Colantonio A. The course and prognostic factors of cognitive outcomes after traumatic brain injury: a systematic review and meta-analysis. *Neurosci Biobehav Rev.* 2019;99:198-250. doi:10.1016/j.neubiorev.2019.01.011
17. D'Souza A, Mollayeva S, Pacheco N, Javed F, Colantonio A, Mollayeva T. Measuring change over time: a systematic review of evaluative measures of cognitive functioning in traumatic brain injury. *Front Neurol.* 2019;10:353. doi:10.3389/fneur.2019.00353
18. Lennon MJ, Brooker H, Creese B, et al. Lifetime traumatic brain injury and cognitive domain deficits in late life: the PROTECT-TBI Cohort Study. *J Neurotrauma.* 2023;40(13-14):1423-1435. doi:10.1089/neu.2022.0360
19. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet*. 2017;390(10113):2673-2734. doi:10.1016/s0140-6736(17)31363-6
20. Yu J-T, Xu W, Tan C-C, et al. Evidence-based prevention of Alzheimer's disease: systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials. *J Neurol Neurosurg Psychiatry*. 2020;91(11):1201-1209. doi:10.1136/jnnp-2019-321913
21. Kulshreshtha A, Goetz M, Alonso A, et al. Association between cardiovascular health and cognitive performance: a twins study. *J Alzheimer's Dis.* 2019;71(3):957-968. doi:10.3233/jad-190217
22. Plassman BL, Williams JW Jr., Burke JR, Holsinger T, Benjamin S. Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. *Ann Intern Med.* 2010;153(3):182-193. doi:10.7326/0003-4819-153-3-201008030-00258
23. Page WF. The NAS-NRC twin registry of WWII military veteran twins. National Academy of Sciences-National Research Council. *Twin Res.* 2002;5:493-496. doi:10.1375/136905202320906345
24. Brandt J, Spencer M, Folstein M. The telephone interview for cognitive status. *Neuropsychiatry Neuropsychol Behav Neurol.* 1988;1(2):111-117.
25. Welsh K, Breitner J, Magruder-Habib K. Detection of dementia in the elderly using telephone screening of cognitive status. *Neuropsychiatry Neuropsychol Behav Neurol.* 1993;6:103-110.
26. de Jager CA, Budge MM, Clarke R. Utility of TICS-M for the assessment of cognitive function in older adults. *Int J Geriatr Psychiatry*. 2003;18(4):318-324. doi:10.1002/gps.830
27. Plassman BL, Newman TT, Welsh K, Helms MJ, Breitner J. Properties of the telephone interview for cognitive status. Application in Epidemiological and Longitudinal Studies. *Neuropsychiatry Neuropsychol Behav Neurol.* 1994;7:235-241.
28. Gallo JJ, Breitner JC. Alzheimer's disease in the NAS-NRC Registry of aging twin veterans, IV. Performance characteristics of a two-stage telephone screening procedure for Alzheimer's dementia. *Psychol Med.* 1995;25(6):1211-1219. doi:10.1017/s0033291700033183
29. Knopman DS, Roberts RO, Geda YE, et al. Validation of the telephone interview for cognitive status-modified in subjects with normal cognition, mild cognitive impairment, or dementia. *Neuroepidemiology*. 2010;34(1):34-42. doi:10.1159/000255464
30. Xiong GL, Plassman BL, Helms MJ, Steffens DC. Vascular risk factors and cognitive decline among elderly male twins. *Neurology*. 2006;67(9):1586-1591. doi:10.1212/01.wnl.0000242730.44003.1d
31. Potter GG, Plassman BL, Helms MJ, Steffens DC, Welsh-Bohmer KA. Age effects of coronary artery bypass graft on cognitive status change among elderly male twins. *Neurology*. 2004;63(12):2245-2249. doi:10.1212/01.wnl.0000147291.49404.0a
32. Harrell FE, SpringerLink. *Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis*. Springer International Publishing; 2015.
33. Hrubec Z, Neel JV. The national Academy of Sciences—National Research Council Twin Registry: ten years of operation. *Prog Clin Biol Res.* 1978;24 Pt B:153-172.
34. Jablon S, Neel JV, Gershowitz H, Atkinson GF. The NAS-NRC twin panel: methods of construction of the panel, zygosity diagnosis, and proposed use. *Am J Hum Genet.* 1967;19(2):133-161.
35. Reed T, Plassman BL, Tanner CM, Dick DM, Rinehart SA, Nichols WC. Verification of self-report of zygosity determined via DNA testing in a subset of the NAS-NRC twin registry 40 years later. *Twin Res Hum Genet.* 2005;8(4):362-367. doi:10.1375/twin.8.4.362
36. Saunders AM, Strittmatter WJ, Schmechel D, et al. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. *Neurology*. 1993;43(8):1467-1472. doi:10.1212/wnl.43.8.1467
37. Kohler MJ, Hendrickx MD, Powell-Jones A, Bryan-Hancock C. A systematic review of cognitive functioning after traumatic brain injury in individuals aged 10-30 years. *Cogn Behav Neurol.* 2020;33(4):233-252. doi:10.1097/wnn.0000000000000236
38. Hume CH, Wright BJ, Kinsella GJ. Systematic review and meta-analysis of outcome after mild traumatic brain injury in older people. *J Int Neuropsychol Soc.* 2022;28(7):736-755. doi:10.1017/s1355617721000795
39. Eramudugolla R, Bielak AA, Bunce D, Easteal S, Cherbuin N, Anstey KJ. Long-term cognitive correlates of traumatic brain injury across adulthood and interactions with APOE genotype, sex, and age cohorts. *J Int Neuropsychol Soc.* 2014;20(4):444-454. doi:10.1017/s1355617714000174
40. Franklin RJ, Zhao C, Sim FJ. Ageing and CNS remyelination. *Neuroreport*. 2002;13(7):923-928. doi:10.1097/00001756-200205240-00001
41. Sahu M, Prasuna JG. Twin studies: a unique epidemiological tool. *Indian J Community Med.* 2016;41(3):177-182. doi:10.4103/0970-0218.183593
42. Kaprio J, Silventoinen K. Advanced methods in twin studies. In: Teare MD, ed. *Genet Epidemiol*. Humana Press; 2011:143-152.
43. Lee T, Sachdev P. The contributions of twin studies to the understanding of brain ageing and neurocognitive disorders. *Curr Opin Psychiatry*. 2014;27(2):122-127. doi:10.1097/yco.0000000000000039
44. Lawrence DW, Comper P, Hutchison MG, Sharma B. The role of apolipoprotein E epsilon (ε)-4 allele on outcome following traumatic brain injury: a systematic review. *Brain Inj.* 2015;29(9):1018-1031. doi:10.3109/02699052.2015.1005131
45. Padgett CR, Summers MJ, Skilbeck CE. Is APOE ε4 associated with poorer cognitive outcome following traumatic brain injury? A meta-analysis. *Neuropsychology*. 2016;30(7):775-790. doi:10.1037/neu0000270
46. Sarmiento K, Thomas KE, Daugherty J, et al. Emergency department visits for sports- and Recreation-related traumatic brain injuries among children - United States, 2010-2016. *MMWR Morb Mortal Wkly Rep.* 2019;68(10):237-242. doi:10.15585/mmwr.mm6810a2
47. Coronado VG, Haileyesus T, Cheng TA, et al. Trends in sports- and recreation-related traumatic brain injuries treated in US emergency departments: the National Electronic Injury Surveillance System-All Injury Program (NEISS-AIP) 2001-2012. *J Head Trauma Rehabil.* 2015;30(3):185-197. doi:10.1097/htr.0000000000000156
48. Fischer H. *A Guide to U.S. Military Casualty Statistics: Operation Freedom's Sentinel, Operation Inherent Resolve, Operation New Dawn, Operation Iraqi Freedom, and Operation Enduring Freedom*. Congressional Research Service, 2015. Report no. RS22452.
49. Traumatic Brain Injury Center of Excellence. *DOD TBI worldwide numbers*. Updated July 11, 2023. Accessed May 5, 2021. https://health.mil/Military-Health-Topics/Centers-of-Excellence/Traumatic-Brain-Injury-Center-of-Excellence/DOD-TBI-Worldwide-Numbers

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