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Mild Traumatic Brain Injury, Loss of Consciousness and Dementia in Veterans

Running head: Mild Traumatic Brain Injury and Dementia

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KEY POINTS

Question. Is mild traumatic brain injury without loss of consciousness associated with an increased risk of dementia diagnosis in Veterans?

Findings. In this propensity-matched cohort study of more than 350,000 Veterans with and without traumatic brain injuries, mild traumatic brain injury without loss of consciousness was associated with more than a two-fold increase in the risk of dementia diagnosis, even after adjusting for medical and psychiatric comorbidities.

Meaning. Even mild traumatic brain injuries that do not result in loss of consciousness may have long-term neurodegenerative consequences.

Tweet:

Mild traumatic brain injury without loss of consciousness associated with doubled dementia diagnosis risk in Veterans.

ABSTRACT

Importance: Traumatic brain injury (TBI) is common in both Veteran and civilian populations. Prior studies have linked moderate and severe TBI with increased dementia risk, but the association between dementia and mild TBI—particularly mild TBI without loss of consciousness (LOC)—remains unclear.

Objective: To examine the association between TBI severity, LOC and dementia diagnosis in Veterans.

Design, Setting and Participants: Retrospective cohort study of all patients diagnosed with a TBI in the Veterans Health Administration (VHA) healthcare system from 10/1/2001 – 9/30/2014 (n=178,779) and a propensity-matched comparison group (n=178,779). Patients with dementia at baseline were excluded.

Exposure: TBIs were identified through the Comprehensive TBI Evaluation database, which is restricted to Iraq and Afghanistan Veterans, and the National Patient Care Database, which includes all-era Veterans. TBI severity was classified as mild without LOC; mild with LOC; mild with LOC unknown or moderate/severe using Department of Defense or Defense and Veterans Brain Injury Center criteria based on the most severe injury recorded.

Main Outcome: International Classification of Diseases 9th edition codes were used to identify dementia diagnoses during follow-up and medical and psychiatric comorbidities during the two years prior to the index date.

Results: Veterans had a mean age of nearly 50 years at baseline; 9% were female and 72% were non-Hispanic white. Differences between Veterans with and without TBI were small. Almost 3% of Veterans without TBI developed dementia compared to more than 6% of those with TBI. After adjustment for demographics and medical and psychiatric comobidities, adjusted hazard ratios

(95% confidence intervals) for dementia were 2.36 (2.10, 2.66) for mild TBI without LOC, 2.51 (2.29, 2.76) for mild TBI with LOC, 3.19 (3.05, 3.33) for mild TBI with LOC unknown and 3.77 (3.63, 3.91) for moderate/severe TBI.

Conclusions and Relevance: In this retrospective cohort study of more than 350,000 Veterans, even mild TBI without LOC was associated with more than a two-fold increase in the risk of dementia diagnosis. Studies of strategies to determine mechanisms, prevention and treatment of TBI-related dementia in Veterans are urgently needed.

INTRODUCTION

Traumatic brain injury (TBI) was one of the earliest risk factors identified for Alzheimer's disease and dementia.[1] Although not all studies have found an association,[2-7] the majority of studies including several meta-analyses have found that moderate and severe TBI are associated with increased risk or earlier onset of Alzheimer's disease and dementia,[8-18] particularly in those with genetic risk factors such as one or more apolipoprotein-E e4 alleles.[19-22] However, the association between mild TBI and dementia remains controversial,[11,12] and few studies have specifically examined the effects of mild TBI without loss of consciousness (LOC).[4]

Mild TBI is extremely common in the general population and is especially high in military personnel. Approximately 2.8 million TBIs occurred in the U.S. in 2013,[23] and the vast majority (~80%) of these were mild.[24] A recent survey found that 17% of Iraq and Afghanistan troops reported experiencing a mild TBI during deployment and, of these, 59% reported more than one mild TBI.[25] Most of these are caused by shock waves from blasts rather than blunt trauma and do not necessarily result in LOC.[26]

There also is growing awareness that mild, repeated TBIs are closely related to chronic traumatic encephalopathy (CTE), a neurodegenerative disease associated with repeated head trauma.[27] Recent autopsy studies have identified CTE in professional athletes who participate in American football, boxing, soccer, wrestling, ice hockey, rugby and baseball.[28-33] Severity of neuropathology is correlated with years of exposure to contact sports, rather than number of concussions, suggesting that subconcussive injuries contribute to disease progression.[27,34] CTE also has been identified in military veterans exposed to repeated TBI.[35]

The objective of this study was to examine the association between TBI and diagnosis of dementia in Veterans who receive care in the Veterans Health Administration (VHA) healthcare

system. In particular, we sought to determine whether Veterans who experience mild TBI without LOC are more likely to be diagnosed with dementia.

METHODS

<u>Study Population</u>

We performed a retrospective cohort study that included all VHA patients who received a TBI diagnosis from 10/1/2001 to 9/30/2014 and a propensity-matched comparison sample. TBI diagnoses came from two sources: 1) the Comprehensive Traumatic Brain Injury Evaluation (CTBIE) database and 2) VHA inpatient and outpatient visits (National Patient Care Databases, NPCD).

CTBIE is an accruing national database that began in 2007 and includes Iraq and Afghanistan-era Veterans who have separated from military service, enrolled in VHA healthcare, and received a comprehensive TBI evaluation. Veterans may be referred for a comprehensive TBI evaluation if they screen positive for TBI; they are informed prior to screening that they may have sustained a moderate to severe TBI; or they report symptoms suggestive of TBI or concussion during a VA clinical visit. All TBI evaluations are performed by a neurologist or a trained allied health professional, either within VHA or through another facility reimbursed by VA. The CTBIE database includes detailed information on the final determination of TBI status as well as duration of LOC, alteration of consciousness (AOC) and post-traumatic amnesia (PTA). Veterans who are referred but not evaluated or who receive evaluations that are not captured in the CTBIE database are not included. We identified all Iraq and Afghanistan Veterans who received a TBI diagnosis through CTBIE from October 2007 to October 2014.

In addition, we identified all other VHA patients who received an inpatient or outpatient TBI diagnosis as part of routine clinical care using a comprehensive list of International Classification of Diseases 9 (ICD-9) codes created by the Defense and Veterans Brain Injury Center (DVBIC) and the Armed Forces Health Surveillance Branch (AFHSB) for TBI surveillance (2012 criteria, see below).[36]

For all participants with TBI, we determined the first fiscal year in which a TBI was diagnosed. In addition, as a proxy measure for repeated TBIs, we determined the number of years in which each Veteran had at least one TBI diagnosis prior to a diagnosis of dementia or censoring. We hypothesized that a TBI diagnosed in a subsequent year would be more likely to reflect a new event rather than ongoing care for the index event.

To identify a comparison sample of Veterans without TBI, we first selected a 2% random sample of all patients who received VHA care from 10/1/2001 to 9/30/2014. We then used propensity matching to select one Veteran without TBI for each Veteran with TBI. We performed propensity score matching with no replacement using nearest-neighbor caliper matching with caliper width of 0.2 SDs of the logit of the propensity score utilizing Stata software. Propensity score matching was conducted on the entire sample (CTBIE and NPCD data) matching any TBI and no TBI groups using all covariates.

The 'index date' for those with TBI was defined as the date of the most severe TBI. If TBIs were comparable in severity, the index date was defined as the first TBI recorded. For participants without TBI, the index date was defined as the random selection date (between 10/1/2001 and 9/30/2014). Individuals with a dementia diagnosis at the time of the index date or during the two previous years were excluded (see below). For all participants, starting with the index date, we extracted dates and diagnoses for all subsequent inpatient and outpatient visits.

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, Office of Research Protections, Human Research Protection Office. Informed consent was waived because many study participants had died or were no longer receiving care through VHA when these analyses were performed.

TBI Severity

A variety of criteria exist to define TBI severity,[37] and a recent study identified more than 50 different definitions of mild TBI.[38] Department of Defense coding guidelines from 2010 define mild TBI as TBI with normal structural imaging, LOC of 0 to 30 minutes, AOC of a moment up to 24 hours, and PTA of 0 to 1 day.[39] DVBIC, AFHSB and the Centers for Disease Control (CDC) have collaborated to develop a standard TBI surveillance case definition using ICD9/10 codes.[36]

For the current study, we classified the most severe TBI as none, mild or moderate/severe. We then separated mild TBIs into those without LOC, with LOC or with LOC unknown. In patients whose TBI was diagnosed through CTBIE, TBI severity was defined using the more stringent DOD criteria.[39] In patients whose TBI was diagnosed through ICD-9 codes, TBI severity was defined using DVBIC 2012 Criteria (see eAppendices 1 and 2).[36] Patients whose TBI severity could not be classified were excluded.

Dementia

Prevalent dementia at baseline was defined using a comprehensive list of ICD-9 codes recommended by the VA Dementia Steering Committee (2016 version, eAppendix 3).

Individuals with a dementia code at the index date or during the previous two years were excluded. Incident dementia during follow-up was classified using a slightly modified version of the VA Steering Committee ICD-9 codes in which we excluded prion disease (046.11, 046.19, 046.3, 046.79) and alcohol/drug-induced dementia (291.2, 292.82).

Other Measures

Demographic information, medical comorbidities and psychiatric conditions were obtained from the VHA inpatient and outpatient files. Demographic data were based on self-report and included age at index date, sex and race/ethnicity (categorized as non-Hispanic white, non-Hispanic black, Hispanic or other/unknown). In addition, we used zip code at the index date and 2000 U.S. Census data to classify veterans as living in broad educational and income strata. Education was dichotomized as ≤ 25% versus > 25% of the adult population completing a college education (bachelor's degree or higher). Income was categorized into tertiles of median income for adults <75 years or ≥75 years.

Medical comorbidities and psychiatric disorders were coded as 'present' at baseline if they were coded at the index date or during the previous two years using standard ICD-9 codes. Medical comorbidities included: diabetes mellitus, hypertension, myocardial infarction, cerebrovascular disease, and peripheral vascular disease. Psychiatric conditions included: mood disorder (depression, dysthymia, bipolar disorder), anxiety, post-traumatic stress disorder, substance use disorder (alcohol or drug abuse), tobacco use and sleep disorder (sleep apnea, insomnia, hypersomnia, parasomnia, and circadian rhythm disorders).

Analyses

Baseline characteristics of Veterans were compared as a function of TBI using t-tests for continuous variables and Chi-square analysis for categorical variables. Cumulative incidence of dementia as a function of age and TBI severity was examined graphically. Cox proportional hazards models were used to examine time to dementia diagnosis with censoring at death or last medical encounter and age as the timescale. Models were unadjusted and adjusted in steps for 1) demographics; 2) demographics and medical comorbidities; and 3) demographics, medical comorbidities and psychiatric disorders. In addition, sensitivity analyses were performed stratified based on TBI data source (CTBIE versus NPCD) and comparing Veterans with TBIs coded in single versus multiple years. Cox proportional hazards model assumptions were checked for all final models. P-values were two-sided with statistical significance defined as p<0.05. Analyses were performed using SAS version 9.4.

RESULTS

Our final cohort included 178,779 Veterans with TBI and a propensity-matched comparison sample of 178,779 Veterans without TBI. Most TBIs were identified through NPCD only (85%) while 7% were from CTBIE only and 8% were included in both datasets. Overall, TBI severity was 10% mild without LOC, 13% mild with LOC, 31% mild with LOC unknown and 46% moderate/severe. TBIs identified through CTBIE were more likely to be mild (85%) than those identified through NPCD (52%) (eAppendix 4). Veterans from CTBIE were younger (mean age 33 vs. 51 years) and had fewer medical comorbidities (diabetes: 2% vs. 4%; cerebrovascular disease: <1% vs. 5%) and more psychiatric comorbidities (PTSD: 20% vs. 11%).

Veterans with and without TBI were generally well-matched (Table 1). Study participants had a mean age of 49 ± 18 years at their index date; 9% were women and the race/ethic

distribution was 72% non-Hispanic white, 16% non-Hispanic black, 2% Hispanic and 10% other/unknown. Four percent had a history of diabetes mellitus; 11% had hypertension; 19% had a mood disorder, and 11% had PTSD. Study participants were followed for a mean (SD) of 4.2 (3.4) years until dementia, death or their most recent clinical visit (whichever occurred first).

A total of 4,698 (2.6%) cases of incident dementia were diagnosed in Veterans without TBI, compared to 10,835 (6.1%) in those with TBI. After adjustment for age, medical comorbidities and psychiatric disorders, the adjusted hazard ratio (HR) (95% confidence interval, CI) for dementia diagnosis was 2.36 (2.10, 2.66) for mild TBI without LOC; 2.51 (2.29, 2.76) for mild TBI with LOC; 3.19 (3.05, 3.33) for mild TBI with LOC unknown; and 3.77 (3.63, 3.91) for moderate/severe TBI (Table 2). Figure 1 shows that cumulative incidence of dementia based on age at diagnosis increased progressively with TBI severity. The mean time from index date to dementia diagnosis was 3.6 ± 3.0 years in those with TBI and 4.8 ± 3.7 years in those without TBI. Dementia diagnosis occurred an average of 1.5 years earlier in those with versus without TBI in NPCD and 1.8 years earlier in CTBIE, with little evidence of difference in time to diagnosis by TBI severity."

Sensitivity analyses yielded similar results. When stratifying based on TBI data source, the adjusted hazard ratios (95% confidence intervals) were 2.20 (0.99-4.88) in CTBIE versus 2.27 (2.02-2.55) in NPCD for mild TBI without LOC; 3.20 (1.48-6.90) in CTBIE versus 2.49 (2.31-2.80) in NPCD for mild TBI with LOC; and 5.94 (2.73-12.93) in CTBIE versus 3.44 (3.22-3.57) in NPCD for moderate/severe TBI. All mild TBIs with LOC unknown were from NPCD. Most patients with TBI had a TBI code in a single year (81%) versus multiple years (19%), and the adjusted risk of dementia was similar in both groups (single year HR, 3.46; 95% CI: 3.34,

3.58; multiple year HR, 3.41; 95% CI: 3.23, 3.60). Cox proportional hazards model checks did

not reveal any major violations of model assumptions.

DISCUSSION

In this cohort of more than 350,000 Veteran patients with and without TBI, we found a

dose response relationship between TBI severity and dementia diagnosis. Even mild TBI without

LOC was associated with more than a two-fold increase in the risk of receiving a dementia

diagnosis. This association remained strong after adjustment for demographics, medical

comorbidities and psychiatric conditions and was consistent in sensitivity analyses. These results

confirm prior studies including a 2008 Institute of Medicine report that have found an association

between moderate/severe TBI and risk of dementia.[1,9,11,12,21,40] In addition, although prior studies

of the association between mild TBI and dementia have been mixed,[2-6] our study adds to the

weight of evidence suggesting that mild TBI is also associated with increased dementia diagnosis

risk.[13-15,37,41]

Our results differ from several recent cohort studies that found no association between

self-reported mild TBI and dementia risk.[4,5,7] These differences may be due to differences in how

TBIs were identified. Self-reported TBIs are likely to be less specific than injuries identified

through the medical record, which could potentially bias results toward the null.

We are aware of only one prior study that has specifically examined the association

between mild TBI without LOC and dementia risk.[42] This study utilized a retrospective, case-

control study design in which TBI status was determined in 2,233 patients with Alzheimer's

disease and 14,668 first-degree family members based on informant interviews and medical

record review. TBI with and without LOC were both associated with greater odds of dementia,

with evidence of a dose-response relationship. This design has several limitations, including the potential for recall bias when classifying TBI status and selection bias based on using first-degree relatives. Our study used a more rigorous cohort design in which TBI and dementia were both ascertained using similar methods in the same study population. In addition, we examined mild TBI with and without LOC.

There are several potential mechanisms that have been proposed to explain the association observed between TBI and dementia.[43] First, TBI can damage brain structure as a direct result of the injury.[43] Diffuse axonal injury is common in all severities of TBI.[44,45] Autopsy and neuroimaging studies also have shown that a single moderate to severe TBI can cause marked cerebral atrophy six months post-injury that may progress for many years. It is possible that these TBI-related brain changes, when combined with dementia-related neuropathological changes, lead to increased risk and earlier onset of dementia symptoms.

Second, TBI may lead directly to neuropathological changes that cause Alzheimer's disease such as deposition of tau in neurofibrillary tangles and amyloid-β (Aβ) in plaques. Neurofibrillary tangles are one of the most consistent pathologies observed in CTE.[43] Although amyloid-β (Aβ) pathology is less consistently observed following TBI, an autopsy study in 39 TBI survivors found both plaques and tangles in greater density and wider distribution than age-matched, uninjured controls.[46] Furthermore, plaques tended to be diffuse in short-term TBI survivors and fibrillary in long-term TBI survivors, which is similar to patterns observed in early- versus late-stage Alzheimer's.[46]

Other neuropathological changes that have been linked with both TBI and dementia include white matter degeneration and neuroinflammation. It also is possible that mechanisms may differ based on TBI severity. For example, mild TBI without LOC may increase dementia

risk primarily by accelerating atrophy, while moderate/severe TBI may have a more direct effect on Aβ and tau.

An alternative explanation for our results is that dementia diagnoses in these Veterans reflect ongoing cognitive and functional impairment associated with their original injuries. For example, a Veteran might suffer from cognitive impairment immediately following their TBI, and a clinician might code this as dementia if they are still experiencing cognitive impairment that is severe enough to interfere with daily function several years later. If this is occurring, it suggests that even mild TBI without LOC is associated with greater risk of long-term cognitive and functional impairment in these Veterans.

Strengths and Limitations

Our study has several important strengths. First, we performed a longitudinal study in a large cohort, giving us ample power to detect associations and to adjust for a wide range of potential confounders. In particular, our sample size was large enough to examine mild TBI without LOC as a distinct category. Second, we included TBIs diagnosed through either the comprehensive TBI evaluation (CTBIE) or VHA inpatient and outpatient records (NPCD). CTBIE includes TBI evaluations performed outside the VHA system, enabling us to capture a larger number of TBIs and to stratify results using the two data sources. Third, we selected our comparison sample using propensity matching to minimize the potential for confounding due to factors that predispose certain Veterans to experience TBIs.

Several limitations also should be considered when interpreting these results. This was a retrospective study using medical record data based on clinician diagnoses, which do not necessarily reflect consensus definitions for TBI or dementia. This likely resulted in an under-

diagnosis of dementia, particularly in the earlier stages. In addition, data on dementia subtypes were limited. All TBIs were diagnosed within the VHA healthcare system; therefore, results may not generalize to TBIs that do not result in medical care or are treated outside the VHA system. There also was heterogeneity in our working definition of TBI, and we were not able to quantify the number, types or causes of TBIs experienced. We do not know whether TBIs occurred in military or non-military settings, although it is likely that CTBIE included primarily deployment-related TBIs. We also did not have information on history of TBIs. To the extent that misclassification occurred at random, it would tend to bias results toward the null. Additional research is critically needed to determine the mechanisms underlying the association observed between TBI and dementia—including mild TBI without LOC—so that effective treatment and prevention strategies can be developed.

Conclusion

In this large, retrospective cohort study of VHA patients, we observed a dose-response relationship between TBI severity and dementia diagnosis. Even mild TBI without loss of consciousness was associated with more than a two-fold increase in the risk of dementia diagnosis after adjusting for demographic, medical and psychiatric comorbidities.

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AUTHOR CONTRIBUTIONS

Conception and design (DEB, ALB, WJB, KY)

Acquisition and analysis of data (ALB, WJB, KY)

Drafting of the manuscript and approval of final manuscript (DEB, ALB, RCG, KHS, WJB,

KY).

CONFLICTS OF INTEREST

None

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FIGURE LEGENDS

Cumulative Incidence of Dementia by Traumatic Brain Injury (TBI) Severity.

The unadjusted cumulative incidence of dementia (age of dementia diagnosis) is shown as a function of traumatic brain injury (TBI) severity. After adjustment for demographics, medical conditions and psychiatric disorders, there was a dose-response relationship between TBI severity and dementia diagnosis with hazard ratios (95% confidence intervals) of 2.36 (2.10, 2.66) for mild TBI without loss of consciousness (LOC); 2.51 (2.29, 2.76) for mild TBI with LOC; 3.19 (3.05, 3.33) for mild TBI with LOC unknown and 3.77 (3.63, 3.91) for moderate/severe TBI.

Table 1. Baseline characteristics of 357,558 veterans with or without TBI

	No TBI (N=178,779)	Any TBI (N=178,779)
Demographic		
Age, y, mean (SD)	49.95 (18.02)	49.00 (18.42)
Female, n (%)	16,835 (9.42)	16,415 (9.18)
Race		
Non-Hispanic White	130,955 (73.25)	128,181 (71.70)
Non-Hispanic Black	29,475 (16.49)	27,806 (15.55)
Hispanic	2,931 (1.64)	3,620 (2.02)
Other/Unknown	15,418 (8.63)	19172 (10.53)
>25% college-educated in zip code	93,442 (52.27)	94,011 (52.59)
Median income tertile in zip code		
Low tertile (<$24,632)	51,753 (28.95)	49,984 (27.96)
Middle tertile	61,449 (34.37)	61,054 (34.15)
High tertile (>$32,452)	65,577 (36.68)	67,741 (37.89)
Medical		
Diabetes mellitus	7,652 (4.23)	7,008 (3.92)
Hypertension	20,104 (11.25)	19,597 (10.96)
Myocardial infarction	2,977 (1.67)	2,643 (1.48)
Cerebrovascular disease	8,175 (4.57)	7,445 (4.16)
Peripheral vascular disease	4,121 (2.31)	3,603 (2.02)
Psychiatric		
Mood disorder	37,262 (20.84)	32,132 (17.97)
Anxiety	17,898 (10.01)	15,766 (8.82)
Posttraumatic stress disorder	21,970 (12.29)	16,809 (9.40)
Substance abuse	15,748 (8.81)	13,523 (7.56)
Smoking or tobacco use	19,461 (10.89)	18,353 (10.27)
Sleep disorder	7,049 (3.94)	6,497 (3.63)

Values are N (%) unless otherwise specified. Veterans with and without TBI were matched using propensity scores, and differences

between groups are not clinically meaningful.

Table 2. Unadjusted and adjusted risk of dementia by TBI severity (N=357,558)

	Hazard Ratio (95% Confidence Interval) [d]					
	No TBI (N=178,779)	**Any TBI** (N=178,779)	**Mild TBI, Without LOC** (N=17,759)	**Mild TBI, With LOC** (N= 23,097)	**Mild TBI, LOC unknown** (N= 55,004)	**Moderate/Severe TBI** (N=82,919)
Unadjusted	Ref	3.41 (3.29-3.53)**	2.29 (2.04-2.58)**	2.48 (2.26-2.72)**	3.11 (2.97-3.25)**	3.75 (3.61-3.89)**
Model 1 [a]	Ref	3.41 (3.30-3.53)**	2.32 (2.06-2.61)**	2.49 (2.27-2.73)**	3.14 (3.00-3.28)**	3.73 (3.60-3.88)**
Model 2 [b]	Ref	3.41 (3.29-3.53)**	2.34 (2.08-2.63)**	2.50 (2.28-2.75)**	3.16 (3.02-3.31)**	3.71 (3.57-3.85)**
Model 3 [c]	Ref	3.45 (3.33-3.57)**	2.36 (2.10-2.66)**	2.51 (2.29-2.76)**	3.19 (3.05-3.33)**	3.77 (3.63-3.91)**

[a] Model 1: adjusted for demographic (gender, race, education, income).

[b] Model 2: adjusted for demographic and medical condition (diabetes, hypertension, myocardial infarction, cerebrovascular disease, peripheral vascular disease).

[c] Model 3: adjusted for demographic, medical conditions, and psychiatric disorders (mood disorder, anxiety, posttraumatic stress disorder, substance use disorder, tobacco use, and sleep disorder).

[d] No TBI is the reference group.

**p<.0001